

## Research Article

# The Role of Immune-Inflammation Biomarkers to Predict the Response of Nivolumab in Second Line Treatment of Advanced Stage Non-Small Cell Lung Cancer

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### Abstract

**Objectives:** In this study, the relationship between response to second-line nivolumab treatment in advanced non-small cell lung cancer (NSCLC) and systemic immune inflammation index (SII) was investigated.

**Methods:** One hundred and twenty-nine patients with advanced NSCLC who received nivolumab in second line between July 2018 and July 2023 were included. The optimum cutoff value for neutrophil/lymphocyte ratio (NLR), SII, platelet/lymphocyte ratio (PLR) and body mass index (BMI) was calculated. Progression free survival (PFS) and overall survival (OS) were evaluated. Univariate and multivariate analysis were performed for all parameters for prognostic evaluation.

**Results:** In univariate analysis, patients with low SII found longer PFS and OS (HR = 1.762 for PFS, 95% CI 1.053-2.949, p=0.031, for OS HR=1.433, 95% CI 1.011-2.031, p=0.043).

However, in multivariate analysis, no significance was found between low SII and OS (HR=1.614 for OS, 95%CI 0.984-2.648, p=0.058). No statistically significant relationship was found between NLR, PLR, BMI and Glasgow prognostic score (GPS) with OS and PFS. OS was found to be longer in patients with programmed cell death ligand 1 (PD-L1) of 1% and above and without liver metastasis (p=0.031 and p=0.040, respectively).

**Conclusion:** Low SII before nivolumab treatment was associated with long PFS. A significant correlation was found between PD-L1 of 1% and above and OS.

**Keywords:** Nivolumab, Non-small cell lung cancer, Systemic immune-inflammation index

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Lung cancer is the most prevalent form of malignancy worldwide and ranks first in cancer-related mortality.<sup>[1]</sup>

<sup>2</sup> The GLOBOCAN cancer statistics show that lung cancer

was diagnosed in 41,264 people in Turkey in 2020. A total of 37,070 people lost their lives due to this disease.<sup>[3]</sup> Non-small cell lung cancer (NSCLC) constitutes 90% of all lung

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cancers, and more than half of the patients are diagnosed when they are metastatic stage.<sup>[4]</sup> The first-line treatment option in cancer patients without targetable driver mutations is platinum-based chemotherapy. In cancer patients who progress under first-line chemotherapy, 2<sup>nd</sup>-line treatment options are limited, and the expected overall survival is below 12 months despite treatment.<sup>[5]</sup>

With the discovery of immunotherapy agents in recent years, paradigms have changed in second-line treatment in lung cancer. The interaction between programmed cell death ligand 1 (PDL1) on tumor cells and immune infiltrating cells and programmed cell death 1 (PD1) on T cells triggers the escape of tumor cells from the immune system.<sup>[6]</sup> As a human immunoglobulin G4 (IgG4) PD1 antibody, nivolumab disrupts the signaling between T cells and tumor cells and enhances antitumor immunity.<sup>[7]</sup> In two large randomized phase 3 trials in 2015, second-line nivolumab treatment in NSCLC showed superiority in comparison to standard docetaxel chemotherapy in terms of its overall survival (OS) rate, progression free survival (PFS) rate and overall response rate (ORR).<sup>[8, 9]</sup> However, nivolumab is an expensive treatment, and this agent creates a long-term response in only one in every five patients. The lack of a reliable marker to predict response to treatment also makes patient selection difficult. Although PDL1 level is considered as a potential marker, it is not sufficient alone due to intra-tumor heterogeneity, different test methods and differences in thresholds. Although high tumor mutation load is a promising method for predicting treatment response, it has not yet entered routine use in clinical practices.<sup>[10]</sup>

Inflammation has a significant part in tumor development and progression in many types of cancer.<sup>[11]</sup> Neutrophils, lymphocytes and platelets are hematologic inflammatory parameters and are frequently used in clinical practices to predict tumor prognosis.<sup>[12]</sup> Especially the neutrophil/lymphocyte ratio (NLR) and the platelet/lymphocyte ratio (PLR) are related with prognosis in many tumor types.<sup>[13-15]</sup> According to recent studies, high NLR and PLR values are related to poor clinical outcomes in response to immunotherapy.<sup>[16, 17]</sup> Systemic immune inflammation index (SII) is a scoring system obtained by multiplying neutrophil count and PLR and has been used in various tumor types to predict prognosis and treatment response.<sup>[18, 19]</sup> A study of metastatic renal cell tumor patients treated with nivolumab has shown that high SII levels were associated with low ORR and short OS.<sup>[20]</sup> Another inflammation-based marker used to predict treatment response and prognosis is the Glasgow-prognostic score (GPS). The GPS, which is grouped according to serum concentrations of C reactive protein (CRP) and albumin, is a potential predictor of prognosis for patients with NSCLC.<sup>[21, 22]</sup> The correlation between

GPS and the body-mass index (BMI) and the treatment efficacy of nivolumab were evaluated in a previous study.<sup>[23]</sup> In the study, patients with high BMI were observed to have longer OS, and no significant relationship was found between GPS and OS or PFS.

In conclusion, minimally invasive and reliable predictive markers are needed to predict response to nivolumab treatment, which may have high treatment cost, early progression in some patients and serious toxicity potential. The rationale of this study was to explore the role of SII, NLR, PLR, GPS and BMI in projecting treatment response in NSCLC patients undergoing nivolumab monotherapy in their 2<sup>nd</sup> line of treatment.

## Methods

We retrospectively analyzed 129 patients in total who had inoperable or metastatic NSCLC and developed progressive disease after first-line chemotherapy, had no targetable driver mutation or translocation, and received nivolumab in second-line treatment between July 2018 and July 2023. The version 8 of the tumor-node-metastasis (TNM) classification was used for staging. An intravenous nivolumab dose of 3 mg/kg every 14 days was provided until the disease progressed, or unacceptable toxic effect was observed. Patients, who were 18 years old or older, were pathologically diagnosed with NSCLC, progressed after first-line chemotherapy and started nivolumab treatment in the second line were included in the study. Being under 18 years of age, having pregnancy, using systemic steroids and having history of autoimmune disease were considered as exclusion criteria. All procedure of the study was granted by the University Ethics Committee (number: B.30.2.AYD.0.00.00-050.06.04/88). This study was performed in compliance with the International Conference of Harmonization Guidelines for Clinical Practice and by adhering to the principles put forth in the 1964 Declaration of Helsinki. Written informed consent was given by all included patients.

Before nivolumab treatment was started, the weight and height of the patients were recorded, and their BMI was calculated using the formula of "kilogram (kg) / height (m<sup>2</sup>)". The optimal BMI cutoff point was found to be 26.2 by ROC analysis according to OS (AUC: 0.439, sensitivity: 37.3%, specificity: 67.1%). All hematologic and biochemical laboratory parameters were measured within 1 week before the patients started nivolumab treatment. Their GPS scores were divided into 3 groups: CRP <1 mg/dl and albumin ≥3.5 mg/dl were considered for GPS score 0, only high CRP or only low albumin was considered for GPS score 1, albumin <3.5 mg/dl and CRP ≥1 mg/dl was considered for GPS

score 2. NLR was defined as neutrophil/lymphocyte, PLR as platelet/lymphocyte, and SII as platelet x neutrophil/lymphocyte. Cutoff points for all three inflammatory indices were found by ROC analysis according to OS.

The therapy response was evaluated by The Response Evaluation Criteria in Solid Tumors (RECIST, ver. 1.1.). Treatment response levels were categorized in 4 groups (complete remission (CR), partial remission (PR), stable disease (SD) and progressive disease (PD)). The duration between the initial of the nivolumab therapy and the death or disease progression was described as PFS. OS was defined as the duration between the date of initial diagnosis and last follow-up or the date of death. ORR and disease control rate (DCR) were determined to be the percentage of patients respectively who entered PR+CR and SD+PR+CR.

### Statistical Analysis

Statistical analysis was performed with IBM Statistical Package for the Social Sciences (SPSS ver. 20 for Mac) software. Normal distribution of data sets and variance homogeneity were evaluated with Kolmogorov-Smirnov test. All variables were stated as median and range. Cut-off values of laboratory results were found according to the maximum Youden index by ROC analysis. According to cut-off points, Kaplan Meier survival curves were drawn for OS and PFS. Univariate and multivariate analyses were done by Cox regression model, and hazard ratios were calculated with 95% confidence interval. Statistically significant value for p was accepted <0.05.

## Results

### Patients

Table 1 demonstrates the main characteristics of 129 patients. The mean age of all patients at diagnosis was 65 years (range 40-82), 109 (84.5%) of them were male and 20 (15.5%) were female. The ECOG performance score was 0-1 in 113 patients (87.6%) and 2 in 16 patients (12.4%). Histologic subtypes were squamous cell carcinoma in 55 patients (42.6%) and non-squamous cell carcinoma in 74 patients (57.4%). The number of patients who had never smoked was 23 (17.8%) and the number of patients who smoked or quit smoking was 106 (82.2%). The PDL1 expression was not evaluated in 56 (43.4%) patients, 26 (20.2%) patients had PDL1 score 0, 36 (27.9%) patients had PDL1 score between 1-49, and 11 (8.5%) patients had PDL1 score  $\geq$ 50. The median BMI value of the patients was 24.4 (16.3-39.1). Among the patients, the mean number of nivolumab treatment cycles was 6 (1-87). There was a history of radiotherapy in 83 patients (64.3%). The number of patients receiving bone modifying agents (zoledronic acid or denosumab)

**Table 1.** Patient baseline characteristics

Characteristics	Patients (n)
Total number of patients	129
Sex	
Men/women	109/20
Age at diagnosis	65 (40-82)
ECOG PS, n (%)	
0	65 (50.4)
1	48 (37.2)
2	16 (12.4)
Histological classification	
Adenocarcinoma/squamous cell carcinoma/others	60/55/14
Current or former/never smokers	106/23
BMI	24.4 (16.3-39.1)
Prior radiation therapy	
Yes/no	83/46
Administration cycles of nivolumab	6 (1-87)
Treatment response	
PR	39
SD	10
PD	67
NE	13
Metastatic sites	
Pleura	27
Bone	64
Liver	25
Lung	64
Brain	27
Adrenal	25
PD-L1 (%)	
0	26
1-49	36
$\geq$ 50	11
Unknown	56
GPS	
0	33
1	64
2	32

ECOG PS, Eastern Cooperative Oncology Group performance status; BMI, Body mass index; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated; PD-L1, programmed death-ligand 1; GPS, Glasgow prognostic score.

was 49 (38%). The GPS score was 0 in 33 (25.6%) patients, 1 in 64 (49.6%) patients and 2 in 32 (24.8%) patients. Patient's laboratory parameters are presented in Table 2.

### Treatment Response and Survival Analysis

For all patients included in the study, the median PFS was 5.8 months (95% CI 5.1-6.4 months), and the median OS was 16.2 months (95% CI 13.9-18.4) (Fig. 1 a, b). At the data

**Table 2.** Patients baseline laboratory parameters

Laboratory data	Median (IQR)
LDH (U/L)	207 (181-285)
CRP (mg/L)	25.10 (9.44-63.40)
Albumin (g/dL)	3.80 (3.34-4.10)
Neutrophils (K/ul)	5.48 (4.01-8.41)
Lymphocytes (K/ul)	1.30 (0.85-1.81)
Thrombocytes (B/mm <sup>3</sup> )	267 (205-352)
RDW (%)	15.30 (14.25-17.05)
Hemoglobin (g/dL)	11.60 (10.40-13.00)
NLR	4.46 (2.48-7.32)
PLR	203.81 (127.06-318.32)
SII	1067.40 (575.69-2119.16)

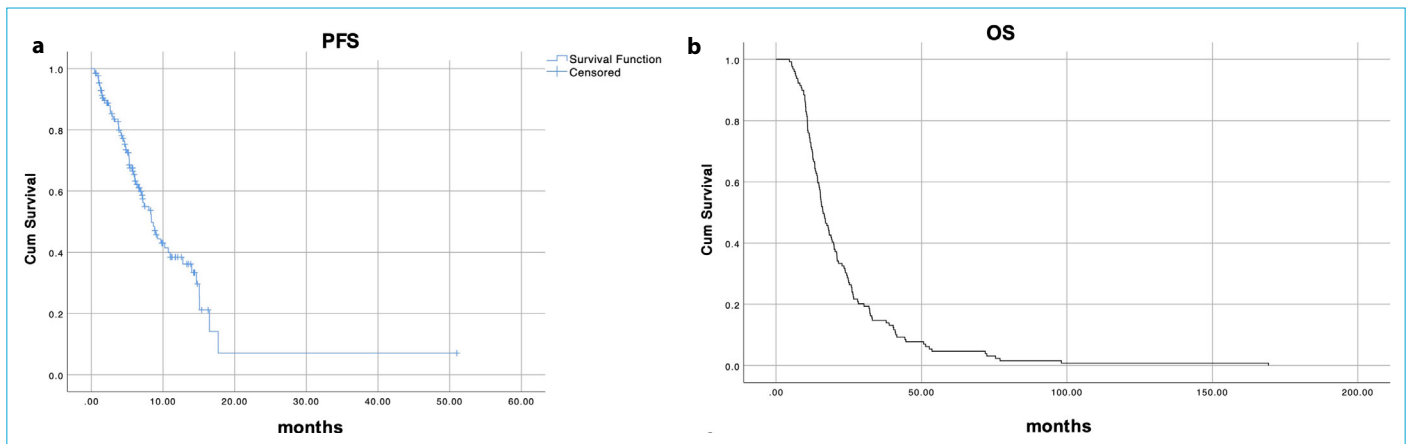
LDH: lactate dehydrogenase; CRP: C-reactive protein; RDW: Red cell distribution; NLR: neutrophil to lymphocyte ratio; PLR: thrombocyte to lymphocyte ratio; SII: systemic immune-inflammation index.

cutoff date of July 18, 2023, 59 patients had died and 70 were alive. Treatment response was not evaluated in 13 of the patients; and the ORR and DCR for the evaluated 116

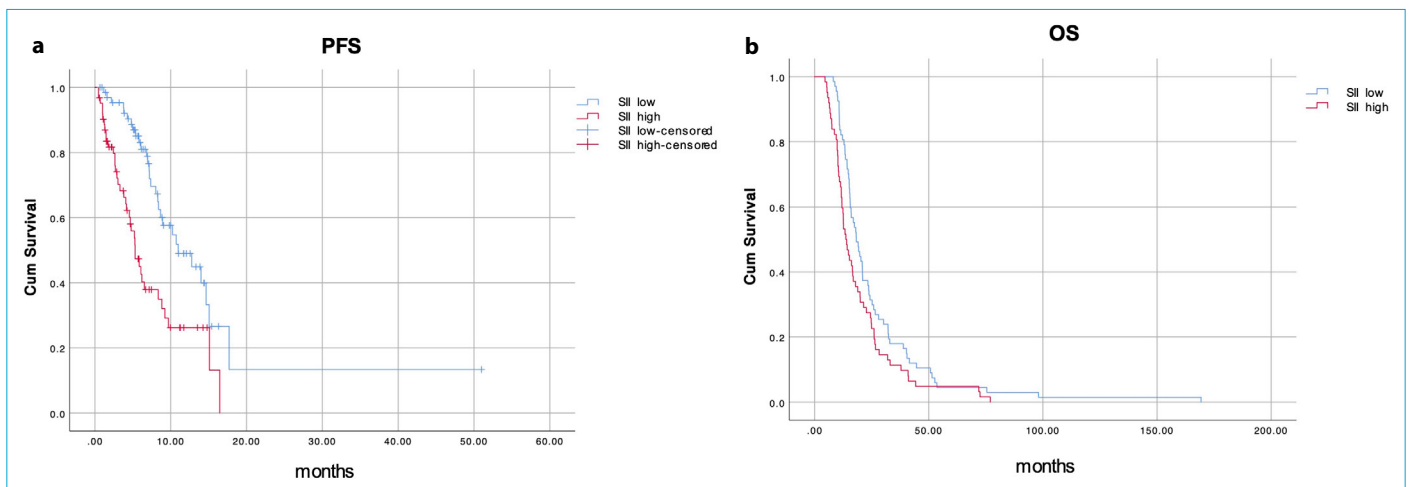
patients were 33.6% and 42.2%, respectively. No patient showed CR; however, PR, SD, and PD were observed in 33.6%, 8.6%, and 57.8% of the patients, respectively.

Based on the ROC analysis, cut-off point for SII to predict PFS and OS was 1133.8 (AUC: 0.701, specificity: 67.1% and sensitivity 66.1 %). The median PFS was found 7.1 months (6.3-7.9, 95%CI) in the low SII group and 4.2 months (2.8-5.5, 95%CI) in the high SII group, whenever the patients were assigned into 2 groups according to the cut-off point. There was a significant difference between groups (p=0.001). Also, the low SII group had significantly longer median OS then the high SII group (median OS 13.7 months [11.1-16.3] vs 18.3 months [15.1-21.5], p=0.042) (Fig. 2 a, b).

Cut-off value for NLR was calculated 4.43, with high sensitivity and specificity (72.9%, 68.6%, respectively and AUC: 0.752). The median PFS was found 7.1 months (6.4-7.8, 95%CI) in the low NLR group and 4.5 months (3.4-5.7, 95%CI) in the high NLR group, with a statistically significant difference (p=0.002). Although there was a numerical difference between the two groups for median OS, it did not



**Figure 1.** Kaplan-Meier curves of PFS (a) and OS (b) among 129 patients.



**Figure 2.** Kaplan-Meier curves of PFS (a) and OS (b) according to SII at baseline.

reach statistical significance (m OS 15.2 months [12.4-17.9, 95%CI] vs 18.03 months [14.1-21.9, 95%CI],  $p=0.425$ ) (Fig. 3 a, b). The ROC curve results showed that cutoff point for PLR to predict OS and PFS was 178.4, with a sensitivity of 72.9%, specificity of 55.7%, and AUC of 0.644. No significant difference was observed between the low and high PLR groups in terms of PFS and OS (m PFS 5.3 months [4.4-6.1, 95%CI] vs. 6.6 months [5.6-7.7, 95% CI],  $p=0.116$ , m OS 15 months [11.9-18, 95%CI] vs. 17 months [14.1-19.8, 95% CI],  $p=0.411$ ) (Fig. 4 a, b).

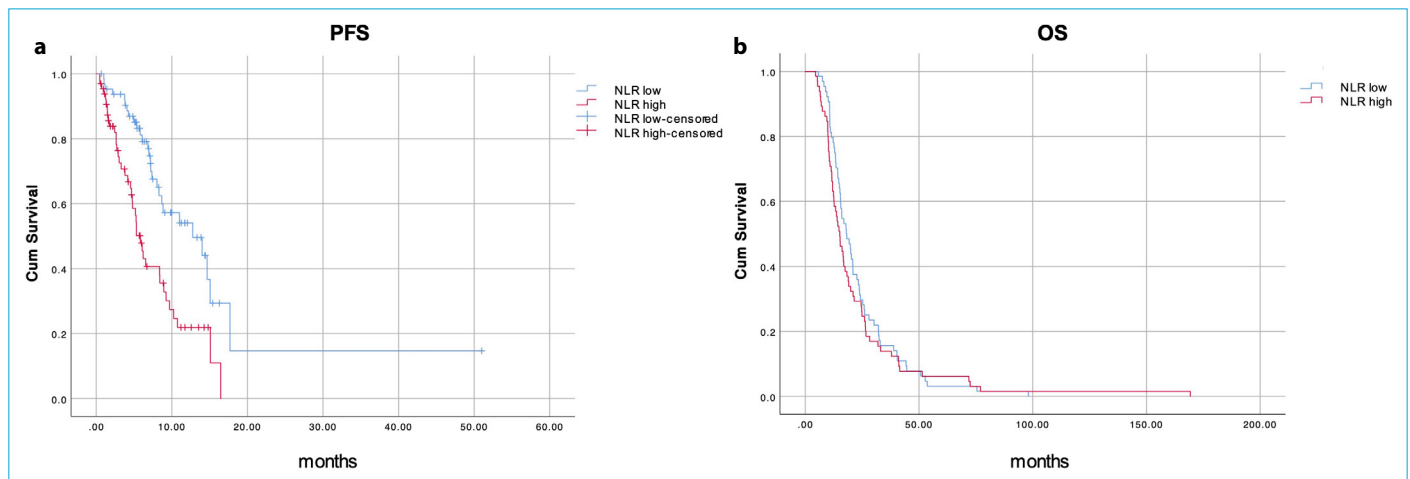
The median PFS was found to be 8 months (6.7-9.4, 95% CI) in patients with BMI <26.2 and 10.2 months (6.2-14.3, 95% CI) in patients with BMI  $\geq$ 26.2 ( $p=0.278$ ). The median OS was 15.2 months (12.8-17.6, 95% CI) in patients with BMI <26.2 and 18 months (15-21.1, 95% CI) in patients with BMI  $\geq$ 26.2 ( $p=0.494$ ). Again, no significant difference was determined between the PFS and OS median values of the groups when they were evaluated for GPS (median PFS 8.9 months vs. 6.2 months [ $p=0.191$ ], median OS 17.9 months

vs. 14.2 months [ $p=0.101$ ] for GPS 0-1 vs. <2, respectively).

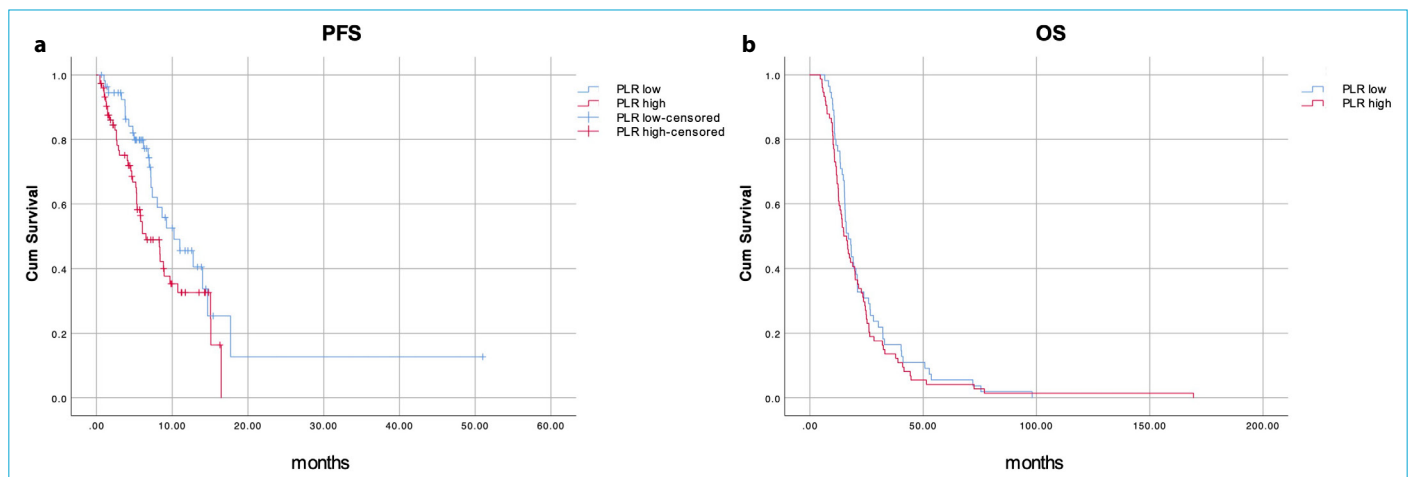
When PFS and OS were evaluated according to the use of bone-modifying agents, no significant difference was observed between the two groups. The group receiving zoledronic acid and denosumab had a median PFS of 6.2 months (4.5-7.9, 95% CI), whereas the median PFS was 5.4 months (4.7-6.1, 95% CI) in the group not receiving zoledronic acid and denosumab ( $p=0.988$ ). Median OS was 15.4 months (12.8-17.9, 95% CI) in the group receiving bone modifiers and 16.7 months (13.8-19.6, 95% CI) in the group not receiving bone modifiers ( $p=0.170$ ).

### Univariate and Multivariate Analyses

The Cox regression model was used to conduct the univariate and multivariate analyses of all patients based on PFS and OS (Tables 3, 4). The relationship of PFS and OS with metastasis site, previous radiotherapy history, NLR, PLR, SII, smoking, histology, BMI, GPS, PD L1 level, gender, ECOG, age and use of bone modifying agents were investigated.



**Figure 3.** Kaplan-Meier curves of PFS (a) and OS (b) according to NLR at baseline.



**Figure 4.** Kaplan-Meier curves of PFS (a) and OS (b) according to PLR at baseline.

**Table 3.** Univariate analysis of progressive free survival

Characteristics	Univariate analysis HR (95% CI)	p
Age at diagnosis (<65 vs ≥65)	0.786 (0.467-1.324)	0.366
Gender(male/female)	0.781 (0.370-1.651)	0.518
ECOG PS (0-1 vs 2)	0.557 (0.221-1.404)	0.215
Smoking history (ever vs never)	1.311(0.643-2.674)	0.456
Prior radiation therapy (no vs yes)	1.004 (0.579-1.741)	0.987
Histology (squamous vs non-squamous)	0.718 (0.430-1.199)	0.205
GPS (0-1 vs 2)	1.478 (0.806-2.711)	0.206
PD-L1 (≥1 vs 0)	0.812 (0.396-1.664)	0.570
BMI (<26.2 vs ≥26.2)	0.955 (0.555-1.643)	0.867
Use of bisphosphonate (no vs yes)	0.993 (0.584-1.688)	0.978
Pleural metastasis (no vs yes)	1.824 (0.990-3.359)	0.054
Bone metastasis (no vs yes)	1.408 (0.839-2.362)	0.195
Liver metastasis (no vs yes)	1.652 (0.903-3.023)	0.104
Lung metastasis (no vs yes)	1.002 (0.599-1.676)	0.994
Brain metastasis (no vs yes)	1.408 (0.779-2.543)	0.257
Adrenal metastasis (no vs yes)	0.777 (0.366-1.650)	0.512
NLR (<4.43 vs ≥4.43)	1.567 (0.936-2.621)	0.087
PLR (<178.4 vs ≥178.4)	1.204 (0.719-2.017)	0.480
SII (<1133.8 vs ≥1133.8)	1.762 (1.053-2.949)	0.031

In the univariate analyses, patients with SII <1133.8 were found to have longer PFS (p=0.031).

In the univariate analyses for OS, lack of bone and liver metastasis, SII <1133.8 and PD L1 level were determined

as factors significantly related to OS, while in the multivariate analyses, lack of liver metastasis and PD L1 level were determined to be significantly related to survival (Table 4).

## Discussion

Immunotherapies are important for the treatment of advanced NSCLC patients without targetable executive mutations.<sup>[24]</sup> Although nivolumab has proven superior to standard chemotherapy in the 2<sup>nd</sup> line, less than 20% of patients show PFS at the end of 2 years of treatment.<sup>[25]</sup> Inflammatory cells and systemic immune inflammation markers have a key part in tumor development and prognosis prediction in NSCLC, as in many solid tumor types.<sup>[26]</sup> In addition, sarcopenia has a negative prognostic feature in NSCLC patients treated with ICI.<sup>[27]</sup> In this study, we investigated the role of NLR, PLR, SII, GPS and BMI in predicting prognosis and treatment response in NSCLC patients treated with nivolumab in the 2<sup>nd</sup> line.

Neutrophils and platelets in the tumor microenvironment, which are related to tumor progression, as well as poor prognosis, contribute to the inflammatory process.<sup>[28,29]</sup> Numerous researchers have investigated the role of NLR and PLR in the prediction of response to nivolumab treatment.<sup>[30-32]</sup> According to Bagley et al., PFS and OS were significantly longer among patients with NLR <5 before nivolumab treatment, but NLR did not predict response

**Table 4.** Univariate and multivariate analysis of overall survival

Characteristics	Univariate analysis HR (95 % CI)	p	Multivariate analysis HR (95 % CI)	p
Age at diagnosis (<65 vs. ≥ 65)	0.789 (0.554-1.122)	0.187		
Gender(male/female)	0.955 (0.590-1.546)	0.850		
ECOG PS (0-1 vs. 2)	0.960 (0.568-1.624)	0.880		
Smoking history (ever vs. never)	1.104 (0.702-1.738)	0.667		
Prior radiation therapy (no vs. yes)	0.958 (0.666-1.378)	0.816		
Histology(squamous vs nonsquamous)	1.015 (0.715-1.441)	0.935		
GPS (0-1 vs. 2)	1.405 (0.934-2.113)	0.103		
PD-L1 (≥1 vs. 0)	0.550 (0.330-0.917)	0.022	0.558 (0.329-0.947)	0.031
BMI (<26.2 vs. ≥26.2)	0.880 (0.611-1.269)	0.495		
Use of bisphosphonate (no vs. yes)	1.285 (0.897-1.840)	0.172		
Pleural metastasis (no vs. yes)	1.111 (0.726-1.701)	0.627		
Bone metastasis (no vs. yes)	1.440 (1.015-2.043)	0.041	1.589 (0.950-2.658)	0.078
Liver metastasis (no vs. yes)	1.967 (1.257-3.080)	0.003	1.936 (1.031-3.635)	0.040
Lung metastasis (no vs. yes)	0.778 (0.545-1.109)	0.165		
Brain metastasis (no vs. yes)	1.353 (0.879-2.083)	0.169		
Adrenal metastasis (no vs. yes)	1.026 (0.662-1.590)	0.909		
NLR (<4.43 vs. ≥4.43)	1.152 (0.814-1.630)	0.425		
PLR (<178.4 vs. ≥178.4)	1.159 (0.816-1.645)	0.411		
SII (<1133.8 vs. ≥1133.8)	1.433 (1.011-2.031)	0.043	1.614 (0.984-2.648)	0.058

to nivolumab treatment.<sup>[33]</sup> Diem et al. reported high NLR to be significantly related to OS and low response rates, while no significant result was found between PFS and NLR.<sup>[34]</sup> A study of patients receiving pembrolizumab and nivolumab has shown that pretreatment NLR and PLR were not associated with PFS or response, but high NLR at week 6 post-treatment may be prognostic and predictive.<sup>[35]</sup> Putzu et al. revealed that baseline NLR and PLR were not associated with survival outcomes.<sup>[17]</sup> While the median PFS in our study was significantly longer in patients with NLR <4.43, there was a numerical difference in their median OS values, but statistical significance could not be demonstrated between them. The univariate and multivariate analyses did not show a link between NLR and PLR and PFS and OS.

SII is a more sensitive marker to indicate inflammation and predict prognosis than NLR and PLR. In a study of 1383 early and locally advanced operated colorectal cancer patients, pretreatment SII was shown to be an independent prognostic indicator for OS and PFS.<sup>[36]</sup> Liu et al. showed that the optimal cutoff point of SII determined by ROC analysis was an independent prognostic and predictive parameter in 44 NSCLC patients treated with nivolumab.<sup>[37]</sup> In another study, baseline SII was not associated with PFS and OS, but SII value at week 6 was significantly associated with PFS.<sup>[17]</sup> In our study, longer PFS and OS were obtained in the patient group with low SII. While a significant relationship was found between SII, PFS and OS in the univariate analyses, no significant relationship was found between SII, PFS and OS in the multivariate analyses. The reason for this difference may be related to the median SII value in some studies and racial differences.

Preclinical studies have shown that increased adipose tissue induces immune defense mechanism and becomes an important source for cytokines and chemokines.<sup>[38]</sup> The mechanism here is due to a decrease in adiponectin-mediated activation of regulatory T cells and acceleration of the proinflammatory process through the CD40 pathway.<sup>[39]</sup> A retrospective study of NSCLC, RCC, and melanoma patients who underwent ICI treatment evaluated the relationship between BMI and OS and PFS, and found that the median PFS and the median OS were significantly longer in patients with BMI >30 in comparison to patients with BMI <24.9.<sup>[40]</sup> Dimitrakopoulos et al. conducted a study with NSCLC patients receiving pembrolizumab or nivolumab, but found no relationship between BMI and OS and PFS.<sup>[41]</sup> In our study, no correlation was determined between BMI and OS and PFS. This result may be because of the higher BMI cutoff value in our study compared to other studies in the literature.

Liver metastasis in lung cancer cases has an incidence in the range of 3-20%, and its presence adversely affects prognosis.<sup>[42, 43]</sup> Liver metastasis is associated with poor responses and short survival in immunotherapy-treated patients. The mechanism has been shown to be related to induce apoptosis of CD8+ lymphocytes in the systemic circulation by the tumor microenvironment in the liver.<sup>[44]</sup> In the 3-year follow-up results of the CheckMate 017 and CheckMate 057 studies, the median OS was 6.8 months in the patient group with liver metastasis treated by nivolumab.<sup>[45]</sup> In line with the literature, liver metastasis was a poor prognostic indicator in our study and survival was found to be shorter in this group.

Although PDL1 expression levels alone are not a sufficient biomarker for patient selection for immunotherapy, a meta-analysis including 8 randomized controlled trials found a 34% reduction in mortality risk in patients testing positive for PDL1 and 20% in those testing negative for PDL1. However, in terms of OS, longer OS was seen in both PDL1 positive and negative patients compared to the standard arm.<sup>[46]</sup> In our study, significantly longer OS was obtained in the PDL1 positive group. PDL1 is still not recommended as a reliable predictive marker due to differences in PDL1 measurement methods between laboratories and diverse scoring systems.

Our study had several limitations. Firstly, the analysis in this study was retrospective, and treatment response assessments were subjective according to the physician. Moreover, the sample was small, and PDL1 value was unknown nearly half of the patients. However, our study significantly contributes to the literature as it is the first study evaluating serum immune inflammation markers in predicting response to nivolumab treatment in the 2<sup>nd</sup> line in Turkish patients. Prospective studies with a larger patient population are required to deliver cost-effective treatments to the right patient at the right time.

#### Disclosures

**Ethics Committee Approval:** This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Aydın University (number: B. 30.2.AYD.0.00.00-050.06.04/88).

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