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Pretreatment prediction of pathological complete response and baseline psychosocial burden in HER2-positive breast cancer during neoadjuvant therapy: development and temporal internal validation of a nomogram

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Abstract: We developed and temporally internally validated a pretreatment nomogram for predicting pathological complete response (pCR) in human epidermal growth factor receptor 2 (HER2)-positive breast cancer and examined cross-sectional associations among systemic inflammation, model-derived pCR probability, and baseline psychosocial burden. This ambispective single-center cohort included women receiving neoadjuvant chemotherapy plus HER2-directed therapy followed by surgery. Patients treated from January 2019 to December 2023 formed the training cohort (n=198), and those treated from January to August 2024 formed a same-center temporal validation cohort (n=48). Psychosocial support need was defined as Distress Thermometer score ≥ 4 , Hospital Anxiety and Depression Scale-Anxiety score ≥ 8 , or Hospital Anxiety and Depression Scale-Depression score ≥ 8 . Among 315 screened patients, 246 had complete data. pCR occurred in 72 training patients (36.36%) and 17 validation patients (35.42%). The final nomogram retained tumor size, clinical nodal status, hormone receptor status, and standardized neutrophil-to-lymphocyte ratio (NLR). Discrimination was acceptable in the training cohort (AUC=0.776; optimism-corrected AUC=0.758) and temporal validation cohort (AUC=0.769), although validation estimates were imprecise. Overall, 125 patients (50.81%) met the psychosocial support-need endpoint. Lower NLR-containing predicted pCR probability was associated with support need (OR=1.49 per 0.10 decrease), but this association attenuated after direct NLR adjustment (OR=1.13), indicating limited incremental psychosocial value beyond inflammation. The nomogram showed acceptable pretreatment pCR prediction performance, whereas psychosocial associations should be interpreted as non-causal clinical-inflammatory correlations requiring prospective multicenter validation.

Keywords: HER2-positive breast cancer; neoadjuvant therapy; pathological complete response; nomogram; neutrophil-to-lymphocyte ratio; distress; anxiety; psycho-oncology.

1. Introduction

Breast cancer remains the most frequently diagnosed malignancy among women worldwide and continues to impose substantial clinical and psychosocial burden [1]. Human epidermal growth factor receptor 2 (HER2)-positive breast cancer is a biologically distinct subtype characterized by HER2 overexpression or amplification and substantial responsiveness to HER2-directed therapy [2]. In early-stage and locally advanced disease, neoadjuvant chemotherapy combined with trastuzumab, pertuzumab, or both has become an important treatment strategy because it permits *in vivo* assessment of treatment response, may facilitate surgical downstaging, and informs post-neoadjuvant treatment decisions [3].

Pathological complete response (pCR), commonly defined as absence of

residual invasive carcinoma in the breast and axillary lymph nodes (ypT0/is ypN0), is associated with improved long-term outcomes in HER2-positive breast cancer, although its strength as a surrogate varies by subtype and treatment setting [4,5]. Pretreatment estimation of pCR probability may therefore support structured discussion of response uncertainty. Established predictors of pCR in HER2-positive disease include tumor burden, nodal status, hormone receptor (HR) status, HER2-targeted treatment pattern, and molecular or immune-related features [6,7].

Peripheral blood inflammatory indices, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), are inexpensive markers of host inflammatory and immune status [8]. In HER2-positive breast cancer, elevated inflammation has been linked in several studies to lower pCR rates or poorer survival, although findings are not uniform across regimens and populations [9,10]. These markers are biologically plausible because neutrophil-predominant inflammation, platelet-mediated tumor protection, and impaired lymphocyte-mediated antitumor immunity may influence sensitivity to systemic therapy [11].

Systemic inflammation also intersects with psycho-oncology. Distress, fatigue, sleep disruption, depression, and impaired quality of life have been associated with inflammatory activation in cancer populations, but these relationships are complex, bidirectional, and strongly confounded by disease burden and treatment context [12,13]. For patients beginning neoadjuvant therapy, baseline psychosocial assessment is clinically important because distress and anxiety may affect communication, treatment understanding, adherence, and patient-centered decision-making [14]. The Distress Thermometer (DT) and Hospital Anxiety and Depression Scale (HADS) are widely used screening instruments, and the DT cutoff of 4 has been validated in Chinese cancer populations [15-17].

The present study developed and temporally internally validated a pretreatment nomogram for predicting pCR in HER2-positive breast cancer using routine clinicopathological and hematologic variables. In parallel, we evaluated associations between inflammatory markers, model-derived pCR probability, and baseline patient-reported psychosocial outcomes. Because NLR is included in the pCR model and is also associated with psychosocial outcomes, we prespecified circularity-aware sensitivity analyses comparing a clinical model without NLR, the NLR-containing model, NLR alone, and incremental-value models. The purpose was not to establish a causal pathway from predicted response to distress, but to examine whether a pretreatment clinical-inflammatory profile is associated with psychosocial support need.

2. Materials and methods

2.1. Study design and reporting framework

This was an ambispective single-center observational cohort study comprising a clinical prediction component and a nested baseline psycho-oncology analysis. Clinical, treatment, laboratory, imaging, and pathological variables were retrospectively extracted from electronic medical records. Psychosocial outcomes were collected prospectively as routine pretreatment supportive-care assessments before the first neoadjuvant cycle and before any model-derived pCR probability could be communicated. The integrated statistical analyses were performed retrospectively after de-identification and data lock.

Women treated from January 2019 to December 2023 were assigned to the

training cohort for model development. Women treated from January 2024 to August 2024 were assigned to a same-center temporal internal validation cohort. This validation was not considered external validation because patients were treated in the same institution under the same clinical and laboratory infrastructure. The study was reported according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidance for multivariable prediction models, and the risk of bias was self-assessed using the Prediction model Risk Of Bias ASsessment Tool (PROBAST) [18, 19].

2.2. Patient selection and data sources

Consecutive women aged 18-75 years with histologically confirmed HER2-positive invasive breast carcinoma who received neoadjuvant systemic therapy followed by definitive breast surgery with axillary evaluation were screened. HER2 positivity was defined as immunohistochemistry (IHC) 3+ or IHC 2+ with HER2 gene amplification confirmed by fluorescence in situ hybridization (FISH), in accordance with the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) HER2 testing guideline [20]. HR positivity was defined as estrogen receptor and/or progesterone receptor nuclear staining in at least 1% of invasive tumor cells [21].

Clinical stage was assigned according to the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 8th edition [22]. Clinical nodal status was determined using physical examination and axillary ultrasonography in all patients, with breast magnetic resonance imaging, mammography, and/or image-guided fine-needle aspiration or core biopsy used when clinically indicated. A patient was classified as clinically node-positive when axillary nodes were suspicious on imaging and/or biopsy-proven positive before neoadjuvant therapy.

Patients were excluded if they had distant metastasis at initial diagnosis, bilateral breast cancer, previous malignancy, acute infection within 2 weeks before blood sampling, chronic inflammatory disease, autoimmune disease, hematological disease, systemic corticosteroid treatment within 4 weeks before blood sampling, immunosuppressive therapy, incomplete neoadjuvant therapy before surgery, missing surgical pathology, no complete blood count within 7 days before treatment, or incomplete baseline patient-reported outcome assessment. A complete flow diagram was constructed. Baseline variables available for the 246 included patients and the broader group of 69 excluded screened patients were compared descriptively to characterize the screened population. Because the excluded group comprised both patients excluded before final eligibility confirmation and patients who were potentially eligible after initial clinical screening but were subsequently excluded because prespecified treatment-completion and/or complete analytic-data requirements were not met, this comparison was not interpreted as a specific analysis of selection bias arising from the complete-case strategy.

2.3. Neoadjuvant treatment, staging, and pathological assessment

All patients received neoadjuvant chemotherapy combined with HER2-directed therapy according to institutional protocols and multidisciplinary decision-making. Regimens were recorded separately rather than collapsed into a single taxane-based category. The principal regimens were docetaxel/carboplatin plus trastuzumab with or without pertuzumab; weekly paclitaxel plus trastuzumab with or without pertuzumab; anthracycline-taxane sequential chemotherapy plus HER2-directed therapy; and other institutional taxane-containing regimens. Trastuzumab was given with an 8 mg/kg loading dose followed by 6 mg/kg every 21 days. Pertuzumab, when administered,

was given with an 840 mg loading dose followed by 420 mg every 21 days. Treatment delays, dose reductions, and completion of planned chemotherapy cycles were abstracted from medical records.

Pertuzumab use increased during the study period after broader institutional adoption of dual HER2 blockade. Therefore, trastuzumab alone versus trastuzumab plus pertuzumab was recorded explicitly and assessed descriptively. The prediction model was not intended to select or omit standard HER2-directed therapy.

Surgery was performed approximately 3-5 weeks after completion of neoadjuvant treatment. Surgical specimens were fixed in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Standard breast biomarker panels were performed on the Ventana BenchMark ULTRA platform. pCR was defined in every included patient as ypT0/is ypN0, meaning absence of residual invasive carcinoma in both the breast and axillary lymph nodes; residual ductal carcinoma in situ alone was not considered residual invasive disease. Two experienced breast pathologists reviewed surgical specimens independently, and discrepant interpretations were resolved by joint microscopic reassessment.

2.4. Peripheral inflammatory markers

Peripheral venous blood was collected between 07:00 and 09:00 after overnight fasting within 7 days before the first neoadjuvant treatment cycle. A 2-mL blood sample anticoagulated with dipotassium ethylenediaminetetraacetic acid (K2-EDTA) was analyzed within 2 hours using a Sysmex XN-9000 automated hematology analyzer under routine internal quality-control procedures. Absolute neutrophil count, absolute lymphocyte count, platelet count, and albumin were recorded.

NLR was calculated as absolute neutrophil count divided by absolute lymphocyte count. PLR was calculated as platelet count divided by absolute lymphocyte count. SII was calculated as platelet count multiplied by absolute neutrophil count and divided by absolute lymphocyte count. For the final model, NLR was standardized using the training-cohort mean and standard deviation: $NLR_z = (NLR - 3.10) / 1.18$. NLR was retained in the primary model because it showed stable contribution, lower collinearity than SII, and straightforward clinical interpretation. Counts outside institutional laboratory reference intervals were summarized descriptively; no institutional normal ranges were available for calculated NLR, PLR, or SII.

2.5. Psychosocial assessment and composite support-need endpoint

Baseline patient-reported outcomes were administered within 7 days before the first neoadjuvant cycle in a quiet consultation room by trained oncology nurses. The administration procedure was part of routine pretreatment supportive-care assessment throughout the study period and did not change materially between 2019 and 2024. Clinical outcome extractors and pathologists were blinded to questionnaire results, and questionnaire data were entered before the pCR outcome was known.

Validated Chinese versions of the DT, HADS, Functional Assessment of Cancer Therapy-Breast (FACT-B), Fear of Progression Questionnaire-Short Form (FoP-Q-SF), and Decision Conflict Scale (DCS) were used where available [15-17,23-27]. The DT is a 0-10 single-item distress screen. HADS contains anxiety (HADS-A) and depression (HADS-D) subscales, each ranging from 0 to 21. FACT-B assesses breast cancer-specific quality of life, with higher total scores indicating better quality of life. FoP-Q-SF ranges from 12 to 60, with higher scores indicating greater fear of progression. DCS scores were transformed to a 0-100 scale, with higher scores indicating greater decisional uncertainty.

Psychosocial support need was defined as a composite endpoint met when any of the following criteria was present: DT ≥ 4 , HADS-A ≥ 8 , or HADS-D ≥ 8 . The definition was selected because DT ≥ 4 is widely used for clinically relevant distress screening and HADS subscale scores ≥ 8 are commonly used to identify possible anxiety or depression requiring further assessment in medical and oncology settings [15-17]. The composite endpoint was used for pragmatic supportive-care triage; individual DT, HADS-A, and HADS-D thresholds were also evaluated in sensitivity analyses. When a questionnaire had fewer than 10% missing items, the score was prorated according to the instrument manual; patients without valid scale-level scores were excluded from the analytic cohort.

2.6. Model development and temporal internal validation

Candidate predictors were selected based on clinical availability before neoadjuvant therapy, biological plausibility, and prior literature rather than automatic univariate screening alone. Candidate variables included age, menopausal status, tumor size, clinical nodal status, HR status, exact chemotherapy regimen, HER2-targeted treatment pattern, albumin, NLR, PLR, and SII. Because NLR, PLR, and SII share hematologic components, they were not entered simultaneously into the primary model. Collinearity was assessed using variance inflation factors, with values ≥ 5 considered unacceptable.

The training cohort contained 72 pCR events. The final NLR-containing model used 4 predictor parameters, corresponding to 18.0 pCR events per parameter. The broader candidate set comprised 12 effective parameters and was used for descriptive and sensitivity modeling, not for a fully automated stepwise selection procedure. Continuous variables were retained as continuous predictors. Potential nonlinearity for age, tumor size, NLR, PLR, SII, and albumin was evaluated using restricted cubic splines with 3 knots and likelihood ratio tests. Prespecified interactions among HR status, dual HER2 blockade, NLR, and tumor size were explored and retained only if clinically plausible and statistically supported.

The final multivariable logistic regression model was developed in the training cohort. The regression equation was then applied without recalibration to the temporal internal validation cohort. Discrimination was assessed using the area under the receiver operating characteristic curve (AUC) and the concordance index (C-index). Calibration was assessed using calibration plots, calibration intercept, calibration slope, Brier score, and Hosmer-Lemeshow test, with greater emphasis placed on intercept, slope, and graphical performance than on the Hosmer-Lemeshow test.

2.7. Circularity-aware and incremental-value analyses

Because NLR was both a component of the pCR nomogram and a correlate of psychosocial outcomes, we performed sensitivity analyses to address potential mathematical circularity. First, a clinical pCR model excluding NLR was fitted using tumor size, clinical nodal status, and HR status. Second, the NLR-containing model and the clinical model were compared for their associations with the composite psychosocial support-need endpoint. Third, NLR alone was evaluated as a predictor of psychosocial support need. Fourth, incremental value beyond NLR alone was assessed using change in AUC with a bootstrap 95% confidence interval, change in Brier score, and a likelihood-ratio test for the nested models.

These analyses were designed to clarify whether model-derived pCR probability provided information beyond NLR and whether observed associations should be interpreted as independent psychosocial prediction. We did not interpret baseline

distress as a consequence of actual pCR status, because psychosocial assessments occurred before treatment and before pCR was known. Similarly, because patients did not know their model-derived pCR probability, associations between predicted probability and distress were interpreted as associations with pretreatment clinical-inflammatory profiles, not as effects of communicating a low probability.

2.8. Decision curve analysis

Decision curve analysis (DCA) was exploratory. The threshold probability was conceptualized as a clinician-defined probability at which additional response counseling and scheduled psychosocial re-screening would be considered, not as a threshold for changing or withholding standard HER2-directed neoadjuvant therapy. In this context, the 'flag all' strategy meant that all patients would receive intensified response counseling beyond routine care, whereas 'flag none' meant that no patient would receive model-triggered additional counseling beyond routine distress screening. Because no actual management decision was evaluated in this retrospective analysis, DCA results were interpreted cautiously and were not used as evidence of clinical utility.

2.9. Statistical analysis

Continuous variables were assessed for distributional form using the Shapiro-Wilk test and visual inspection. Normally distributed variables were summarized as mean $\pm$ standard deviation and compared with Student's *t* test. Non-normally distributed variables were summarized as median and interquartile range and compared with the Mann-Whitney *U* test. Categorical variables were summarized as number and percentage and compared using chi-square or Fisher exact tests as appropriate.

Bootstrap resampling with 1,000 iterations was used to estimate optimism-corrected discrimination and 95% confidence intervals (CIs) for AUC, Brier score, calibration intercept, calibration slope, sensitivity, specificity, predictive values, accuracy, and net benefit when feasible. *P* values for logistic-regression coefficients were based on two-sided Wald tests, and nested incremental models were compared using a likelihood-ratio test. Exact *P* values are reported except when $P < 0.001$. Analyses were performed using R version 4.1.1 and SPSS Statistics version 26.0. A two-sided $P < 0.05$ was considered statistically significant.

2.10. Ethical considerations

The study protocol was approved by the Institutional Review Board of The First Affiliated Hospital of Chengdu Medical College (approval number: 2024-KY-105). The review board waived written informed consent for retrospective analysis of de-identified clinical data and de-identified routine pretreatment psychosocial assessments. The psychosocial questionnaires were part of routine clinical supportive-care evaluation rather than an additional research intervention. All procedures were conducted in accordance with the Declaration of Helsinki and institutional data-protection standards.

3. Results

3.1. Patient selection and characteristics of excluded screened patients

A total of 315 women with HER2-positive invasive breast cancer were screened. Of the 69 excluded screened patients, 46 were excluded before final eligibility confirmation, whereas 23 were potentially eligible after initial clinical

screening but were subsequently excluded because prespecified treatment-completion and/or complete analytic-data requirements were not met. The final analytic cohort comprised 246 patients, including 198 in the training cohort and 48 in the temporal internal validation cohort (**Figure 1**). The most common reasons for exclusion were systemic inflammatory or immunologic conditions or recent steroid/immunosuppressive exposure (n=18), de novo distant metastasis (n=14), incomplete baseline psychosocial assessment (n=10), and incomplete or discontinued neoadjuvant therapy before surgery (n=9).

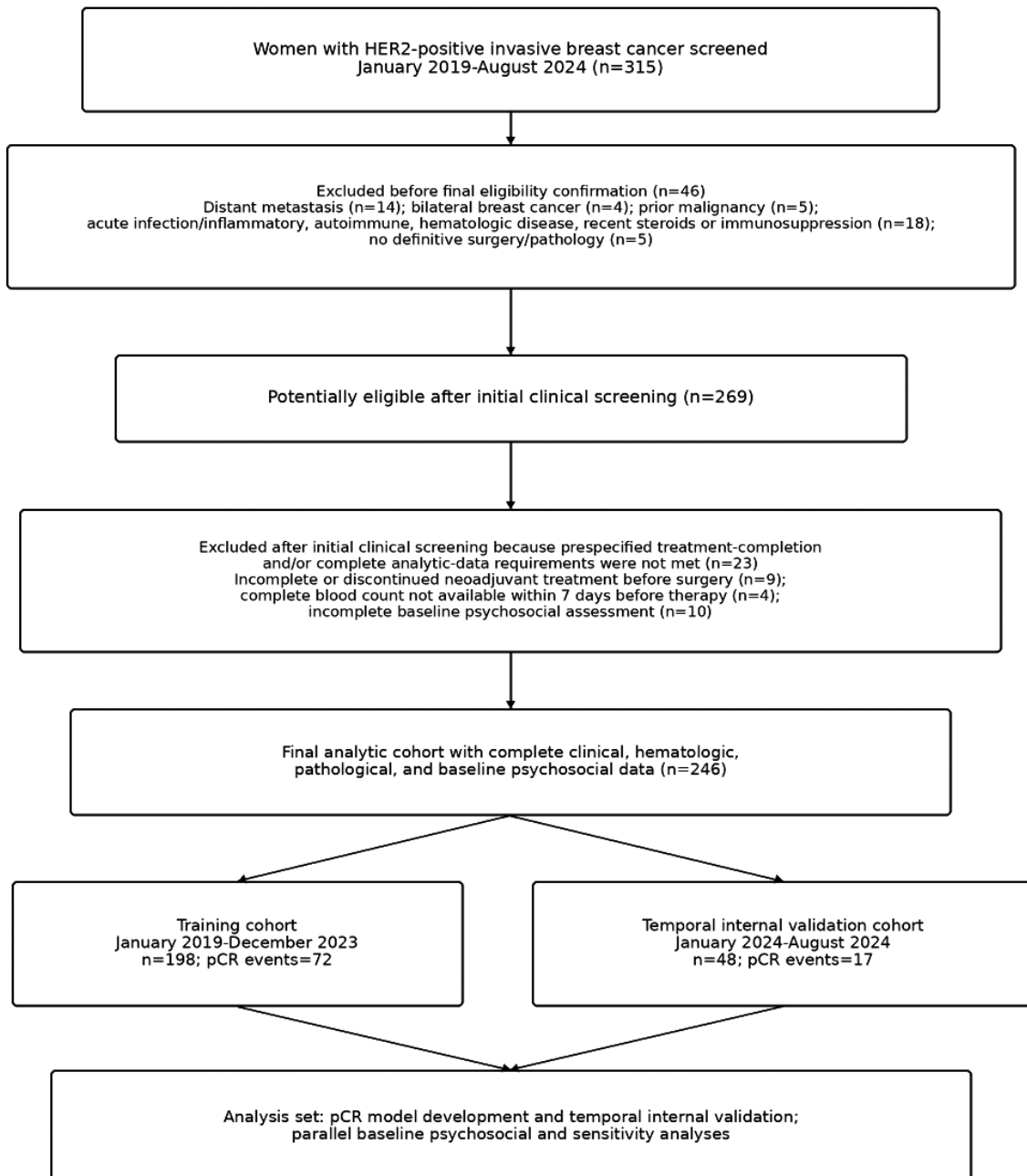


Figure 1. Patient flow diagram. Of the 69 excluded screened patients, 46 were excluded before final eligibility confirmation, whereas 23 were potentially eligible after initial clinical screening but were subsequently excluded because prespecified treatment-completion and/or complete analytic-data requirements were not met. Complete psychosocial data, pretreatment complete blood count, completion of neoadjuvant therapy, and postoperative pathological assessment were required for inclusion.

Supplementary Table S1 provides an exploratory comparison of the 246 included patients with the broader group of 69 excluded screened patients using available baseline variables. The excluded group includes both the 46 patients excluded before final eligibility confirmation and the 23 patients who were potentially eligible after initial clinical screening but were subsequently excluded because prespecified treatment-completion and/or complete analytic-data requirements were not met; consequently, the comparison does not isolate selection bias introduced by the complete-case requirement. No statistically significant differences were observed in age, menopausal status, tumor size, clinical nodal status, HR status, or baseline stage, whereas dual HER2 blockade was numerically more common among included patients. These findings are descriptive and do not exclude selection bias, particularly because missing psychosocial assessments may be related to unmeasured distress, socioeconomic circumstances, or questionnaire adherence.

3.2. Baseline characteristics and treatment patterns

The training and temporal internal validation cohorts were broadly comparable with respect to age, menopausal status, tumor size, clinical nodal status, HR status, HER2 testing category, clinical stage, HER2-targeted treatment pattern, inflammatory markers, pCR rate, and baseline psychosocial scores (**Table 1**). pCR was achieved in 72 of 198 patients (36.36%) in the training cohort and 17 of 48 patients (35.42%) in the temporal validation cohort. Additional information on laboratory values outside institutional reference intervals and questionnaire reliability is provided in **Supplementary Table S2**.

Table 1. Baseline clinical, inflammatory, and psychosocial characteristics of the training and temporal internal validation cohorts.

Characteristic	Training cohort (n=198)	Temporal internal validation cohort (n=48)	P value
Age, years	52.3 +/- 8.7	51.9 +/- 8.4	0.781
Postmenopausal status	100 (50.51%)	24 (50.00%)	0.949
Tumor size, cm	3.2 (2.1-4.5)	3.1 (2.0-4.3)	0.675
Clinical node-positive disease	88 (44.44%)	21 (43.75%)	0.930
Hormone receptor-positive disease	130 (65.66%)	31 (64.58%)	0.888
HER2 IHC 3+	177 (89.39%)	43 (89.58%)	0.974
HER2 IHC 2+ / FISH amplified	21 (10.61%)	5 (10.42%)	0.974
AJCC clinical stage IIA	49 (24.75%)	12 (25.00%)	0.942
AJCC clinical stage IIB	67 (33.84%)	15 (31.25%)	0.942
AJCC clinical stage IIIA	58 (29.29%)	16 (33.33%)	0.942
AJCC clinical stage IIIB-IIIC	24 (12.12%)	5 (10.42%)	0.942
Dual HER2 blockade	118 (59.60%)	31 (64.58%)	0.526
pCR achieved	72 (36.36%)	17 (35.42%)	0.903
NLR	3.1 +/- 1.2	3.0 +/- 1.1	0.604

Continuation Table:

Characteristic	Training cohort (n=198)	Temporal internal validation cohort (n=48)	P value
PLR	152 (108-224)	150 (104-218)	0.756
SII	781 (548-1006)	765 (536-982)	0.646
Albumin, g/dL	3.9 +/- 0.5	4.0 +/- 0.4	0.391
DT score	3.3 +/- 1.4	3.2 +/- 1.3	0.652
HADS-A score	6.0 +/- 2.8	5.9 +/- 2.5	0.811
HADS-D score	4.7 +/- 2.3	4.5 +/- 2.1	0.583
FACT-B total score	97.8 +/- 13.4	98.6 +/- 12.7	0.704
FoP-Q-SF score	33.1 +/- 6.8	32.7 +/- 6.5	0.712
DCS score	30.6 +/- 9.8	29.8 +/- 9.1	0.610
Psychosocial support need	102 (51.52%)	23 (47.92%)	0.653

Note. Data are mean +/- SD, median (interquartile range), or n (%). AJCC, American Joint Committee on Cancer; DCS, Decision Conflict Scale; DT, Distress Thermometer; FACT-B, Functional Assessment of Cancer Therapy-Breast; FISH, fluorescence in situ hybridization; FoP-Q-SF, Fear of Progression Questionnaire-Short Form; HADS-A/HADS-D, Hospital Anxiety and Depression Scale-Anxiety/Depression; IHC, immunohistochemistry; NLR, neutrophil-to-lymphocyte ratio; pCR, pathological complete response; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index.

Exact neoadjuvant regimens and treatment completion data are shown in **Table 2**. The most common regimen was docetaxel/carboplatin with trastuzumab with or without pertuzumab. Dual HER2 blockade was used in 149 of 246 patients (60.57%). Pertuzumab use increased after 2020, reflecting institutional adoption and drug-access changes, and remained frequent in the 2024 temporal validation cohort. This temporal change may represent a treatment-distribution shift and may also coincide with case-mix differences between the development and validation periods. Planned chemotherapy cycles were completed by 226 patients (91.87%); dose reduction of at least one cytotoxic drug occurred in 39 patients (15.85%), and treatment delay longer than 7 days occurred in 31 patients (12.60%).

Table 2. Neoadjuvant treatment details and pathological response by regimen.

Treatment characteristic	Training cohort (n=198)	Temporal validation cohort (n=48)	Full cohort (n=246)
Docetaxel/carboplatin + trastuzumab +/- pertuzumab	98 (49.49%)	24 (50.00%)	122 (49.59%)
Weekly paclitaxel + trastuzumab +/- pertuzumab	36 (18.18%)	9 (18.75%)	45 (18.29%)
Anthracycline-taxane sequential + HER2 blockade	40 (20.20%)	9 (18.75%)	49 (19.92%)
Other institutional taxane-containing regimen	24 (12.12%)	6 (12.50%)	30 (12.20%)
Trastuzumab alone	80 (40.40%)	17 (35.42%)	97 (39.43%)
Trastuzumab + pertuzumab	118 (59.60%)	31 (64.58%)	149 (60.57%)

Continuation Table:

Treatment characteristic	Training cohort (n=198)	Temporal validation cohort (n=48)	Full cohort (n=246)
Completed planned chemotherapy cycles	183 (92.42%)	43 (89.58%)	226 (91.87%)
Any cytotoxic dose reduction	30 (15.15%)	9 (18.75%)	39 (15.85%)
Treatment delay >7 days	23 (11.62%)	8 (16.67%)	31 (12.60%)
pCR by docetaxel/carboplatin regimen	40/98 (40.82%)	10/24 (41.67%)	50/122 (40.98%)
pCR by weekly paclitaxel regimen	13/36 (36.11%)	3/9 (33.33%)	16/45 (35.56%)
pCR by anthracycline-taxane regimen	14/40 (35.00%)	3/9 (33.33%)	17/49 (34.69%)
pCR by other regimen	5/24 (20.83%)	1/6 (16.67%)	6/30 (20.00%)

Note. Values are n (%) or events/total (%). Regimens were recorded separately to avoid treating clinically different chemotherapy backbones as equivalent. Percentages may not total exactly 100% because of rounding.

3.3. Clinical and inflammatory variables associated with subsequent pCR

In the training cohort, patients who subsequently achieved pCR had smaller tumors, lower frequency of clinical node-positive disease, and lower frequency of HR-positive disease than those with residual invasive disease. Pretreatment inflammatory burden was also lower among patients who subsequently achieved pCR, as reflected by lower NLR, PLR, SII, and platelet count (**Supplementary Table S3**). Baseline psychosocial scores differed by future pCR status, but these differences were interpreted as pretreatment associations with clinical-inflammatory profiles rather than consequences of treatment response.

3.4. Nomogram development and regression equations

The final NLR-containing model retained tumor size, clinical nodal status, HR status, and standardized NLR (**Table 3**), the corresponding nomogram is shown in **Figure 2**. Larger tumor size, node-positive disease, HR positivity, and higher NLR were independently associated with lower odds of pCR. No retained continuous predictor showed clear evidence of nonlinearity using restricted cubic spline testing, and prespecified interaction terms were not retained (**Supplementary Table S4**).

The final pCR probability for an individual patient can be calculated using the following formula: $\text{logit(pCR)} = 1.986 - 0.431 \times \text{tumor size (cm)} - 1.079 \times \text{clinical node-positive status} - 0.994 \times \text{HR-positive status} - 0.693 \times \text{NLRz}$, where clinical node-positive status is coded 1 for cN-positive and 0 for cN-negative, HR-positive status is coded 1 for HR-positive and 0 for HR-negative, and $\text{NLRz} = (\text{NLR} - 3.10) / 1.18$. The predicted probability is $\text{pCR probability} = 1 / [1 + \exp(-\text{logit})]$. A clinical sensitivity model excluding NLR was also fitted (**Table 3**).

Table 3. Multivariable logistic regression models for predicting pCR in the training cohort.

Model/variable	beta	SE	Adjusted OR (95% CI)	P value
NLR-containing model: intercept	1.986	0.512	-	<0.001
Tumor size, per 1-cm increase	-0.431	0.146	0.65 (0.49-0.87)	0.003

Continuation Table:

Model/variable	beta	SE	Adjusted OR (95% CI)	P value
Clinical node-positive vs node-negative	-1.079	0.357	0.34 (0.17-0.69)	0.003
HR-positive vs HR-negative	-0.994	0.357	0.37 (0.18-0.73)	0.004
NLRz, per SD increase	-0.693	0.206	0.50 (0.33-0.74)	<0.001
Clinical model excluding NLR: intercept	1.563	0.472	-	0.001
Tumor size, per 1-cm increase	-0.402	0.135	0.67 (0.51-0.88)	0.003
Clinical node-positive vs node-negative	-1.006	0.343	0.37 (0.19-0.74)	0.003
HR-positive vs HR-negative	-1.142	0.341	0.32 (0.16-0.62)	<0.001

Note. NLRz=(NLR-3.10)/1.18, using the training-cohort mean and SD. HR, hormone receptor; NLRz, standardized neutrophil-to-lymphocyte ratio.

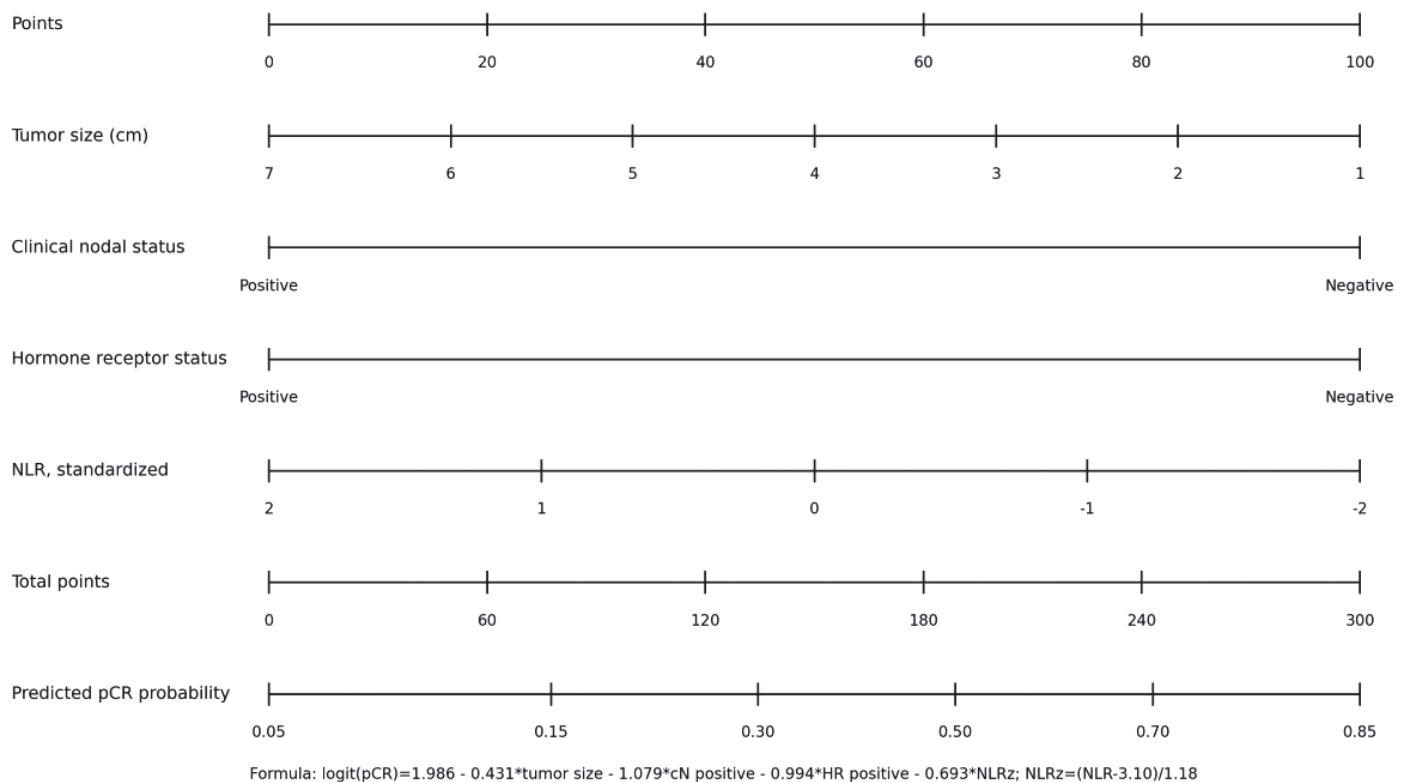


Figure 2. Nomogram for pretreatment pCR prediction.

3.5. Model performance and temporal internal validation

The NLR-containing nomogram showed acceptable discrimination in the training cohort (AUC=0.776, 95% bootstrap CI: 0.702-0.838), with an optimism-corrected AUC of 0.758. When applied without recalibration to the temporal internal validation cohort, the model yielded an AUC of 0.769 (95% bootstrap CI: 0.623-0.897); the corresponding receiver operating characteristic curves are shown in Figure 3. The validation confidence interval was wide because the validation cohort contained only 48 patients and 17 pCR events.

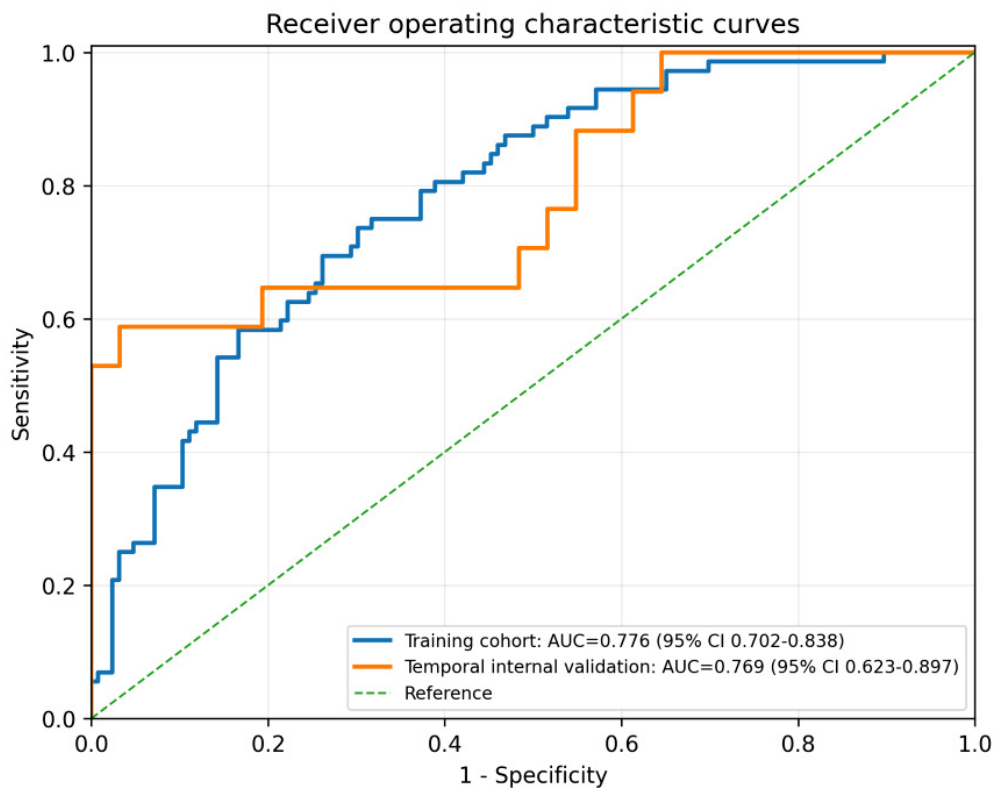


Figure 3. Receiver operating characteristic curves for the NLR-containing pCR prediction nomogram in the training and temporal internal validation cohorts.

Calibration was acceptable in the training cohort and broadly preserved in the temporal validation cohort, but the validation calibration slope and intercept were imprecisely estimated (**Table 4 and Figure 4**). The Brier score was 0.182 in the training cohort and 0.176 in the validation cohort. The Hosmer-Lemeshow tests were non-significant, but these tests were not considered sufficient evidence of calibration because of sample-size limitations. At the prespecified cutoff of 0.424, specificity exceeded sensitivity in both cohorts.

Table 4. Performance of the NLR-containing pCR prediction nomogram.

Performance metric	Training cohort (n=198)	Temporal internal validation cohort (n=48)
pCR events	72 (36.36%)	17 (35.42%)
AUC	0.776 (0.702-0.838)	0.769 (0.623-0.897)
Optimism-corrected AUC	0.758	-
Brier score	0.182 (0.153-0.211)	0.176 (0.113-0.239)
Calibration intercept	0.000 (-0.362 to 0.366)	-0.071 (-0.705 to 0.519)
Calibration slope	0.942 (0.626-1.322)	0.889 (0.420-1.586)
Hosmer-Lemeshow P value	0.311	0.332
Optimal cutoff probability	0.424	0.424
Sensitivity	63.89% (52.34-74.01)	52.94% (31.02-73.83)
Specificity	80.95% (73.25-86.88)	90.32% (75.10-96.65)

Continuation Table:

Performance metric	Training cohort (n=198)	Temporal internal validation cohort (n=48)
Positive predictive value	65.71% (53.36-76.27)	75.00% (46.77-91.11)
Negative predictive value	79.69% (71.67-85.86)	77.78% (62.91-88.06)
Accuracy	74.75% (68.25-80.31)	77.08% (63.48-86.77)
Net benefit at threshold 0.30	0.207 (0.146-0.262)	0.198 (0.061-0.304)
Net benefit at threshold 0.40	0.171 (0.102-0.231)	0.150 (0.022-0.274)

Note. Confidence intervals were estimated by bootstrap resampling when feasible. Validation estimates are imprecise because the temporal validation cohort contained 48 patients and 17 pCR events.

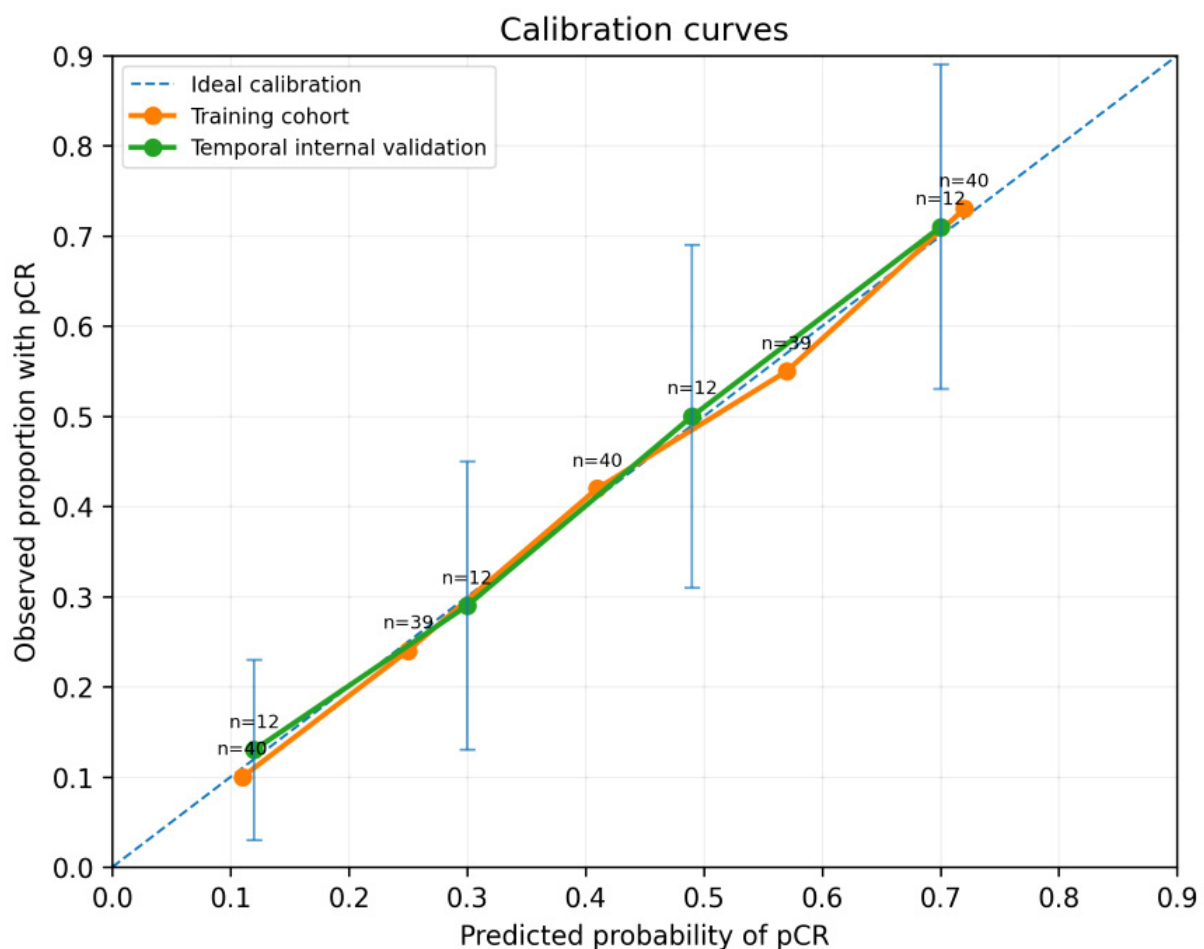


Figure 4. Calibration curves for the pCR prediction nomogram. Error bars in the temporal internal validation cohort illustrate uncertainty due to the small validation sample.

Exploratory decision curve analysis suggested positive net benefit for model-based flagging across a range of threshold probabilities compared with flag-none and, over part of the range, flag-all strategies (**Figure 5**). Because all patients required standard neoadjuvant HER2-directed therapy and no actual referral intervention was evaluated, these findings were interpreted only as exploratory support for prospective study design rather than evidence of established clinical utility.

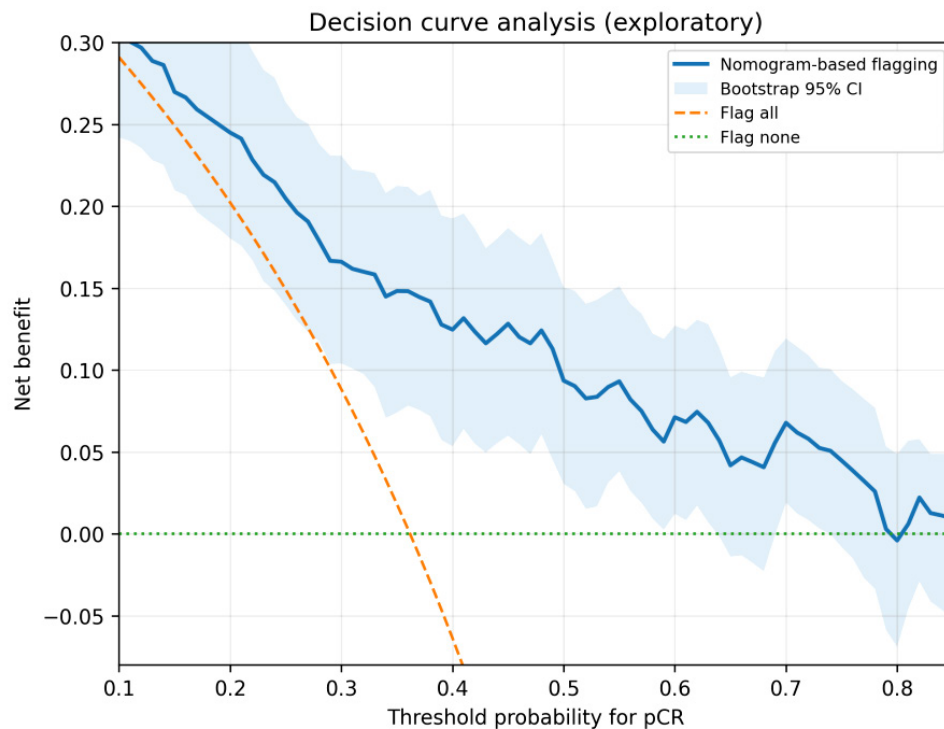


Figure 5. Exploratory decision curve analysis. 'Flag all' denotes intensified response counseling for all patients, and 'flag none' denotes no model-triggered additional counseling beyond routine distress screening. This analysis does not imply treatment selection.

3.6. Inflammatory markers and baseline psychosocial outcomes

In the full cohort, 125 of 246 patients (50.81%) met the composite psychosocial support-need endpoint. NLR and SII were positively correlated with DT, HADS-A, HADS-D, FoP-Q-SF, and DCS scores and inversely correlated with FACT-B total score (**Table 5**). PLR showed weaker but directionally consistent associations. In adjusted linear regression models, NLR and SII remained associated with greater distress, anxiety, depressive symptoms, fear of progression, decision conflict, and lower breast cancer-specific quality of life after adjustment for age, tumor size, nodal status, HR status, and HER2-targeted treatment pattern (**Supplementary Table S5**).

Table 5. Spearman correlations between pretreatment inflammatory markers and baseline psychosocial outcomes in the full cohort.

Psychosocial outcome	NLR rho (P value)	PLR rho (P value)	SII rho (P value)
DT score	0.440 (<0.001)	0.273 (<0.001)	0.432 (<0.001)
HADS-A score	0.484 (<0.001)	0.302 (<0.001)	0.473 (<0.001)
HADS-D score	0.301 (<0.001)	0.214 (0.001)	0.286 (<0.001)
FACT-B total score	-0.428 (<0.001)	-0.281 (<0.001)	-0.462 (<0.001)
FoP-Q-SF score	0.458 (<0.001)	0.265 (<0.001)	0.441 (<0.001)
DCS score	0.408 (<0.001)	0.239 (<0.001)	0.397 (<0.001)

Note. DCS, Decision Conflict Scale; DT, Distress Thermometer; FACT-B, Functional Assessment of Cancer Therapy-Breast; FoP-Q-SF, Fear of Progression Questionnaire-Short Form; HADS-A/HADS-D, Hospital Anxiety and Depression Scale-Anxiety/Depression; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index.

Instrument reliability within the analytic cohort was acceptable to high for multi-item scales: Cronbach's alpha was 0.84 for HADS-A, 0.80 for HADS-D, 0.89 for FACT-B, 0.91 for FoP-Q-SF, and 0.88 for DCS. DT was not evaluated using internal consistency because it is a single-item screening tool.

3.7. Predicted pCR probability and circularity-aware psychosocial analyses

Results of the circularity-aware analyses are summarized in **Table 6**. In complementary descriptive analyses, when patients were stratified into tertiles of NLR-containing predicted pCR probability, observed pCR rates increased across the low, intermediate, and high predicted-probability groups, whereas distress, anxiety, depressive symptoms, fear of progression, decision conflict, and psychosocial support need decreased (**Table 7**). The prevalence of the composite support-need endpoint was 75.61% in the low predicted-probability group, 47.56% in the intermediate group, and 29.27% in the high group.

The age-adjusted association between lower NLR-containing predicted pCR probability and psychosocial support need was statistically significant (OR=1.49 per 0.10 decrease, 95% CI: 1.30-1.71, $P<0.001$). However, because NLR contributes to the nomogram and is itself associated with psychosocial outcomes, this association was attenuated after direct adjustment for NLR (OR=1.13, 95% CI: 0.96-1.33, $P=0.142$). The clinical pCR model excluding NLR showed a weaker association with psychosocial support need, and its association also attenuated after NLR adjustment. Adding model-derived pCR probability to NLR alone provided only modest and statistically uncertain incremental value (delta AUC=0.015, 95% bootstrap CI: -0.010 to 0.043; delta Brier=-0.006; likelihood-ratio $P=0.091$; **Table 6**). Similar patterns were observed in analyses of individual DT, HADS-A, and HADS-D thresholds (**Supplementary Table S5**). These results suggest that the psychosocial association of predicted pCR probability is largely explained by the inflammatory and clinical components of the model rather than by pCR probability as an independent psychosocial determinant.

Table 6. Circularity-aware analyses for the composite psychosocial support-need endpoint.

Analysis	Estimate	Model performance or incremental value	Wald P value for OR
NLR alone, per SD increase	OR=1.91 (1.37-2.67)	AUC=0.696; Brier=0.218	<0.001
Clinical pCR probability without NLR, per 0.10 decrease	OR=1.22 (1.07-1.39)	AUC=0.641; Brier=0.238	0.003
NLR-containing pCR probability, per 0.10 decrease	OR=1.49 (1.30-1.71)	AUC=0.711; Brier=0.214	<0.001
Clinical pCR probability + NLR adjustment	OR=1.08 (0.94-1.24)	-	0.276
NLR-containing pCR probability + NLR adjustment	OR=1.13 (0.96-1.33)	-	0.142
NLR + NLR-containing probability vs NLR alone	delta AUC=0.015 (95% bootstrap CI: -0.010 to 0.043)	delta Brier=-0.006; likelihood-ratio $P=0.091$	-

Note. The endpoint was DT ≥ 4 OR HADS-A ≥ 8 OR HADS-D ≥ 8 . Odds ratios are for psychosocial support need. P values in the final column are two-sided Wald tests for the reported odds ratios. For the nested incremental comparison, change in AUC is reported with a bootstrap 95% confidence interval, change in Brier score is descriptive, and the likelihood-ratio P value is shown explicitly in the incremental-value column. Integrated discrimination improvement was not retained in the final reporting. The attenuation after direct NLR adjustment supports interpretation as a composite clinical-inflammatory association rather than an independent psychosocial prediction effect.

Table 7. Baseline psychosocial outcomes according to tertiles of NLR-containing predicted pCR probability in the full cohort.

Outcome	Low predicted pCR probability (n=82)	Intermediate predicted pCR probability (n=82)	High predicted pCR probability (n=82)	P value
Median predicted pCR probability	0.18 (0.12-0.24)	0.34 (0.29-0.41)	0.59 (0.50-0.71)	<0.001
Observed pCR	16 (19.51%)	30 (36.59%)	43 (52.44%)	<0.001
DT score	3.8 +/- 1.3	3.2 +/- 1.3	2.8 +/- 1.2	<0.001
HADS-A score	7.4 +/- 2.5	5.9 +/- 2.9	4.8 +/- 2.3	<0.001
HADS-D score	5.7 +/- 2.2	4.7 +/- 2.2	4.0 +/- 2.2	<0.001
FACT-B total score	91.9 +/- 12.7	98.0 +/- 12.8	103.9 +/- 11.4	<0.001
FoP-Q-SF score	37.2 +/- 6.3	32.2 +/- 6.5	29.8 +/- 6.3	<0.001
DCS score	35.5 +/- 10.2	29.6 +/- 9.3	26.3 +/- 8.2	<0.001
DT ≥ 4	52 (63.41%)	31 (37.80%)	20 (24.39%)	<0.001
HADS-A ≥ 8	42 (51.22%)	26 (31.71%)	15 (18.29%)	<0.001
HADS-D ≥ 8	24 (29.27%)	13 (15.85%)	8 (9.76%)	0.004
Composite psychosocial support need	62 (75.61%)	39 (47.56%)	24 (29.27%)	<0.001

Note. These are pretreatment associations. Patients did not know their model-derived pCR probability, and actual pCR status was not known at the time of psychosocial assessment.

3.8. Conceptual clinical workflow

A revised conceptual workflow is presented in **Figure 6**. The workflow places validated psychosocial screening at the center of supportive-care referral. The nomogram may assist response-risk communication and identification of a clinical-inflammatory profile associated with baseline distress, but it should not replace DT/HADS-based screening and should not be used to alter HER2-directed neoadjuvant therapy in isolation. The workflow requires prospective validation before clinical implementation.

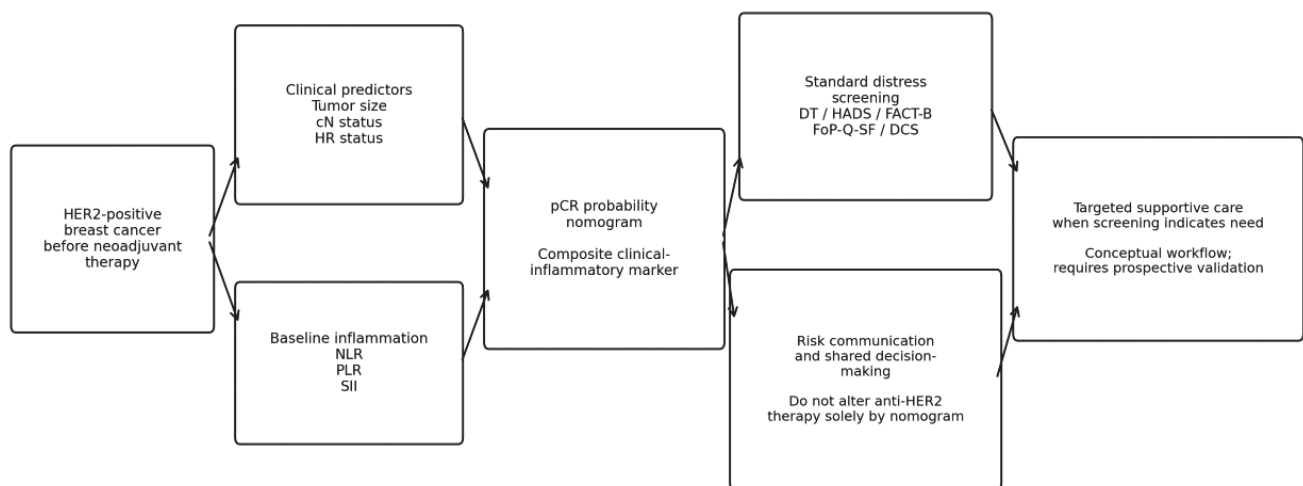


Figure 6. Conceptual workflow integrating pCR prediction with validated psychosocial screening. The workflow requires prospective validation and should not be used to alter HER2-directed treatment intensity in isolation.

4. Discussion

This study developed a pretreatment nomogram for predicting pCR in HER2-positive breast cancer and examined its relationship with baseline psychosocial burden before neoadjuvant therapy. The final model retained tumor size, clinical nodal status, hormone receptor status, and standardized NLR. It showed acceptable discrimination in the training cohort, with an AUC of 0.776 and an optimism-corrected AUC of 0.758, and yielded a similar AUC point estimate of 0.769 in the same-center temporal validation cohort. However, the validation estimates remained imprecise because the validation cohort included only 48 patients and 17 pCR events. Moreover, performance observed within the same institutional infrastructure should not be interpreted as evidence of transportability to other institutions or healthcare systems.

The pCR rate in this cohort was 36.36% in the training set and 35.42% in the validation set. This rate was lower than that reported in several contemporary HER2-positive neoadjuvant trials, but it remained clinically plausible for a real-world cohort with heterogeneous regimens and changing access to dual HER2 blockade. In the PHERGain phase 2 trial, an 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET)- and pCR-adapted treatment strategy achieved a 3-year invasive disease-free survival of 94.8% in group B [28]. In the real-world NeoPower study, pCR was achieved in 46% of patients receiving pertuzumab, trastuzumab, and chemotherapy and in 40% of controls, while pCR was associated with improved distant relapse-free survival [29]. Hormone receptor status remains an important determinant of response. In the WSG-TP-II trial, pCR was 23.7% with endocrine therapy plus trastuzumab and pertuzumab and 56.4% with paclitaxel plus trastuzumab and pertuzumab in hormone receptor-positive and HER2-positive disease [30]. The adverse association between hormone receptor positivity and pCR in the present model is consistent with these data. Genomic tools provide additional biological resolution. In a PHERGain correlative analysis, the HER2DX pCR score was associated with pCR, and pCR rates were 50.4%, 35.8%, and 23.2% in HER2DX pCR-high, intermediate, and low groups, respectively [31]. The present nomogram has a different clinical position because it relies on routinely available pretreatment variables rather than genomic testing.

Beyond biological heterogeneity, access to HER2-directed therapy is a structural determinant of real-world response rates. In a Brazilian real-world comparison of public and private healthcare settings, Antonini et al. documented substantial differences in trastuzumab availability; receipt of trastuzumab was associated with markedly higher pCR rates in both institutional cohorts, and differences in response were accompanied by differences in long-term outcomes [32]. Accordingly, local reimbursement, availability, and adoption of trastuzumab and pertuzumab may alter baseline pCR risk, treatment distributions, and predictor-outcome relationships. The temporal increase in pertuzumab use in the present study may therefore reflect both treatment-distribution shift and associated case-mix change. Same-center temporal validation evaluates reproducibility under one institutional infrastructure, whereas transportability across institutions, countries, and healthcare systems with different access patterns remains untested and may require model recalibration or updating.

The incorporation of NLR reflects the established link between host inflammation and neoadjuvant response. In a multicenter analysis of 1,274 clinically node-positive breast cancer patients, low NLR and low pan-immune-inflammation value were independently associated with nodal pCR, with odds ratios of 0.71 and

0.63, respectively [33]. In the present study, higher standardized NLR was associated with lower odds of pCR, with an adjusted odds ratio of 0.50 per standard deviation increase. A retrospective study of 1,994 breast cancer patients receiving neoadjuvant therapy reported a pCR rate of 19.2% and an inflammatory-marker-based nomogram AUC of 0.754 [34], which is close to the discrimination observed in this study. In young breast cancer patients, pretreatment pan-immune-inflammation value (PIV), hormone receptor status, HER2 status, and Ki-67 were independent predictors of pCR, and pCR rates differed markedly across PIV and hormone receptor subgroups [35]. These studies support the use of inflammatory indices as accessible adjunctive markers, while also defining their moderate predictive ceiling.

The psychosocial findings extend the model from treatment response prediction to baseline supportive-care assessment. In this cohort, 50.81% of patients met the composite psychosocial support-need endpoint. A 2024 meta-analysis including 34 studies and 13,828 breast cancer patients reported a pooled psychological distress prevalence of 50%, which closely matches the present estimate [36]. Fear of progression was also clinically relevant. A cross-sectional study of 151 breast cancer patients reported a mean FoP-Q-SF score of 35.87 ± 9.24 and found that fear of progression was negatively correlated with self-management efficacy and family functioning [37]. A Chinese meta-analysis including 9,689 breast cancer patients reported a pooled FoP-Q-SF mean score of 33.84 [38]. The FoP-Q-SF scores in the present study were therefore within a clinically credible range. In broader cancer populations, PLR, NLR, and the lymphocyte-to-monocyte ratio (LMR) have been associated with cancer-related fatigue and quality of life [39]. Consistently, NLR and SII in this cohort correlated positively with distress, anxiety, depressive symptoms, fear of progression, and decision conflict, and inversely with FACT-B scores.

The circularity-aware analyses are essential for interpreting the psychosocial results. NLR was included in the pCR model and was also associated with psychosocial outcomes. The association between lower NLR-containing predicted pCR probability and psychosocial support need was significant before direct NLR adjustment, with an odds ratio of 1.49 per 0.10 decrease. After adjustment for NLR, this association attenuated to an odds ratio of 1.13 and was no longer statistically significant. Adding model-derived pCR probability to NLR alone produced only modest and statistically uncertain incremental value. Therefore, the nomogram-derived probability should be viewed as a composite clinical-inflammatory profile associated with baseline psychosocial burden, rather than as an independent psychosocial predictor.

This study has clear clinical boundaries. The nomogram can support structured pretreatment discussion of response probability, but it should not replace validated distress screening or clinical assessment and should not be used to alter HER2-directed neoadjuvant therapy in isolation. The study was single-center, the same-center temporal validation cohort was small, and no external validation was performed. Psychosocial outcomes were measured only at baseline, and treatment patterns changed over time. In addition, the descriptive comparison with 69 excluded screened patients encompassed heterogeneous exclusion pathways and cannot specifically quantify selection bias arising from exclusions due solely to incomplete analytic data. Prospective multicenter validation across healthcare systems with different HER2-treatment access patterns, together with repeated patient-reported outcomes, is required before model-guided psychosocial workflows can be implemented.

Supplementary materials: Supplementary Tables S1–S7 provide additional information on patient inclusion and exclusion, laboratory and questionnaire quality indicators, baseline characteristics by future pCR status, model-development diagnostics, psychosocial sensitivity analyses, and TRIPOD/PROBAST reporting and risk-of-bias assessments.

Author contributions: Conceptualization, XL; investigation, XL and QZ; data curation, QZ and QH; formal analysis, QZ; validation, QH; writing—original draft preparation, XL; writing—review and editing, QH; supervision, XL. All authors have read and agreed to the published version of the manuscript.

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Ethical approval: The study protocol was approved by the Institutional Review Board of The First Affiliated Hospital of Chengdu Medical College (approval number: 2024-KY-105). All procedures were conducted in accordance with the Declaration of Helsinki and institutional data-protection standards.

Informed consent statement: The review board waived written informed consent for retrospective analysis of de-identified clinical data and de-identified routine pretreatment psychosocial assessments. The psychosocial questionnaires were part of routine clinical supportive-care evaluation rather than an additional research intervention.

Data availability statement: The de-identified dataset used for the final analyses is available from the corresponding author on reasonable request and subject to institutional data-sharing approval.

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Conflict of interest: The authors declare no conflicts of interest.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2024;74(3):229-263. doi:10.3322/caac.21834.
2. Swain SM, Shastry M, Hamilton E. Targeting HER2-positive breast cancer: advances and future directions. *Nat Rev Drug Discov.* 2023;22(2):101-126. doi:10.1038/s41573-022-00579-0.
3. Harbeck N. Neoadjuvant and adjuvant treatment of patients with HER2-positive early breast cancer. *Breast.* 2022;62(Suppl 1):S12-S16. doi:10.1016/j.breast.2022.01.006.
4. Broglio KR, Quintana M, Foster M, Olinger M, McGlothlin A, Berry SM, et al. Association of pathologic complete response to neoadjuvant therapy in HER2-positive breast cancer with long-term outcomes: a meta-analysis. *JAMA Oncol.* 2016;2(6):751-760. doi:10.1001/jamaoncol.2015.6113.
5. Davey MG, Browne F, Miller N, Lowery AJ, Kerin MJ. Pathological complete response as a surrogate to improved survival in human epidermal growth factor receptor-2-positive breast cancer: systematic review and meta-analysis. *BJS Open.* 2022;6(3):zrac028. doi:10.1093/bjsopen/zrac028.
6. Hännikäinen EN, Mattson J, Karihtala P. Predictors of successful neoadjuvant treatment in HER2-positive breast cancer. *Oncol Lett.* 2023;26(4):434. doi:10.3892/ol.2023.14021.
7. Ding J, Yang Y, Jiang L, Wu W, Shao Z. Predictive factors of pathologic complete response in HER2-positive and axillary lymph node positive breast cancer after neoadjuvant paclitaxel, carboplatin plus with trastuzumab. *Oncotarget.* 2017;8(34):56626-56634. doi:10.18632/oncotarget.17993.

8. Wu HY, Lin CY, Tzeng YD, Hung CC, Liu SI, Yin CH, et al. Preoperative systemic inflammation response index: clinicopathologic predictor of pathological complete response in HER2-positive breast cancer patients receiving neoadjuvant systemic therapy. *J Chin Med Assoc.* 2024;87(2):226-235. doi:10.1097/JCMA.0000000000001034.
9. Chen X, Cai Q, Deng L, Chen M, Xu M, Chen L, et al. Association of inflammatory blood markers and pathological complete response in HER2-positive breast cancer: a retrospective single-center cohort study. *Front Immunol.* 2024;15:1465862. doi:10.3389/fimmu.2024.1465862.
10. Pang J, Ding N, Yin N, Xiao Z. Systemic immune-inflammation index as a prognostic marker in HER2-positive breast cancer patients undergoing trastuzumab therapy. *Sci Rep.* 2024;14(1):6578. doi:10.1038/s41598-024-57343-0.
11. Xie J, Guo Z, Zhu Y, Ma M, Jia G. Peripheral blood inflammatory indexes in breast cancer: a review. *Medicine (Baltimore).* 2023;102(48):e36315. doi:10.1097/MD.00000000000036315.
12. Lacourt TE, Tripathy D, Swartz MC, LaVoy EC, Heijnen CJ. Distress and inflammation are independently associated with cancer-related symptom severity. *Compr Psychoneuroendocrinol.* 2024;20:100269. doi:10.1016/j.cpnec.2024.100269.
13. Omari M, Amaadour L, El Asri A, Benbrahim Z, Mellas N, El Rhazi K, et al. Psychological distress and coping strategies in breast cancer patients under neoadjuvant therapy: a systematic review. *Womens Health (Lond).* 2024;20:17455057241276232. doi:10.1177/17455057241276232.
14. Riba MB, Donovan KA, Ahmed K, Andersen B, Braun II, Breitbart WS, et al. NCCN Guidelines Insights: Distress Management, Version 2.2023. *J Natl Compr Canc Netw.* 2023;21(5):450-457. doi:10.6004/jnccn.2023.0026.
15. Tang LL, Zhang YN, Pang Y, Zhang HW, Song LL. Validation and reliability of Distress Thermometer in Chinese cancer patients. *Chin J Cancer Res.* 2011;23(1):54-58. doi:10.1007/s11670-011-0054-y.
16. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* 1983;67(6):361-370. doi:10.1111/j.1600-0447.1983.tb09716.x.
17. Vodermaier A, Linden W, Siu C. Screening for emotional distress in cancer patients: a systematic review of assessment instruments. *J Natl Cancer Inst.* 2009;101(21):1464-1488. doi:10.1093/jnci/djp336.
18. Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *BMJ.* 2015;350:g7594. doi:10.1136/bmj.g7594.
19. Wolff RF, Moons KGM, Riley RD, Whiting PF, Westwood M, Collins GS, et al. PROBAST: A tool to assess the risk of bias and applicability of prediction model studies. *Ann Intern Med.* 2019;170(1):51-58. doi:10.7326/M18-1376.
20. Wolff AC, Somerfield MR, Dowsett M, et al. Human epidermal growth factor receptor 2 testing in breast cancer: ASCO-College of American Pathologists guideline update. *J Clin Oncol.* 2023;41(22):3867-3872. doi:10.1200/JCO.22.02864.
21. Allison KH, Hammond MEH, Dowsett M, McKernin SE, Carey LA, Fitzgibbons PL, et al. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP guideline update. *J Clin Oncol.* 2020;38(12):1346-1366. doi:10.1200/JCO.19.02309.
22. Giuliano AE, Connolly JL, Edge SB, Mittendorf EA, Rugo HS, Solin LJ, et al. Breast cancer-major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin.* 2017;67(4):290-303. doi:10.3322/caac.21393.
23. Brady MJ, Cella DF, Mo F, Bonomi AE, Tulskey DS, Lloyd SR, et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument. *J Clin Oncol.* 1997;15(3):974-986. doi:10.1200/JCO.1997.15.3.974.
24. Wan C, Zhang D, Yang Z, Tu X, Tang W, Feng C, et al. Validation of the simplified Chinese version of the FACT-B for measuring quality of life for patients with breast cancer. *Breast Cancer Res Treat.* 2007;106(3):413-418. doi:10.1007/s10549-007-9511-1.
25. Mehnert A, Herschbach P, Berg P, Henrich G, Koch U. Fear of progression in breast cancer patients-validation of the short form of the Fear of Progression Questionnaire (FoP-Q-SF). *Z Psychosom Med Psychother.* 2006;52(3):274-288. doi:10.13109/zptm.2006.52.3.274.
26. Mahendran R, Liu J, Kuparasundram S, Griva K. Validation of the English and simplified Mandarin versions of the Fear of Progression Questionnaire-Short Form in Chinese cancer survivors. *BMC Psychol.* 2020;8(1):10. doi:10.1186/s40359-020-0374-0.
27. O'Connor AM. Validation of a decisional conflict scale. *Med Decis Making.* 1995;15(1):25-30. doi:10.1177/0272989X9501500105.
28. Pérez-García JM, Cortés J, Ruiz-Borrego M, Colleoni M, Stradella A, Bermejo B, et al. 3-year invasive disease-free survival

- with chemotherapy de-escalation using an 18F-FDG-PET-based, pathological complete response-adapted strategy in HER2-positive early breast cancer (PHERGain): a randomised, open-label, phase 2 trial. *Lancet*. 2024;403(10437):1649-1659. doi:10.1016/S0140-6736(24)00054-0.
29. Canino F, Barbolini M, De Giorgi U, Fontana T, Gaspari V, et al. Safety and efficacy analysis of neoadjuvant pertuzumab, trastuzumab and standard chemotherapy for HER2-positive early breast cancer: real-world data from NeoPower study. *BMC Cancer*. 2024;24(1):735. doi:10.1186/s12885-024-12506-0.
 30. Gluz O, Nitz U, Christgen M, et al. Efficacy of endocrine therapy plus trastuzumab and pertuzumab vs de-escalated chemotherapy in patients with hormone receptor-positive/ERBB2-positive early breast cancer: the Neoadjuvant WSG-TP-II Randomized Clinical Trial. *JAMA Oncol*. 2023;9(7):946-954. doi:10.1001/jamaoncol.2023.0646.
 31. Llombart-Cussac A, Pérez-García J, Brasó-Maristany F, et al. HER2DX Genomic Assay in HER2-positive early breast cancer treated with trastuzumab and pertuzumab: a correlative analysis from the PHERGain phase II trial. *Clin Cancer Res*. 2024;30(18):4123-4130. doi:10.1158/1078-0432.CCR-24-0464.
 32. Antonini M, Mattar A, Pereira da Costa Pinheiro DJ, Maia IB, Teixeira MD, Amorim AG, et al. Disparities in access to anti-HER2 therapies in neoadjuvant chemotherapy: a prognostic analysis based on real-world data comparing Brazil's public and private healthcare systems. *Breast*. 2025;80:104417. doi:10.1016/j.breast.2025.104417.
 33. Gasparri ML, Albasini S, Truffi M, Favilla K, Tagliaferri B, Piccotti F, et al. Low neutrophil-to-lymphocyte ratio and pan-immune-inflammation-value predict nodal pathologic complete response in 1274 breast cancer patients treated with neoadjuvant chemotherapy: a multicenter analysis. *Ther Adv Med Oncol*. 2023;15:17588359231193732. doi:10.1177/17588359231193732.
 34. Wang H, Huang Z, Xu B, Zhang J, He P, Gao F, et al. The predictive value of systemic immune-inflammatory markers before and after treatment for pathological complete response in patients undergoing neoadjuvant therapy for breast cancer: a retrospective study of 1994 patients. *Clin Transl Oncol*. 2024;26(6):1467-1479. doi:10.1007/s12094-023-03371-7.
 35. Li F, Wang Y, Dou H, Chen X, Wang J, Xiao M. Association of immune inflammatory biomarkers with pathological complete response and clinical prognosis in young breast cancer patients undergoing neoadjuvant chemotherapy. *Front Oncol*. 2024;14:1349021. doi:10.3389/fonc.2024.1349021.
 36. Tang WZ, Mangantig E, Iskandar YHP, Cheng SL, Yusuf A, Jia K. Prevalence and associated factors of psychological distress among patients with breast cancer: a systematic review and meta-analysis. *BMJ Open*. 2024;14(9):e077067. doi:10.1136/bmjopen-2023-077067.
 37. Zhuang J, Wang Y, Wang S, Hu R, Wu Y, Chen L. Fear of disease progression, self-management efficacy, and family functioning in patients with breast cancer: a cross-sectional relationship study. *Front Psychol*. 2024;15:1400695. doi:10.3389/fpsyg.2024.1400695.
 38. He JL, Xu HQ, Yang J, Hou DJ, Gong XY, Lu XY, et al. Fear of disease progression among breast cancer patients in China: a meta-analysis of studies using the fear of progression questionnaire short form. *Front Psychol*. 2023;14:1222798. doi:10.3389/fpsyg.2023.1222798.
 39. Yu H, Tan L, Xue B, Feng L, Fang P, Meng X, et al. Platelet-to-lymphocyte, neutrophil-to-lymphocyte and lymphocyte-to-monocyte ratios are related to cancer-related fatigue and quality of life in patients with cancer: a cross-sectional study. *BMJ Open*. 2023;13(12):e075398. doi:10.1136/bmjopen-2023-075398.

Supplementary Material

Supplementary Table S1. Comparison of included patients and excluded screened patients with available baseline information

Characteristic	Included patients (n=246)	Excluded screened patients with available baseline information (n=69)	P value
Age, years	52.2 ± 8.6	53.4 ± 9.3	0.302
Postmenopausal status	124 (50.41%)	37 (53.62%)	0.637
Tumor size, cm	3.2 (2.1–4.5)	3.4 (2.2–4.8)	0.218
Clinical node-positive disease	109 (44.31%)	35 (50.72%)	0.347
Hormone receptor-positive disease	161 (65.45%)	47 (68.12%)	0.679
HER2 IHC 3+	220 (89.43%)	61 (88.41%)	0.811
AJCC anatomical stage III	103 (41.87%)	31 (44.93%)	0.651
Planned dual HER2 blockade	149 (60.57%)	35 (50.72%)	0.088
Routine baseline PRO form available and valid	246 (100.00%)	59 (85.51%)	<0.001
CBC available within 7 days before treatment	246 (100.00%)	65 (94.20%)	0.001
Definitive postoperative pathology available	246 (100.00%)	64 (92.75%)	<0.001

Note. Values are mean ± SD, median (interquartile range), or n (%). The excluded group comprises all 69 excluded screened patients: 46 patients excluded before final eligibility confirmation and 23 patients who were potentially eligible after initial clinical screening but were subsequently excluded because prespecified treatment-completion and/or complete analytic-data requirements were not met. This is an exploratory descriptive comparison using available variables; it does not specifically estimate selection bias arising from exclusions due solely to incomplete analytic data. P values are unadjusted and should be interpreted descriptively. PRO, patient-reported outcome; CBC, complete blood count; AJCC, American Joint Committee on Cancer; IHC, immunohistochemistry.

Supplementary Table S2. Laboratory values outside institutional reference ranges and questionnaire reliability

S2A. Laboratory values outside reference ranges

Marker	Reference interval	Outside range, n (%)	Direction
Absolute neutrophil count, ×10 ⁹ /L	1.8–6.3	23 (9.35%)	19 high; 4 low
Absolute lymphocyte count, ×10 ⁹ /L	1.1–3.2	34 (13.82%)	5 high; 29 low
Platelet count, ×10 ⁹ /L	125–350	18 (7.32%)	14 high; 4 low
Albumin, g/dL	3.5–5.5	28 (11.38%)	0 high; 28 low
NLR	No fixed institutional reference range	Not classified	Modeled as a continuous standardized predictor

Continuation Table:

Marker	Reference interval	Outside range, n (%)	Direction
PLR	No fixed institutional reference range	Not classified	Assessed in sensitivity/ candidate models
SII	No fixed institutional reference range	Not classified	Assessed in sensitivity/ candidate models

Note. Inflammatory ratios were not dichotomized using normal-range thresholds because no universally accepted clinical reference range exists for NLR, PLR, or SII in this setting.

S2B. Internal consistency and administration quality indicators

Instrument	Scale structure	Cronbach alpha	Administration/scoring note
Distress Thermometer	Single-item 0–10 scale	Not applicable	Standardized nurse-administered screening form
HADS-Anxiety	7 items	0.84	All items completed in the analysis set
HADS-Depression	7 items	0.80	All items completed in the analysis set
FACT-B total score	37 items	0.89	Scored according to the instrument manual
FoP-Q-SF	12 items	0.91	Higher values indicate greater fear of progression
Decision Conflict Scale	16 items	0.88	Transformed to a 0–100 score

Note. Cronbach alpha values refer to the analytic cohort.

Supplementary Table S3. Baseline characteristics in the training cohort according to future pCR status

Characteristic	Future pCR group (n=72)	Future non-pCR group (n=126)	P value
Age, years	51.8 ± 8.2	52.5 ± 8.9	0.584
Postmenopausal status	37 (51.39%)	63 (50.00%)	0.849
Tumor size, cm	2.8 (1.8–3.7)	3.5 (2.3–4.8)	0.002
Clinical node-positive disease	22 (30.56%)	66 (52.38%)	0.003
Hormone receptor-positive disease	32 (44.44%)	98 (77.78%)	<0.001
Taxane-based neoadjuvant chemotherapy	55 (76.39%)	95 (75.40%)	0.876
Dual HER2 blockade	48 (66.67%)	70 (55.56%)	0.128
NLR	2.6 ± 0.9	3.4 ± 1.3	<0.001
PLR	139 (96–198)	166 (116–238)	0.014
SII	552 (405–706)	864 (635–1112)	<0.001
Platelet count, ×10 ⁹ /L	194 (151–242)	278 (226–329)	<0.001
Albumin, g/dL	4.0 ± 0.4	3.9 ± 0.5	0.132
DT score	2.8 ± 1.1	3.6 ± 1.4	<0.001
HADS-Anxiety score	5.1 ± 2.3	6.7 ± 2.8	<0.001
HADS-Depression score	4.0 ± 2.0	5.1 ± 2.4	0.001
FACT-B total score	103.1 ± 11.7	94.8 ± 13.2	<0.001

Continuation Table:

Characteristic	Future pCR group (n=72)	Future non-pCR group (n=126)	P value
FoP-Q-SF score	30.4 ± 6.1	34.7 ± 6.8	<0.001
Decision Conflict Scale score	27.6 ± 8.5	32.3 ± 10.1	0.001
Composite psychosocial support need	27 (37.50%)	75 (59.52%)	0.003

Note. Psychosocial scores were obtained before treatment and before pCR status was known; comparisons should therefore be interpreted as baseline associations with future response, not consequences of response.

Supplementary Table S4. Model-development diagnostics

S4A. Restricted cubic spline tests for nonlinearity

Continuous predictor	P for nonlinearity
Age	0.648
Tumor size	0.312
NLR	0.428
PLR	0.394
SII	0.226
Albumin	0.581

Note. Continuous predictors were retained as linear terms because no prespecified predictor showed evidence of clinically meaningful nonlinearity.

S4B. Prespecified interaction screening

Interaction term	P value
Hormone receptor status × dual HER2 blockade	0.343
NLR × hormone receptor status	0.411
NLR × dual HER2 blockade	0.528
Tumor size × clinical nodal status	0.219

Note. No interaction was retained in the final model because interaction terms were not statistically or clinically stable in the training cohort.

S4C. Collinearity diagnostics

Candidate predictor	Variance inflation factor
Tumor size	1.22
Clinical node-positive disease	1.19
Hormone receptor-positive disease	1.07
NLR	1.16
PLR	2.85
SII	4.72

Note. NLR, PLR, and SII share hematological components and were therefore assessed in separate candidate models rather than simultaneously entered into the primary model.

S4D. Candidate pCR prediction models in the training cohort

Model	Predictors	AUC (95% CI)	Brier score
Clinical model excluding NLR	Tumor size, clinical nodal status, hormone receptor status	0.713 (0.639–0.780)	0.201
NLR-containing model	Tumor size, clinical nodal status, hormone receptor status, NLRz	0.776 (0.702–0.838)	0.182
SII-containing model	Tumor size, clinical nodal status, hormone receptor status, SIIz	0.768 (0.695–0.832)	0.185
PLR-containing model	Tumor size, clinical nodal status, hormone receptor status, PLRz	0.734 (0.659–0.801)	0.196

Note. The NLR-containing model was selected for the primary nomogram because it combined discrimination, calibration, parsimony, and interpretability.

Supplementary Table S5. Psychosocial sensitivity analyses

S5A. Adjusted associations between inflammatory markers and continuous psychosocial outcomes

Outcome	Main predictor	β	SE	P value	Adjusted R ²
DT score	NLR, per SD increase	0.46	0.10	<0.001	0.238
DT score	SII, per SD increase	0.41	0.10	<0.001	0.226
HADS-Anxiety score	NLR, per SD increase	0.94	0.18	<0.001	0.271
HADS-Anxiety score	SII, per SD increase	0.89	0.18	<0.001	0.260
HADS-Depression score	NLR, per SD increase	0.51	0.15	0.001	0.154
HADS-Depression score	SII, per SD increase	0.47	0.15	0.002	0.148
FACT-B total score	NLR, per SD increase	-4.88	0.91	<0.001	0.289
FACT-B total score	SII, per SD increase	-5.13	0.91	<0.001	0.301
FoP-Q-SF score	NLR, per SD increase	2.37	0.43	<0.001	0.304
FoP-Q-SF score	SII, per SD increase	2.21	0.44	<0.001	0.291
DCS score	NLR, per SD increase	3.52	0.61	<0.001	0.279
DCS score	SII, per SD increase	3.15	0.62	<0.001	0.263

Note. Models adjusted for age, tumor size, clinical nodal status, hormone receptor status, and HER2-targeted treatment pattern. NLR and SII were modeled separately.

S5B. Individual psychosocial endpoints and circularity-aware adjustment

Endpoint	Predictor	Adjustment set	OR (95% CI)	P value
DT ≥ 4	NLR-containing pCR probability, per 0.10 decrease	Age-adjusted	1.42 (1.23–1.65)	<0.001
DT ≥ 4	NLR-containing pCR probability, per 0.10 decrease	Age + NLR adjusted	1.11 (0.93–1.33)	0.233
HADS-Anxiety ≥ 8	NLR-containing pCR probability, per 0.10 decrease	Age-adjusted	1.37 (1.18–1.60)	<0.001
HADS-Anxiety ≥ 8	NLR-containing pCR probability, per 0.10 decrease	Age + NLR adjusted	1.09 (0.90–1.31)	0.386

Continuation Table:

Endpoint	Predictor	Adjustment set	OR (95% CI)	P value
HADS-Depression ≥ 8	NLR-containing pCR probability, per 0.10 decrease	Age-adjusted	1.27 (1.07–1.52)	0.007
HADS-Depression ≥ 8	NLR-containing pCR probability, per 0.10 decrease	Age + NLR adjusted	1.05 (0.84–1.31)	0.662
Composite support need	NLR-containing pCR probability, per 0.10 decrease	Age-adjusted	1.49 (1.30–1.71)	<0.001
Composite support need	NLR-containing pCR probability, per 0.10 decrease	Age + NLR adjusted	1.13 (0.96–1.33)	0.142

Note. The attenuation after direct NLR adjustment supports the revised interpretation that the pCR probability–psychosocial association is partly driven by shared inflammatory information rather than an independent psychological effect of the probability estimate.

Supplementary Table S6. TRIPOD checklist for prediction-model reporting

TRIPOD item/domain	Reporting requirement	Location in revised manuscript
Title	Identify the study as model development and validation	Title; Abstract
Abstract	Summarize objectives, design, setting, participants, predictors, outcome, model performance, and limitations	Abstract
Background/objectives	Explain rationale and specify objectives	Introduction
Source of data	Describe study design and data source	Methods: Study design
Participants	Eligibility criteria and participant flow	Methods: Patient selection; Figure 1
Outcome	Define outcome and assessment method	Methods: Neoadjuvant treatment and pathological assessment
Predictors	Define predictors and measurement timing	Methods: Predictor assessment; Tables 1–2
Sample size	Report sample size and events	Methods and Results
Missing data	Explain complete-case requirements and missing-questionnaire handling	Methods; Figure 1; Supplementary Table S1
Statistical analysis	Model-building strategy, handling of continuous predictors, validation, and performance metrics	Methods: Statistical analysis
Model specification	Regression coefficients and full formula	Results; Table 3; Figure 2
Model performance	Discrimination, calibration, and clinical utility metrics	Results; Table 4; Figures 3–5
Model updating	Specify whether recalibration or updating was performed	Methods; Results
Participants/results	Participant characteristics by cohort	Results; Table 1
Development results	Predictors retained and model estimates	Results; Table 3
Validation results	Temporal internal validation performance	Results; Table 4
Limitations	Discuss selection bias, small temporal validation cohort, and absence of external validation	Discussion

Continuation Table:

TRIPOD item/domain	Reporting requirement	Location in revised manuscript
Interpretation	Provide cautious interpretation consistent with design	Discussion and Conclusion
Implications	Discuss need for prospective testing before clinical implementation	Discussion; Figure 6
Supplementary resources	Provide additional diagnostics and checklists	Supplementary Tables S1–S7

Note. Checklist prepared according to the TRIPOD statement for transparent reporting of multivariable prediction models.

Supplementary Table S7. PROBAST-oriented risk-of-bias and applicability self-assessment

Domain	Judgment	Rationale	Revision response
Participants	Moderate risk	Single-center cohort; complete-case inclusion requiring valid PRO and analytic data may introduce selection bias. The descriptive comparison with 69 heterogeneous excluded screened patients cannot isolate selection bias arising specifically from exclusions due solely to incomplete analytic data.	Clarified patient flow and terminology, explicitly limited Supplementary Table S1 to a descriptive comparison, and retained selection bias as a limitation.
Predictors	Low risk	Predictors were routinely available before neoadjuvant therapy and measured before outcome ascertainment.	Specified measurement timing, HER2/HR definitions, and NLR standardization.
Outcome	Low risk	pCR was assessed by postoperative pathology using ypT0/is ypN0; pathologists were not involved in questionnaire data collection.	Clarified pCR definition and pathology review procedure.
Analysis	Moderate to high risk	Temporal validation cohort was small; sensitivity estimates are imprecise; no external validation; complete-case analysis.	Added bootstrapped CIs, circularity-aware analyses, and conservative interpretation.
Applicability	Moderate concern	Findings reflect one institution and local temporal changes in access to trastuzumab and pertuzumab; same-center temporal validation does not establish transportability.	Distinguished same-institution temporal performance from external transportability and called for validation across healthcare systems with different treatment-access patterns.
Overall	Moderate risk of bias	Limitations remain despite enhanced reporting and sensitivity analyses.	Conclusion limited to associative and hypothesis-generating implications.

Note. This self-assessment is intended to improve transparency; it is not a substitute for formal independent PROBAST evaluation.