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Association of Inflammatory Markers with Treatment Response in Immune Checkpoint Inhibitors

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ABSTRACT Objective: The neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) are markers of systemic inflammation. NLR and PLR can predict the treatment outcomes of metastatic cancer for patients treated with immune checkpoint inhibitors (ICI). In this study, we investigated whether NLR or PLR is a better predictor of survival outcomes. **Material and Methods:** Between February 2016 and November 2021, 106 patients who had metastatic disease arising from different types of solid tumors treated with ICIs were retrospectively evaluated. The cut-off values of the NLR and PLR were determined by performing ROC curve analysis. Cox regression analysis was performed to evaluate the predictive role of NLR and PLR in progression-free survival (PFS). **Results:** The median age of patients was 62 years (range: 19-84 years), and 60.4% of patients were male. The cut-off values for NLR and PLR were 4.06 and 192.59, respectively. The patients were divided into two groups (low/high) according to the cut-off values. The results of the univariate analysis showed that PFS was significantly longer in the group with low NLR and PLR. High NLR [hazard ratio: 1.95, 95% confidence interval (CI): 1.20-3.15, p=0.006] and ≥2 Eastern Cooperative Oncology Group performance status (hazard ratio: 2.62, 95% CI: 1.61-4.26, p<0.001) were independent negative predictive factors for PFS in the multivariate Cox regression analysis. **Conclusion:** We found that PFS and disease control rate were significantly better in patients with low NLR who were administered immunotherapy. NLR may be a better predictive marker than PLR in cancer patients administered immunotherapy.

Keywords: Immunotherapy; neutrophil-to-lymphocyte ratio; platelet-to-lymphocyte ratio; survival

To understand the link between cancer and the immune system, new therapeutic agents have been developed, targeting specific proteins involved in the immune response, such as cytotoxic T-lymphocyte-associated protein-4 (e.g., ipilimumab) and programmed death (PD)-1 receptors (e.g., nivolumab and pembrolizumab). These therapeutic agents, known as immune checkpoint inhibitors (ICI), have transformed the treatment environment for different types of cancer by providing long-term disease control and increasing survival rates.[1] Although new immunotherapeutic techniques have been introduced, widely accepted predictive and prognostic markers for patient selection in ICI treatment are lacking. Some studies have investigated the potential of PD-L1 expression and tumor mutation burden (TMB) as biomarkers. However, these markers have several limitations, including high costs, inconsistent assay results, the effect of tumor heterogeneity on the expression of PD-L1.[2] the requirement of large tissue samples, invasive biopsy procedures, and no standardized TMB evaluation method.[3] Many researchers now acknowledge the significance of cancer-associated inflammatory responses, including alterations in myelopoiesis and local and systemic inflammation. These inflammatory responses strongly influence tumor development, disease progression, and patient prognosis. The presence of immune cells, particularly cytotoxic CD8-T cells, in the tumor microenvironment is associated with positive outcomes. In con-

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trast, certain types of immune cells like neutrophils, M2 polarized macrophages, and FOXP3-positive regulatory T cells are associated with tumor progression and poor prognosis.[4-6] Before immunotherapy, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) (used as indicators of systemic inflammation) were identified as robust prognostic markers associated with poorer overall survival (OS) in various types of tumors.[7,8] In this retrospective single-center trial, we compared NLR and PLR to determine which marker can better predict the response to immunotherapy.

MATERIAL AND METHODS

A retrospective analysis was conducted using data collected from 110 patients who were treated with ICIs for various types of solid tumors between February 2016 and November 2021. The inclusion criteria for the study were as follows: patients who were 18 years or older, those with histologically confirmed solid tumors with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤3, and patients with measurable unresectable metastatic disease according to the Immune Response Evaluation Criteria in Solid Tumors (iRECIST). Patients with a second primary cancer or those who did not meet the inclusion criteria were excluded from the study. Patient data on parameters including age, sex, comorbidity, smoking status, type of diagnosis, type of ICIs administered, ECOG PS, number of metastatic sites, and hematological and biochemical parameters before treatment with ICIs were collected from their respective files. We could not perform toxicity analysis because of insufficient data. Treatment response was evaluated every 12 weeks using computed tomography or positron emission tomography/computed tomography scans following iRECIST. NLR and PLR were calculated using blood samples collected before ICIs were administered. NLR was determined by dividing the total neutrophil count by the total lymphocyte count, while PLR was calculated by dividing the total platelet count by the total lymphocyte count. The ROC curve analysis was conducted to determine the optimal cut-off values for NLR and PLR. To assess the effect on survival, nine variables were selected for the analysis. These variables were categorized as follows: median age (≤62 years or >62 years), sex (female or male), comorbidity status (yes or no), ECOG PS (0-1 or ≥2), type of tumor [malignant melanoma/renal cell cancer (RCC)/lung cancer/others], line of ICI treatment (first/second/≥third line), number of metastatic sites (1 or ≥2), NLR group (low or high), and PLR group (low or high).

ETHICS STATEMENT

The study was approved by the institutional ethics committee, following the principles in the latest version of the Declaration of Helsinki. As the study was a retrospective one, obtaining informed consent from the patients was not feasible. The Ethics Committee of Ankara City Hospital reviewed the study and confirmed that informed consent was not required for this study. The study design was reviewed and approved by Ethics Committee No. 1 of Ankara City Hospital, with the approval number E1-2289-2022/date: January 12, 2022.

STATISTICAL ANALYSIS

All statistical analyses were conducted using SPSS Version 22.0 for Windows (SPSS Inc., Chicago, IL, USA). The differences in continuous variables between groups were determined by the Mann-Whitney U test, whereas the differences in categorical variables were analyzed by Pearson's chi-square test or Fisher's test. Survival analysis was performed using the Kaplan-Meier method, and the Log-rank test was used for comparisons. Survival time was reported with a 95% confidence interval (CI). All differences were considered statistically significant at $p<0.05$. Significant factors identified in the univariate analysis were further assessed in the multivariate analysis using the Cox regression test. OS was defined as the duration from the initiation of ICI treatment till either the date of death due to any cause or the last follow-up date for surviving patients. progression-free survival (PFS) was defined as the time from the initiation of ICI treatment till either disease progression or death due to any cause.

RESULTS

We included 106 patients, with a median age of 62 years (range: 19-84 years). Most participants were male (60.4%). The most common type of tumor

among the patients was RCC (37.7%), and the predominant immunotherapeutic agent administered was nivolumab (84%). A significant proportion of patients (85.8%) received ICIs as second-line treatment or subsequent therapy. Before starting ICI treatment, multiple metastases were detected in 73.6% of participants. Information on the baseline demographic and disease characteristics of the patients is presented in Table 1. ROC curve analysis was conducted to determine the optimal cut-off values for NLR and PLR. The area under the curve (AUC) for NLR was 0.62 (95% CI: 0.50-0.73; p=0.04), and the best cut-off value was found to be 4.06; the sensitivity and specificity were 44.4% and 79.4%, respectively. The AUC for PLR was 0.64 (95% CI: 0.52-0.76; p=0.01), and the best cut-off value was 192.59; the sensitivity and specificity were 61.1% and 70.6%, respectively. Based on these values, the patients were categorized into two groups: low or high NLR and PLR. The characteristics of the patients in these groups are summarized in Table 2. The median follow-up duration for the patients was 23.0 months (range: 13.5-32.5 months). In the univariate analysis, factors such as ECOG PS (p<0.001), NLR (p<0.001), PLR (p=0.002), age (p=0.20), sex (p=0.29), comorbidity (p=0.63), type of tumor (p=0.16), line of ICI treatment (p=0.99), and the number of metastatic sites (p=0.48) were evaluated. NLR, PLR, and ECOG PS were statistically significant predictive factors for PFS in the univariate analysis. Patients with low NLR showed a higher disease control rate (DCR). The treatment responses to ICIs are presented in Table 3. A multivariate analysis was conducted using the variables that were significant in the univariate analysis; the results showed that NLR (hazard ratio: 1.95, 95% CI: 1.20-3.15, p=0.006) and ECOG PS (0-1/≥2) (hazard ratio: 2.62, 95% CI: 1.61-4.26, p<0.001) can be used as independent predictive factors for survival (Table 4). Patients with an ECOG PS of 0-1 showed a significantly longer median PFS than those with an ECOG PS of ≥2 (8.8 vs. 2.5 months, p<0.001). The results of the Kaplan-Meier survival analysis based on the NLR groups showed a median PFS of 8.6 months in the NLR-low group and 2.4 months in the NLR-high group. The differences between these groups were statistically significant (p<0.001) (Figure 1). Patients with a low NLR had a median OS of 24.6 months (95% CI: 3.5-45.7), while those with a high NLR had a median OS of 3.2 months (95% CI: 1.9-4.6) (p<0.001).

TABLE 1: Clinical and treatment characteristics of the patients.

		n (%)
Age* (years)		62 (19-84)
Gender	Female	42 (39.6)
	Male	64 (60.4)
Comorbidity	No	47 (44.3)
	Single	21 (19.8)
	Multiple	38 (35.8)
Smoking	No	55 (51.9)
	Yes	35 (33.0)
	Ex-smoker	16 (15.1)
Type of tumor	Malignant melanoma	25 (23.6)
	Renal cell cancer	40 (37.7)
	Lung	18 (17.0)
	Lymphoma	4 (3.8)
	Endometrium	2 (1.9)
	Hepatocellular carcinoma	3 (2.8)
	Bladder	4 (3.8)
	Head-neck	2 (1.9)
	Stomach	3 (2.8)
	Neuroendocrine carcinoma	1 (0.9)
	Thymus carcinoma	1 (0.9)
	Malignant mesothelioma	1 (0.9)
	Pancreas	1 (0.9)
	Skin-Merkel cell	1 (0.9)
Line of ICIs treatment	First-line	15 (14.2)
	Second-line	57 (53.8)
	Third-line	27 (25.5)
	Fourth-line	2 (1.9)
	Fifth-line	4 (3.8)
	Sixth-line	1 (0.9)
ICIs treatment type	Nivolumab	89 (84.0)
	Pembrolizumab	3 (2.8)
	Atezolizumab	13 (12.3)
	Ipilimumab	1 (0.9)
ICIs pre-treatment ECOG	0-1	68 (64.2)
	≥2	38 (35.8)
ICIs number of metastatic	Single	28 (26.4)
Sites pre-treatment	Multiple	78 (73.6)

Clinical and treatment characteristics of the patients.
*Presented with median instead of n, min-max instead of %; †ICIs: Immune checkpoint inhibitors.

DISCUSSION

In this study, we assessed the predictive value of pretreatment NLR and PLR in 106 cancer patients who were treated using ICIs. We found that patients with

TABLE 2: Patient groups according to systemic inflammation markers (low or high).

	NLR groups			PLR groups		
	≤4.06	>4.06		≤192.59	>192.59	
	n (%)	n (%)	p value	n (%)	n (%)	p value
Gender			0.52*			0.52*
Female	25 (37.3)	17 (43.6)		19 (36.5)	23 (42.6)	
Male	42 (62.7)	22 (56.4)		33 (63.5)	31 (57.4)	
Age groups			0.08*			0.051*
≤62	39 (58.2)	16 (41.0)		32 (61.5)	23 (42.6)	
>62	28 (41.8)	23 (59.0)		20 (38.5)	31 (57.4)	
ECOG groups before ICIs treatment			0.03*			0.002*
0-1	48 (71.6)	20 (51.3)		41 (78.8)	27 (50.0)	
≥2	19 (28.4)	19 (48.7)		11 (21.2)	27 (50.0)	
Tumor groups			0.70*			0.74*
Malignant melanoma	15 (22.4)	10 (25.6)		14 (26.9)	11 (20.4)	
Renal cell cancer	28 (41.8)	12 (30.8)		20 (38.5)	20 (37.0)	
Lung	10 (14.9)	8 (20.5)		7 (13.5)	11 (20.4)	
Others	14 (20.9)	9 (23.1)		11 (21.2)	12 (22.2)	
Number of metastatic sites before ICIs treatment			0.55*			0.57*
Single	19 (28.4)	9 (23.1)		15 (28.8)	13 (24.1)	
Multiple	48 (71.6)	30 (76.9)		37 (71.2)	41 (75.9)	
Line of ICIs treatment			0.94*			0.09*
First-line	10 (14.9)	5 (12.8)		11 (21.2)	4 (7.4)	
Second-line	36 (53.7)	21 (53.8)		24 (46.2)	33 (61.1)	
≥Third-line	21 (31.3)	13 (33.3)		17 (32.7)	17 (31.5)	
ICIs treatment type			0.02**			>0.999**
Nivolumab	60 (89.6)	29 (74.4)		44 (84.6)	45 (83.3)	
Pembrolizumab	0 (0.0)	3 (7.7)		1 (1.9)	2 (3.7)	
Atezolizumab	6 (9.0)	7 (17.9)		6 (11.5)	7 (13.0)	
Ipilimumab	1 (1.5)	0 (0.0)		1 (1.9)	0 (0.0)	

Patient groups are categorized according to systemic inflammation markers (low and high).
*Pearson's Chi-Square; **Fisher's Exact Test; ***ICIs: Immune checkpoint inhibitors; †ECOG: Eastern Cooperative Oncology Group.

TABLE 3: ICIs treatment responses of all patients according to NLR and PLR groups.

	NLR groups			PLR groups		
	≤4.06	>4.06		≤192.59	>192.59	
	n (%)	n (%)	p value‡	n (%)	n (%)	p value‡
Best response			0.007			0.21
ICIs treatment						
CR	2 (3.0)	0 (0.0)		2 (4.2)	0 (0.0)	
PR	19 (28.4)	5 (12.8)		12 (23.1)	12 (22.2)	
SD	28 (41.8)	11 (28.2)		22 (42.3)	17 (31.5)	
PD	18 (26.9)	23 (59.0)		16 (30.8)	25 (46.3)	
DCR	49 (73.1)	16 (41.0)	0.001	36 (69.2)	29 (53.7)	0.10

Responses to ICI treatment of all patients according to the NLR and PLR groups.†ICIs: Immune checkpoint inhibitors; *CR: Complete response; **PR: Partial response; ***SD: Stable disease; ****PD: Progressive disease; *****DCR (Disease control rate; CR+PR+SD); ‡Fisher's Exact Test

low NLR had better outcomes for the objective response rate, DCR, and PFS when treated with ICIs. NLR was a significant factor in the multivariate analysis and was found to be a better predictive marker

TABLE 4: Univariate and multivariate analysis for progression-free survival.

	Univariate		Multivariate
	p value	HR 95% CI	p value
ECOG groups before ICIs treatment	<0.001		<0.001
0-1		1	
≥2		2.62 (1.61-4.26)	
NLR groups	<0.001		0.006
Low		1	
High		1.95 (1.20-3.15)	
PLR groups	0.002		0.79
Low		1	
High		1.08 (0.58-2.01)	
Age groups (≤62/>62)	0.20		
Gender (female/male)	0.29		
Comorbidity (yes/no)	0.63		
Tumor groups	0.16		
Malignant melanoma			
Renal cell cancer			
Lung			
Others			
Number of metastatic sites before ICIs treatment (single/multiple)	0.48		
Line of ICIs treatment groups	0.99		
First-line			
Second-line			
≥Third-line			

Univariate and multivariate analysis for evaluating progression-free survival.
*HR: Hazard ratio; **CI: Confidence interval; ***ECOG: Eastern Cooperative Oncology Group; †ICIs: Immune checkpoint inhibitors.

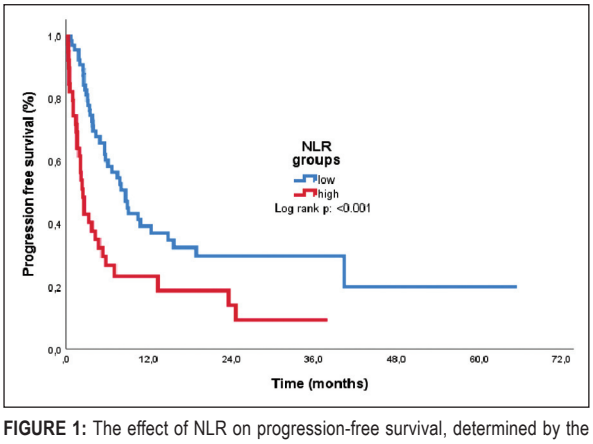

FIGURE 1: The effect of NLR on progression-free survival, determined by the Kaplan-Meier survival analysis.

than PLR. The introduction of ICIs has resulted in substantial advancements in survival rates and quality of life of individuals diagnosed with cancer. Over time, preference for ICIs has increased in the treatment of different types of cancer, such as metastatic non-small cell lung cancer (NSCLC), malignant melanoma, and metastatic RCC. These therapeutic agents now play an important role in the management of specific types of cancer.[9] In our study, ICIs were predominantly used as a treatment option for metastatic renal cell carcinoma, malignant melanoma, and lung cancer. However, no biomarker can reliably predict the response to ICI treatment, and most studies have focused on TMB and molecular markers. However, certain clinical features, such as age, comorbidity, ECOG PS, NLR, PLR, and others, may guide treatment decisions, although their precise role in ICI treatment remains unclear. In a study involving 538 patients with malignant melanoma who received immune checkpoint blockade therapy, older patients (above 60 years) were found to respond better to anti-PD-1 therapy and show better survival outcomes compared to younger patients (below 60 years). This finding suggested that the underlying mechanism might be associated with increased T-regulatory (T-reg) cells and decreased CD8+ T cells in younger patients.[10] In our study, similar PFS rates were recorded between different age groups (≤62 years and >62 years) (p=0.20). This disparity between the studies occurred probably because the effect of age on treatment response and survival outcomes can be influenced by various factors, including the specific type of cancer and the treatment protocol used. High TMB is associated with an increase in immunogenicity, indicating that tumors with more mutations may exhibit higher responsiveness to ICIs. This relationship supports the notion that TMB can act as a biomarker for predicting treatment response to ICIs. Women exhibit stronger immunosuppressive signals than men. This sex-based difference in immune response may contribute to the variation in treatment responses between male and female patients. In some cases, male patients treated with ICIs showed better response rates than female patients.[11] In our study, no significant difference was recorded in survival between male and female patients (p=0.29). This finding suggested that gender may not be a strong predictor of treatment outcomes in the population we examined. In another study on 66 patients with NSCLC who were administered anti-

PD-1 therapy, comorbidity burden was found to predict survival; patients with one or more comorbidities had poorer PFS than those without any comorbidity.[12] Their findings suggested that comorbidities can influence treatment response and prognosis in patients administered anti-PD-1 therapy for NSCLC. In our study, no significant differences were recorded in survival between patients with and without comorbidities (p=0.63). Many studies have investigated the relationship between the number of basal metastatic sites and survival before ICI treatment. In a retrospective study, 391 patients were diagnosed with different types of metastatic cancer and received immunotherapy; in that study, the number of metastatic sites was associated with poorer PFS in the univariate analysis.[13] In our study, although the median PFS (8.8 months/5.2 months; p=0.48, respectively) and median OS (17.1 months/11.2 months; p=0.73, respectively) were different between the groups, according to the number of metastatic sites (single/multiple) in the univariate analysis, the differences were not statistically significant. A meta-analysis of 18 studies conducted with 11,354 patients with various malignancies treated with ICIs found no difference in OS between patients with ECOG 0 and ECOG 1-2. Thus, the researchers concluded that ECOG PS should not be used to determine the choice of immunotherapy; however, we included 11 patients with ECOG PS≥2. Although patients with ECOG PS≥2 are generally excluded from clinical studies, ICIs are widely used to treat these patients, given their toxicity profile.[14] Patients with ECOG≥2 treated with ICIs had a shorter median PFS (2.5 vs. 8.8 months; p<0.001) and OS (4.0 vs. 40.3 months; p<0.001) than the patients with ECOG 0-1. These findings were similar to the results of the Phase IIIb-IV, Checkmate 153 trial, where patients with ECOG 2 were found to have lower median OS (4.0 months) than the general population (9.1 months).[15] Some studies have suggested different cut-off values for NLR and PLR across various types of cancer.[16-18] In a study involving 156 patients with metastatic malignant melanoma and NSCLC treated with anti-PD-1 agents, a cut-off value of 200 was determined for PLR based on previous studies. In this study, we found that patients with a PLR≥200 had poorer PFS than those with a PLR below this threshold.[19] In another study of 220 patients with metastatic NSCLC treated with an anti-PD-1 agent, the cut-off value for PLR was found to be 441.8 using the outcome-based method to make differences in OS between PLR groups more apparent, and in the survival analysis performed, patients with PLR≥441.8 had poorer OS.[20] In this study, we used ROC curves to evaluate the PLR cut-off value (192.59). Although the median PFS was significantly longer in patients with PLR≤192.59 (7.7 months vs. 3.7 months; p=0.002), the difference in PFS was not significant when PLR groups were evaluated in the multivariate analysis (p=0.79). Several studies have highlighted the effect of NLR in predicting the survival of cancer patients treated with ICIs. High NLR, which serves as an indicator of systemic inflammation, was found to be associated with poorer clinical outcomes in different types of cancer treated with ICIs. This correlation was recorded in cancers such as RCC, NSCLC, and malignant melanoma.[21-23] Two meta-analyses that included 14 and 23 studies found that cancer patients with high baseline NLR treated with ICIs had poorer PFS; their findings were similar to those of our study.[24,25] Many studies have also proposed different cut-off values for NLR. In those studies, OS, DCR, and PFS were found to be significantly better in patients with a low NLR.[26-28] In this study, ROC curves were used to calculate the cut-off value for NLR, which was found to be 4.06. The median PFS was 8.6 months in the group with NLR≤4.06 and 2.4 months in the group with NLR>4.06; the difference in median PFS was statistically significant (p<0.001). Our findings confirmed that NLR and ECOG PS were significant predictors in the univariate and multivariate analyses. These results were similar to those of other studies that also emphasized the independent predictive value of NLR and ECOG PS.

This study had some limitations. The retrospective design of the study presented some inherent limitations, such as the potential for selection bias and the inability to establish causality. Additionally, as patients with different tumor types were included and the sample size was small, the generalizability of the findings to a broader population may not be possible. However, our findings were similar to those of other

studies, indicating that our results were reliable and relevant. Similar outcomes across different studies increase the confidence in the evidence supporting the predictive markers identified in our study.

CONCLUSION

In this study, we found that patients with a low NLR had better PFS after they were administered ICI treatment. The association between PLR and PFS was weaker than the association between NLR and PFS. These findings suggested that NLR might be a better predictive marker than PLR in cancer patients undergoing ICI treatment.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Murat Bardakçı, Öznur Bal;* ***Design:*** *Murat Bardakçı, Öznur Bal;* ***Control/Supervision:*** *Murat Bardakçı, Öznur Bal;* ***Data Collection and/or Processing:*** *Murat Bardakçı, Derya Demirtaş Esmer, Emre Hafızoğlu, Hilal Karakaş;* ***Analysis and/or Interpretation:*** *Murat Bardakçı, Öznur Bal, Fahriye Tuğba Köş;* ***Literature Review:*** *Murat Bardakçı, Öznur Bal;* ***Writing the Article:*** *Murat Bardakçı;* ***Critical Review:*** *Muhammed Bülent Akıncı, Bülent Yalçın;* ***References and Fundings:*** *Murat Bardakçı, Öznur Bal;* ***Materials:*** *Murat Bardakçı, Öznur Bal.*

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