A clinical model to predict pathological complete response using early peripheral absolute lymphocyte dynamics in HER2+ breast cancer

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BACKGROUND

- HER2-positive breast cancer is an aggressive subtype in which immune activation plays a key role in treatment response, particularly with HER2-targeted antibody therapy.
- Lymphocytes contribute to antitumor immunity, and tumor-infiltrating lymphocytes correlate with higher rates of pathological complete response (pCR).
- Whether peripheral immune dynamics—specifically absolute lymphocyte count (ALC)—reflect early immunologic response to neoadjuvant therapy (NAT) has not been well established
- Identifying simple, scalable blood-based biomarkers could enable early prediction of treatment efficacy and help tailor HER2-directed therapy intensity.

AIMS

•Evaluate whether baseline ALC and early ALC decline after the first cycle of neoadjuvant therapy predict pathological complete response (pCR) in HER2-positive breast cancer.
•Develop and externally validate an ALC-based predictive model, and evaluate the extent to which ALC metrics enhance predictive performance beyond conventional clinical models.

METHODS

Cohort identification: Patients with stage I–III HER2-positive breast cancer receiving taxane + trastuzumab–based neoadjuvant therapy (2007–2022) were identified from the Oncoshare database, integrating EMR and cancer registry data.
ALC Measurements: The primary exposure was the change in ALC, defined as the ratio of post-treatment to pre-treatment ALC, with pre-treatment ALC measured within 60 days prior to therapy initiation and post-treatment ALC collected 7-35 days after each cycle (range 1-6) or before surgery.
Primary outcome: Pathological complete response (pCR) assessed from pathology reports
Model Development: We collected demographic, tumor, staging, and treatment variables potentially relevant for predicting pCR. Tumor features included ER and PR status and quantitative expression, HER2 status (IHC 1–3+, ratio, and copy number), Ki-67, and grade. Staging variables included T code, N code, and AJCC stage. Treatment variables included chemotherapy regimen, pertuzumab use, cycles completed. Baseline absolute lymphocyte count (ALC) and change in ALC from baseline to cycle 1 (C1) were operationalized using percentile-based binary thresholds from the 10th to 90th percentiles in 10% increments (9 thresholds per ALC metric). We evaluated all 81 pairwise threshold combinations. For each combination, we constructed a predictor set consisting of 1)the binary baseline ALC indicator, 2) the binary ALC-change indicator, and 3)all clinical and demographic variables. We fit a group LASSO logistic regression with 10-fold cross-validation using the lambda.1se criterion. In group LASSO, each variable (and all its dummy-coded levels) is selected or excluded as a unit. Alternative measurements of the same feature (e.g., ER status, ER%, ER 1–3) were treated as distinct variables. For each threshold pair, we selected at lambda.1se and refit a reduced group LASSO model containing only those variables to obtain the final cross-validated error for that threshold pair. The optimal pCR prediction model was defined as the threshold combination yielding the minimum cross validation error
Model validation: The final ALC-based model was externally validated in an independent cohort (n=83) using identical predictors and threshold cut-points.

RESULTS

Table 1: Discovery Cohort Patient Characteristics

	Pathological complete response (pCR)			
	No * N = 79 (49.4%)	Yes * N = 75 (50.6%)	Overall * N = 154	p-value**
Age (years)	55 (45,63)	52 (44,63)	53.00 (45,63)	0.5
Cancer Stage				0.7
I	26 (33%)	28 (37%)	68 (44%)	
II	29 (37%)	29 (39%)	44 (29%)	
III	24 (30%)	18 (24%)	42 (27%)	
Cancer Grade				0.2
I	3 (1%)	3 (4%)	4 (2.6%)	
II	42 (54%)	30 (40%)	72 (47%)	
III	33 (42%)	45 (59%)	78 (51%)	
Race and Ethnicity				0.5
Hispanic	9 (11%)	9 (12%)	18 (12%)	
NH Asian/Pacific Islander	23 (30%)	27 (36%)	50 (33%)	
NH Black	3 (4%)	4 (5%)	7 (4.5%)	
NH White	43 (55%)	36 (47%)	79 (51%)	
Chemotherapy Regimen				0.3
TCH	19 (24%)	12 (16%)	31 (20%)	
TCHP	53 (80%)	61 (68%)	114 (74%)	
THP	6 (7.6%)	3 (4%)	9 (5.8%)	
ER-positive	68 (86%)	43 (57%)	111 (72%)	<0.001
PR-positive	61 (77%)	30 (40%)	91 (59%)	<0.001
HER2 FISH positivity				<0.001
2+	33 (42%)	6 (8%)	39 (25%)	
3+	46 (58%)	69 (92%)	115 (75%)	
T-stage				0.7
T1	11 (14%)	14 (19%)	25 (16%)	
T2	47 (59%)	40 (53%)	87 (56%)	
T3/4	21 (27%)	21 (28%)	42 (27%)	
N-stage				0.2
Node Positive	36 (46%)	42 (56%)	78 (51%)	
Node Negative	43 (54%)	33 (44%)	76 (49%)	
Baseline ALC*	1.6 (1.2,1.97)	1.91 (1.6,2.4)	1.71 (1.41,2.2)	<0.001
ALC change***	0.14 (-0.11, 0.32)	0.30 (0.21,0.44)	0.24 (0.04,0.41)	<0.001

* Median (IQR); n (%)
** Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test
*** ALC change: defined as 1 - C1/Baseline, where C1 ALC was measured after the first treatment cycle.
TCH = docetaxel, carboplatin, and trastuzumab; TCHP = docetaxel, carboplatin, trastuzumab, and pertuzumab; THP = paclitaxel, pertuzumab, and trastuzumab; ER = estrogen receptor; NH = non-Hispanic.

Figure 1: Mean absolute lymphocyte counts across Neoadjuvant Therapy
Mean ALC Values by Chemotherapy Cycle, stratified by pCR
Shaded area represents 95% Confidence Intervals

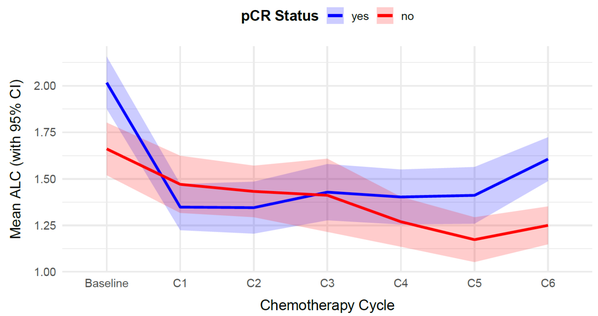
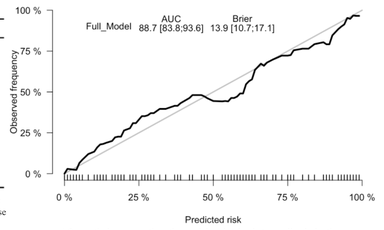


Table 2: Multivariate analysis of variables in ALC-based model to predict pCR

Predictor	Odds Ratio (95% CI)	P value
Baseline ALC≥1.5 K/μL	9.66 (3.41, 31.5)	<0.001
ALC decline ≥ 10%	6.33 (2.36, 18.9)	<0.001
Age	0.96 (0.92, 1.00)	0.076
ER %	0.59 (0.14, 2.47)	0.466
PR Positivity	0.13 (0.03, 0.48)	0.003
HER2 3+	13.9 (4.52, 50.7)	<0.001
T stage T2	0.21 (0.05, 0.75)	0.019
T stage T3/T4	0.32 (0.07, 1.28)	0.116

The model with the lowest cross-validation error defined high-risk patients as those with baseline ALC ≥1.5 K/μL (30th percentile) and an ALC decline ≥0.1 (30th percentile), a.k.a. a 10% decrease from baseline to C1. Five confounding variables were selected: ER positivity (%), PR positive/negative, HER2 IHC (1-3), age, and T code.
N=154

Figure 2: ALC-based model AUC curve (N=154)



After optimism correction, the model maintained strong discriminative performance with an AUC of 85.8%

Figure 3: ALC-based model AUC curve in Validation cohort (N=83)

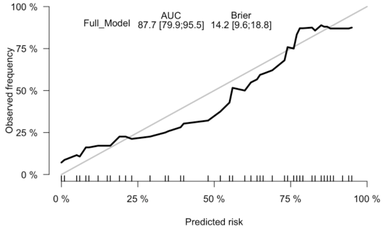


Figure 4: PCR rate by ALC Risk group-Discovery cohort (N=154)

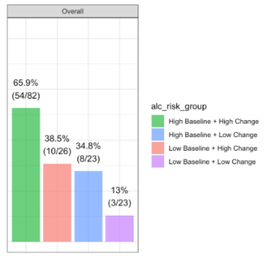


Figure 5: PCR rate by ALC Risk group-Validation cohort (N=83)

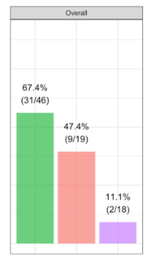
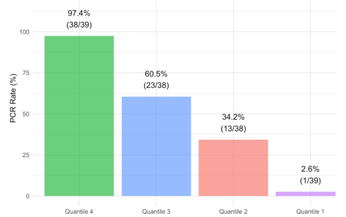


Figure 5: PCR rate by Predicted Risk Quartile-Discovery cohort (N=154)



Patients were stratified into quartiles based on model-predicted PCR probability. The highest risk quartile (quartile 4) achieved a PCR rate of 97.4% in the discovery cohort and 95.2% in the validation cohort.

Figure 6: PCR rate by Predicted Risk Quartile-Validation cohort (N=83)

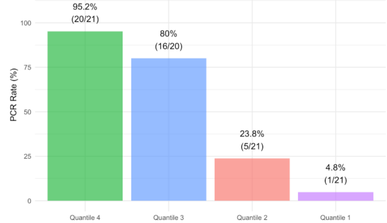


Table 3: Correlation between pCR and long-term clinical outcomes

Characteristic	Overall N = 154[1]	no N = 79[1]	yes N = 75[1]	p-value[2]
Death	14 (9.1%)	9 (11%)	5 (6.7%)	0.3
Local Recurrence	14 (9.1%)	12 (15%)	2 (2.7%)	0.007
Distant Recurrence	19 (12%)	15 (19%)	4 (5.3%)	0.010
Any Recurrence	26 (17%)	21 (27%)	5 (6.7%)	<0.001
Follow-up time (years)	9.1 (7.5, 10.4)	9.2 (7.6, 10.4)	8.5 (7.2, 10.2)	0.5

[1] n (%); Median (Q1, Q3)
[2] Pearson's Chi-squared test; Wilcoxon rank sum test

CONCLUSIONS

- Higher absolute lymphocyte counts (ALC) at baseline and following NAT completion are associated with a higher likelihood of achieving a pathological complete response (pCR) in patients with HER2+ breast cancer
- We developed a model and validated a clinical model using routinely collected clinical values: ALC ≥1.5 K/μL (30th percentile) and an ALC decline ≥0.1 (30th percentile), ER positivity (%), PR positive/negative, HER2 IHC (1-3), age and T stage that was predictive of pCR with a robust AUC in both discovery and validation cohorts
- This ALC-based tool offers a cost-effective and scalable alternative for early response prediction, with potential to inform treatment adaptation strategies in real time.

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