Pretreatment neutrophil-to-lymphocyte ratio is associated with pathologic complete response following neoadjuvant chemo-immunotherapy in early triple-negative breast cancer

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Introduction

- Neoadjuvant immune checkpoint inhibitors (ICI) with chemotherapy is widely used for the management of localized triple-negative breast cancer (TNBC) based on the KEYNOTE-522 trial.[1]
- ICI targets T-lymphocytes by blocking the PD-1/PD-L1 signaling axis between T lymphocytes and tumor cells, thereby eliciting an anti-tumor immune response.
- Emerging studies demonstrate that pre-treatment absolute lymphocyte counts (ALC) and relative lymphocytes counts, as evidenced by the neutrophil-to-lymphocyte ratio (NLR), can predict ICI efficacy in patients with advanced cancer.[2]
- While tumor-infiltrating lymphocytes (TILs) have been associated with improved pathologic complete response (pCR) rates following neoadjuvant chemo-immunotherapy and with improved prognosis in early TNBC, the impact of ALC and NLR in modulating ICI response in early breast cancer is not known.[3,4]
- In this study, we evaluated the association between ALC, NLR, and therapeutic response to chemo-immunotherapy in patients with TNBC.

Methods and Materials

- In this multi-institutional retrospective study, patients with stage I-III TNBC diagnosed between 2019 to 2023 were included who were treated with at least 1 cycle of neoadjuvant ICI and chemotherapy at 2 institutions.
- Pre-treatment laboratory values were collected for all patients.
- An NLR cut-off value of 5 was used based on previous studies which demonstrate that NLR ≥ 5 is associated with worse ICI response.[2]
- Univariate and multivariate logistic regression and Cox proportional hazards models were used to assess the impact of pretreatment NLR on pCR.

Results

Table 1. Patient and tumors characteristics according to NLR status.

	All Patients (n = 372)	Low NLR (NLR < 5) (n=337)	High NLR (NLR ≥ 5) (n=35)	P-value
Age (years), median (range)	54.8 (23.2, 87.7)	55.0 (23.2, 87.7)	50.5 (30.6, 84.0)	0.284
Gender (female)	371 (99.7%)	336 (99.7%)	35 (100.0%)	
Race				0.088
White	188 (50.3%)	171 (50.7%)	17 (48.6%)	
Asian/Pacific Islander	57 (15.3%)	50 (14.8%)	7 (20.0%)	
Black	39 (10.5%)	32 (9.5%)	7 (20.0%)	
Other/Unknown	88 (23.7%)	84 (24.9%)	4 (11.4%)	
Clinical stage				0.876
I	23 (6.2%)	22 (6.5%)	1 (2.9%)	
II	220 (59.1%)	198 (58.8%)	22 (62.9%)	
III	129 (34.7%)	117 (34.7%)	12 (34.3%)	
Estrogen receptor, %				1
0	337 (90.6%)	305 (90.5%)	32 (91.4%)	
1-10	35 (9.4%)	32 (9.5%)	3 (8.6%)	
Pathologic complete response, N (%)	228 (61.3%)	212 (62.9%)	16 (45.7%)	**0.047**

Figure 1. Pre-treatment NLR as a predictor of pCR.

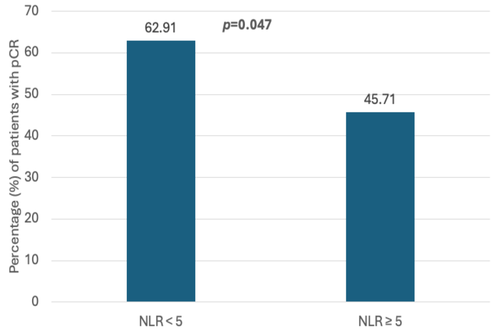


Figure 2. Pre-treatment ALC as a predictor of pCR.

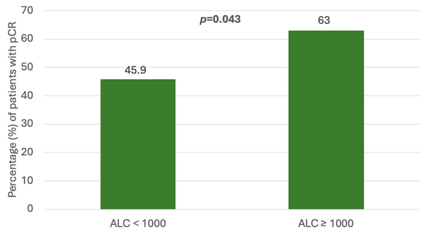
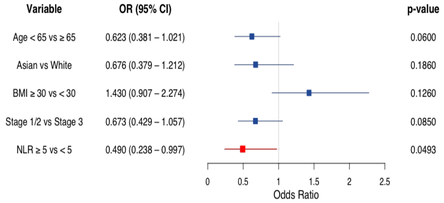


Figure 3. Forest plot for multivariate logistic regression to identify predictors of pCR.



Note: Variables significant at <0.2 level in the univariate analysis were entered into the multivariate analysis and kept if overall significance threshold of 0.05 was met.

Figure 4. Kaplan-Meier estimates of EFS according to baseline NLR status.

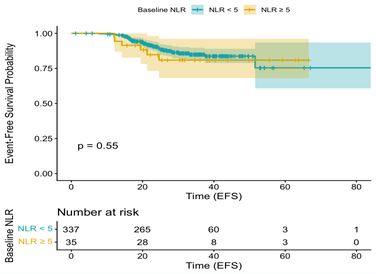
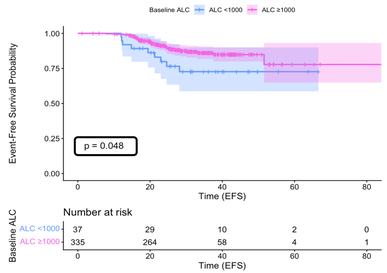


Figure 5. Kaplan-Meier estimates of EFS according to baseline ALC status.



Discussion

- Patients with high NLR at baseline had significantly lower pCR rates compared to those with low NLR (45.7% vs. 62.9%; p=0.047).
- Similarly, baseline lymphopenia was associated with lower pCR rates (45.9% vs. 63.0%; p=0.043) and lower rates of 2-year EFS (79.8% vs. 90.9%; p=0.035).
- Multivariate logistic regression demonstrated that high NLR at baseline was significantly associated with inferior pCR rates (OR 0.49; p=0.049), adjusting for age, race and stage.
- This study reaffirms the predictive value of pre-treatment NLR on ICI responses seen in other advanced solid cancers.
- Limitations of this study include the small sample size of patients with NLR ≥ 5 (n=35) and lack of a control arm without ICI to determine the predictive capacity of NLR on pCR from chemo-IO versus chemotherapy alone, as previous studies show that baseline NLR can predict response to neoadjuvant chemotherapy.[5]

Conclusions

- This is the first study to demonstrate that absolute (and relative) lymphopenia is associated with lower pCR rates in patients with early-stage TNBC treated with neoadjuvant chemo-immunotherapy.
- Further research is needed to further evaluate lymphocyte count as a biomarker of chemo-immunotherapy response in the neoadjuvant and metastatic setting.
- These findings suggest the potential to increase lymphocytes as a therapeutic strategy in patients with early-stage TNBC.

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San Antonio Breast Cancer Symposium
December 9-12, 2025

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