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Baseline Neutrophil-to-Lymphocyte Ratio Predicts Overall Survival in PD-L1-positive Advanced Triple-negative Breast Cancer With Immune-checkpoint-inhibitor Treatment

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Abstract

Background/Aim: Immune checkpoint inhibitors (ICIs) have improved clinical outcomes in patients with advanced triple-negative breast cancer (TNBC); however, substantial heterogeneity exists in treatment durability and survival. Simple blood-based immune markers may provide prognostic information; however, their clinical relevance in ICI-treated TNBC remain unclear.

Patients and Methods: We conducted a retrospective single-center study of patients with advanced TNBC treated with ICIs, including atezolizumab or pembrolizumab. Baseline peripheral immune markers – absolute lymphocyte count (ALC) and neutrophil-to-lymphocyte ratio (NLR) – were evaluated prior to treatment initiation. Time-to-treatment failure (TTF) and overall survival (OS) were analyzed using the Kaplan–Meier method and Cox proportional hazards model.

Results: A total of 43 patients were included. In the Kaplan–Meier analysis, high baseline NLR was significantly associated with both shorter TTF and OS. Low baseline ALC was significantly associated with shorter TTF but not with OS. In the multivariate Cox proportional hazards analysis of TTF, no baseline clinical or immune parameters were identified as independent prognostic factors. In contrast, multivariate analysis for OS demonstrated that high baseline NLR was the only independent prognostic factor.

Conclusion: NLR was independently associated with OS, suggesting it functions as a prognostic marker of systemic inflammatory and immune balance. In contrast, ALC was associated with treatment durability but not long-term survival, indicating its relevance to treatment tolerance rather than survival outcomes. These findings highlight the clinical utility of simple blood-based immune markers for risk stratification in ICI-treated TNBC.

Keywords: Triple-negative breast cancer, immune checkpoint inhibitor, programmed death-ligand 1, neutrophil-to-lymphocyte ratio, absolute lymphocyte count, time-to-treatment failure.

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Introduction

Triple-negative breast cancer (TNBC) is an aggressive subtype characterized by the absence of estrogen receptor (ER), progesterone receptor (PgR), and human epidermal growth factor receptor 2 (HER2) expression (1). Patients with advanced TNBC have historically experienced poor clinical outcomes due to the lack of effective targeted therapies and its aggressive pathology (2). Immune checkpoint inhibitors (ICIs), particularly agents targeting the programmed cell death protein 1 and programmed death-ligand 1 (PD-L1) pathways, have been associated with meaningful survival improvements in patients with PD-L1-positive advanced TNBC, especially when combined with chemotherapy (3–6). Nevertheless, clinical responses to ICIs remain heterogeneous, and reliable biomarkers for predicting treatment durability and survival outcomes in routine clinical practice are needed.

Current biomarker strategies for ICI therapy in TNBC largely focus on tumor-related factors, such as PD-L1 expression, tumor mutational burden, and tumor-infiltrating lymphocytes (7–9). While these biomarkers provide important insights into tumor immune biology, they require tumor tissue, are subject to spatial and temporal heterogeneity, and are not always readily available during treatment initiation. In contrast, peripheral blood-based immune marker analysis represents a simple, inexpensive, and reproducible approach to evaluating host immune status and may offer complementary prognostic information.

Absolute lymphocyte count (ALC) and neutrophil-to-lymphocyte ratio (NLR) have been widely investigated as indicators of systemic immune competence and inflammatory balance (10). Previous studies in breast cancer and other solid tumors have demonstrated that low ALC and high NLR are associated with unfavorable outcomes in patients treated with cytotoxic chemotherapy or molecularly targeted agents (11–14). In immunotherapy, elevated NLR has been correlated with poor survival outcomes, potentially reflecting an immunosuppressive systemic environment driven by neutrophilia and relative lymphopenia (15–19). However, the clinical relevance of baseline ALC and NLR in patients with PD-L1-positive advanced TNBC receiving ICIs is poorly understood, particularly concerning their differential associations with treatment durability and long-term survival.

Therefore, in this study we aimed to investigate the prognostic significance of baseline peripheral immune markers, specifically ALC and NLR, in patients with PD-L1-positive advanced TNBC treated with ICIs. We evaluated their associations with both time-to-treatment failure (TTF) and overall survival (OS) to clarify the endpoint-specific clinical relevance of host immune status and explore the potential utility of simple blood-based biomarkers for risk stratification in ICI-treated TNBC.

Patients and Methods

Patients. This retrospective single-center observational study enrolled patients with PD-L1-positive advanced TNBC who were treated with ICIs at Saitama Medical University International Medical Center (Hidaka, Japan) between October 2021 and December 2025. TNBC was defined as the absence of ER, PgR, and HER2 expression according to the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines (20, 21). PD-L1 expression was assessed by immunohistochemistry using either Ventana SP142 or Dako 22C3 assays, in accordance with approved clinical indications. PD-L1 positivity was defined based on current clinical guidelines, and all evaluations were performed by pathologists at the study institution.

Ethics approval and consent to participate. All procedures were performed in accordance with the ethical standards of the Ethics Committee of Saitama Medical University International Medical Center (approval no.: 19-224) and/or the national research committee, as well as the 1964 Helsinki Declaration and its later amendments and comparable ethical standards. The requirement for written informed consent was waived, given the study's retrospective nature.

Treatment procedures. Patients received ICI-based therapy comprising either atezolizumab or pembrolizumab, administered per the approved dosing schedules and institutional practice at the time of treatment. ICIs were administered in combination with chemotherapy, as per standard clinical indications. Treatment was continued until disease progression, unacceptable toxicity, patient refusal, or death. Dose modification, treatment interruption, or discontinuation was performed at the treating physician's discretion based on clinical judgment and institutional guidelines.

Clinicopathological assessment. Clinicopathological characteristics were retrospectively extracted from electronic medical records. Baseline clinicopathological variables collected at the initiation of ICI therapy included age, Eastern Cooperative Oncology Group performance status (ECOG PS), disease status at metastatic diagnosis (*de novo* or recurrent disease), treatment line, prior exposure to taxane-based chemotherapy, metastatic sites (liver, lung or pleura, brain, bone, and lymph nodes), and the number of metastatic sites. The type of ICI administered (atezolizumab or pembrolizumab) was also recorded.

Assessment of peripheral immune markers. Baseline peripheral blood samples were obtained at the initiation of ICI therapy. Absolute neutrophil count and ALC were measured using an automated hematology analyzer at the study institution. NLR was calculated by dividing the absolute neutrophil count by the ALC. Based on previous studies, patients were stratified into high and low groups using predefined cutoff values, which were not modified for the present dataset (11). ALC was categorized as low (<1,500/μl) or high (≥1,500/μl), and NLR was categorized as low (<3.0) or high (≥3.0) (11, 12, 22, 23).

Clinical outcomes. Primary clinical outcome data including for TTF and OS were retrospectively extracted from electronic medical records. TTF was defined as the interval from the initiation of ICI therapy to treatment discontinuation for any reason, including disease progression, adverse events, or death. OS was defined as the interval from the initiation of ICI therapy to all-cause death or the date of last follow-up.

Statistical analysis. Continuous variables are presented as medians with ranges, and categorical variables as numbers and percentages. Survival curves for TTF and OS were estimated using the Kaplan–Meier method, and differences between groups were compared using the log-rank test. Associations between baseline clinicopathological factors, peripheral immune markers, and clinical outcomes were evaluated using Cox proportional hazards regression model. Variables showing statistical significance in univariate analysis or considered clinically relevant were included in multivariate analysis. All statistical tests were two-sided, and $p<0.05$ was considered statistically significant. Statistical analyses were performed using JMP Student Edition 19 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics. A total of 43 patients with advanced TNBC who received ICI-combined chemotherapy were included in the analysis. The median TTF was 70 d [95% confidence interval (CI)=49–154], and the median OS was 570 d (95%CI=157–796). Baseline clinicopathological characteristics are summarized in Table I. The median age was 57 years (range=38–79 years), and most patients had an ECOG PS of 0 or 1 at treatment initiation. Fifteen patients (34.9%) had *de novo* metastatic disease, while 28 patients (65.1%) had recurrent disease. ICI-combined chemotherapy was administered as first-line treatment in 27 patients (62.8%) and as second-line or later treatment in 16 patients (37.2%). Twenty-one patients (48.8%) received atezolizumab and 22 patients (51.2%) received pembrolizumab. Prior exposure to taxane-based chemotherapy was observed in 28 patients (65.1%). We observed metastatic involvement of the liver in 17 patients (39.5%), lung or pleura in 22 patients (51.2%),

Table I. *Patient characteristics (n=43).*

Variables	n (%)
Median age, years (range)	57 (38-79)
Age, years	
<50	11 (25.6)
≥50	32 (74.4)
ECOG PS	
0	25 (58.1)
1	12 (27.9)
2	3 (7.0)
Unknown	3 (7.0)
Diagnosis	
De novo	15 (34.9)
Recurrence	28 (65.1)
Treatment line	
1st	27 (62.8)
≥2nd	16 (37.2)
ICI	
Atezolizumab	21 (48.8)
Pembrolizumab	22 (51.2)
Prior taxane treatment	
No	15 (34.9)
Yes	28 (65.1)
Liver metastases	
Negative	26 (60.5)
Positive	17 (39.5)
Lung or pleural metastases	
Negative	21 (48.8)
Positive	22 (51.2)
Brain metastases	
Negative	38 (88.4)
Positive	5 (11.6)
Bone metastases	
Negative	25 (58.1)
Positive	18 (41.9)
Lymph node metastases	
Negative	9 (34.9)
Positive	34 (65.1)
Number of metastatic sites	
0-2	28 (65.1)
≥3	15 (34.9)
Absolute lymphocyte count	
Low (<1,500)	32 (74.4)
High (≥1,500)	11 (25.6)
Neutrophil-to-lymphocyte ratio	
Low (<3)	17 (39.5)
High (≥3)	26 (60.5)

ECOG PS: Eastern Cooperative Oncology Group performance status; ICI: immune checkpoint inhibitor.

brain in five patients (11.6%), bone in 18 patients (41.9%), and lymph nodes in 34 patients (65.1%). Fifteen patients (34.9%) had three or more metastatic sites. Regarding baseline peripheral immune markers, low ALC (<1,500/μl) was observed in 32 patients (74.4%) and high NLR (≥3.0) in 26 patients (60.5%).

Association between baseline immune markers and TTF. Kaplan–Meier analysis demonstrated that patients with high baseline NLR experienced significantly shorter TTF compared with those with low baseline NLR (Figure 1A). Similarly, patients with low baseline ALC showed significantly shorter TTF than those with high baseline ALC (Figure 1B). In the univariate Cox proportional hazards analysis, high baseline NLR and low baseline ALC were significantly associated with shorter TTF (Table II). In addition, poorer ECOG PS showed a significant association with shorter TTF. The presence of liver metastases, bone metastases, and increased metastatic sites showed weak association with shorter TTF, although these associations were not statistically significant. Age, treatment line, type of ICI administered, and prior taxane treatment were not significantly associated with TTF. In the multivariate Cox proportional hazards analysis incorporating clinically relevant variables, no baseline clinicopathological or immune parameters were identified as independent prognostic factors for TTF (Table II).

Association between baseline immune markers and OS. Patients with high baseline NLR had significantly inferior OS compared with those with low baseline NLR (Figure 1C). In contrast, baseline ALC was not significantly associated with OS in the Kaplan–Meier analysis (Figure 1D). In the univariate Cox proportional hazards analysis, high baseline NLR was significantly associated with shorter OS (Table III). In addition, ECOG PS and the number of metastatic sites showed significant associations with OS. Age and the presence of liver metastases showed weak associations with shorter OS, although these associations did not reach statistical significance. Baseline ALC was not associated with OS, and treatment line, type of ICI administered, and prior taxane exposure did not demonstrate significant prognostic value. In the multivariate Cox proportional hazards analysis adjusting for relevant clinical variables, high baseline NLR remained the only independent

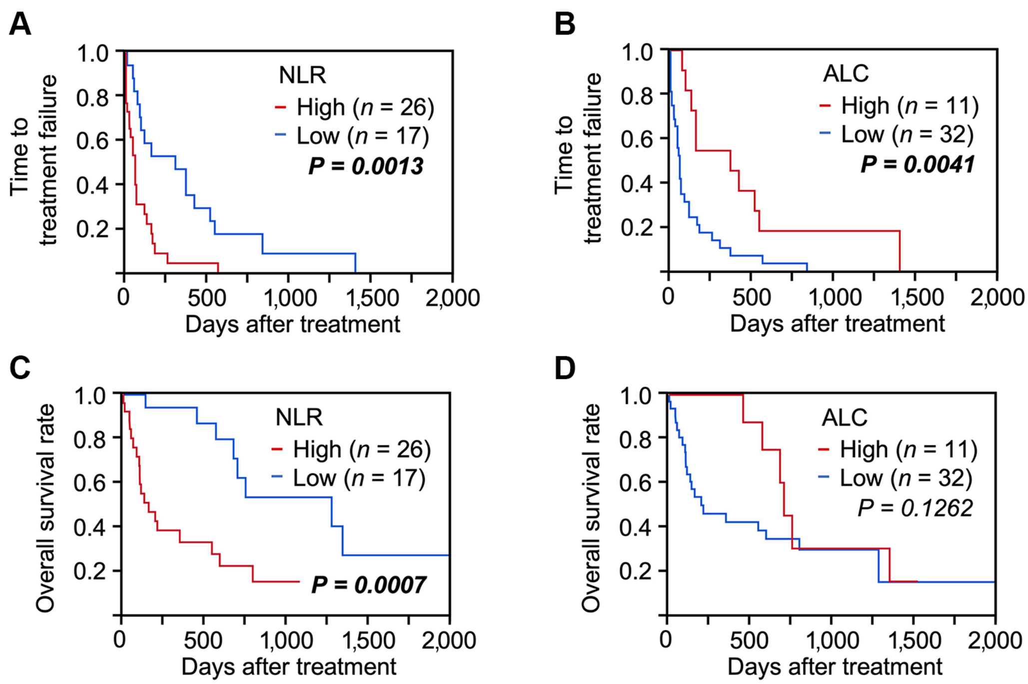

Figure 1. *Association between baseline peripheral immune markers and clinical outcomes in patients with advanced triple-negative breast cancer treated with immune checkpoint inhibitors. Kaplan–Meier curves of the time-to-treatment failure (TTF) and overall survival (OS) stratified by baseline neutrophil-to-lymphocyte ratio (NLR) and absolute lymphocyte count (ALC). (A) TTF according to baseline NLR (high vs. low). (B) TTF according to baseline ALC (low vs. high). (C) OS according to baseline NLR (high vs. low). (D) OS according to baseline ALC (low vs. high). Patients were classified into high and low groups using prespecified cutoff values (NLR ≥3.0 vs. <3.0; ALC <1,500/μl vs. ≥1,500/μl). p-Values were calculated using the log-rank test.*

prognostic factor for OS (Table III). The number of metastatic sites showed a weak association with OS with no statistical significance in the multivariate model.

Discussion

In this retrospective study of patients with PD-L1-positive advanced TNBC treated with ICIs, baseline peripheral immune markers showed distinct prognostic roles. To our knowledge, this represents one of the largest analyses on the association between baseline peripheral immune status and clinical outcomes in this cohort. Elevated baseline NLR was consistently associated with shorter TTF and OS, and remained the only independent prognostic factor for OS in the multivariate analysis. In contrast, low baseline ALC was associated with shorter TTF in the univariate analysis but not independently associated with OS. These findings underscore the importance of host systemic immune status in determining the clinical outcomes of ICI therapy in PD-L1-positive advanced TNBC.

NLR is a widely recognized prognostic marker across various cancer types and treatment modalities, including cytotoxic chemotherapy, molecularly targeted therapy, and immunotherapy (11–15, 17, 24, 25). A recent meta-analysis further confirmed that elevated NLR was significantly associated with inferior overall and progression-free survival across multiple malignancies, including breast cancer, with particularly strong prognostic effects observed in patients receiving immunotherapy (26). Accordingly, the prognostic significance of NLR in the present study should be interpreted with appropriate caution and not be regarded as treatment-specific or predictive of ICI benefits. Rather, NLR reflects the global balance between

Table II. *Univariate and multivariate analyses of clinicopathological parameters and time-to-treatment failure.*

Variables	Univariate	Multivariate		
	p-Value	HR	95%CI	*p*-Value
Time-to-treatment failure				
Age (≥50 *vs.* <50 years old)	0.2127			
ECOG PS (Others *vs.* 0)	**0.0088**	1.25	0.54-2.89	0.6073
Diagnosis (Recurrence *vs.* *De novo*)	0.4646			
Treatment line (≥2 *vs.* 1)	0.3991			
ICI (Atezolizumab *vs.* Pembrolizumab)	0.6215			
Prior taxane treatment (Yes *vs.* No)	0.9170			
Liver metastases (+/–)	0.0675			
Lung or pleural metastases (+/–)	0.6023			
Brain metastases (+/–)	0.2893			
Bone metastases (+/–)	0.0923			
Lymph node metastases (+/–)	0.2496			
Number of metastatic sites (≥3 *vs.* 0-2)	0.0769			
ALC (Low *vs.* High)	**0.0070**	1.97	0.83-4.66	0.1230
NLR (High *vs.* Low)	**0.0025**	1.88	0.74-4.77	0.1866

ECOG PS: Eastern Cooperative Oncology Group performance status; ICI: immune checkpoint inhibitor; ALC: absolute lymphocyte count; NLR: neutrophil-to-lymphocyte ratio. Statistically significant *p*-values are shown in bold.

Table III. *Univariate and multivariate analyses of clinicopathological parameters and overall survival.*

Variables	Univariate	Multivariate		
	p-Value	HR	95%CI	*p*-Value
Time-to-treatment failure				
Age (≥50 *vs.* <50 years old)	0.0708			
ECOG PS (Others *vs.* 0)	**0.0034**	1.49	0.55-4.02	0.4349
Diagnosis (Recurrence *vs.* *De novo*)	0.5298			
Treatment line (≥2 *vs.* 1)	0.6007			
ICI (Atezolizumab *vs.* Pembrolizumab)	0.5249			
Prior taxane treatment (Yes *vs.* No)	0.8773			
Liver metastases (+/–)	0.0508			
Lung or pleural metastases (+/–)	0.1427			
Brain metastases (+/–)	0.1020			
Bone metastases (+/–)	**0.0464**	1.51	0.51-4.46	0.4609
Lymph node metastases (+/–)	0.4894			
Number of metastatic sites (≥3 *vs.* 0-2)	**0.0347**	2.74	0.93-8.06	0.0672
ALC (Low *vs.* High)	0.1561			
NLR (High *vs.* Low)	**0.0012**	4.71	1.42-15.6	**0.0113**

ECOG PS: Eastern Cooperative Oncology Group performance status; ICI: immune checkpoint inhibitor; ALC: absolute lymphocyte count; NLR: neutrophil-to-lymphocyte ratio. Statistically significant *p*-values are shown in bold.

tumor-promoting systemic inflammation and antitumor immune competence, which influences patient outcomes irrespective of treatment type (12).

Despite this nonspecific nature, the independent prognostic impact of baseline NLR was demonstrated within a uniformly PD-L1-positive advanced TNBC cohort receiving ICIs. This cohort represents pathophysiologically eligible patients for immunotherapy, in whom tumor-intrinsic immune evasion mechanisms, as reflected by PD-L1 expression, are accounted for. In the context of immunotherapy, a low NLR prior to nivolumab treatment in esophageal cancer was significantly associated with prolonged OS and progression-free survival, independent of ECOG PS (27). In addition, in advanced breast cancer including non-TNBC subtypes, the Glasgow Prognostic Score (GPS), another host-related inflammatory marker, rather than NLR, was shown to independently predict OS (28). Collectively, these findings support the concept that host-related inflammatory biomarkers, including NLR, play an important prognostic role.

The biological relevance of NLR as a prognostic marker is supported by its composite nature (25). Elevated neutrophil counts are associated with the secretion of pro-inflammatory cytokines, angiogenic factors, and immunosuppressive mediators that facilitate tumor progression, whereas relative lymphopenia reflects impaired immune surveillance and reduced capacity for sustaining effective antitumor immune responses (29–32). Therefore, in immune checkpoint blockade, a high baseline NLR may represent a host environment less capable of translating immune activation into durable tumor control, ultimately resulting in inferior survival outcomes (32). In addition, recent studies have also examined the relationship between NLR and the tumor microenvironment in TNBC. NLR was not significantly correlated with overall tumor-infiltrating lymphocytes (TILs), although a moderate association with the CD8/FoxP3 ratio has been reported (33). These findings suggest that NLR and TILs capture distinct but complementary dimensions of host antitumor immunity.

Although both elevated NLR and low ALC were associated with shorter TTF in univariate analyses, no independent prognostic factors were identified in multivariate analyses. Rather than indicating a lack of biological relevance, this reflects the inherent characteristics of real-world data, in which treatment discontinuation is frequently driven by complex clinical and practical considerations rather than tumor biology or host immune status alone (34, 35). In addition, real-world cohorts inevitably include patients with intrinsically aggressive disease biology and poor prognosis who would be underrepresented or excluded in clinical trials. Such patients may experience rapid disease progression or early clinical deterioration, leading to treatment discontinuation regardless of the specific therapeutic approach. The inclusion of these patients may dilute the association between baseline biomarkers and TTF in real-world analyses.

In contrast to TTF, OS represents a more robust endpoint reflecting the cumulative impact of disease biology and host immune status. In this context, the independent association of baseline NLR with OS supports its role as a marker of long-term prognosis rather than short-term treatment feasibility. Baseline ALC demonstrated a limited prognostic role, while low ALC was associated with shorter TTF which was not correlated with OS. This suggests that ALC may primarily reflect immune reserve and vulnerability to early treatment discontinuation rather than long-term survival prognosis in PD-L1-positive advanced TNBC.

Study limitations. The retrospective single-center design and limited sample size may restrict generalizability and introduce residual confounding. Peripheral immune markers were assessed only at baseline, neglecting the dynamic changes during treatment. Detailed data regarding immune-related adverse events and subsequent therapies were limited, which may influence the TTF and OS outcomes. Finally, because this study included only patients with PD-L1-positive advanced TNBC treated with an ICI plus chemotherapy, the prognostic value of the findings should be interpreted within ICI-treated cohorts and not considered predictive of ICI-associated benefits compared with non-ICI therapies.

In conclusion, this real-world study demonstrated that baseline NLR is a significant independent prognostic factor for OS in patients with PD-L1-positive advanced TNBC treated with an ICI plus chemotherapy. While baseline ALC was associated with treatment durability, it did not independently predict long-term survival. These findings emphasize the complementary roles of tumor- and host-related factors in shaping prognosis in ICI-treated TNBC. Prospective validation in larger cohorts is warranted.

Conflicts of Interest

The Authors declare that they have no competing interests in relation to this study.

Authors' Contributions

AF contributed to study conception and design, data analysis, and manuscript drafting. YI, KM, EM, WI, TK, ANa, AS, ANu, AA, HS, HY, MO, HI, AO, and TS contributed to data acquisition and interpretation. KM, HI, TH, AO, and TS critically revised the manuscript. All Authors approved the final version of the manuscript.

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Artificial Intelligence (AI) Disclosure

During the preparation of this manuscript, a large language model (ChatGPT, OpenAI) was used solely for language editing and stylistic improvements in select paragraphs. No sections involving the generation, analysis, or interpretation of research data were produced by generative AI. All scientific content was created and verified by the authors. Furthermore, no figures or visual data were generated or modified using generative AI or machine learning–based image enhancement tools.

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