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ORIGINAL RESEARCH

Do Inflammatory and Nutritional Markers Predict Prognosis in Metastatic Non-Small Cell Lung Cancer Patients Receiving Nivolumab

Esra Zeynelgil[1], Dilek Çağlayan[2], Selahattin Çelik[1], Hatice Ayyıldız Sevim[1], Hayriye Şahinli[1], Serdar Karakaya[3], Tülay Eren[1]

[1]Department of Medical Oncology, Ankara Etlik City Hospital, Ankara, Turkey; [2]Department of Medical Oncology, Nevşehir State Hospital, Nevşehir, Turkey; [3]Department of Medical Oncology, Ankara Atatürk Sanatoryum Training and Research Hospital, Ankara, Turkey

Correspondence: Esra Zeynelgil, Etlik City Hospital, Medical Oncology Department, Varlık Neighborhood, Halil Sezai Erkut Street, No: 5, Yenimahalle, Ankara, 06170, Turkey, Email esra23.05@hotmail.com

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Objective: To investigate the prognostic value of clinical and inflammatory markers predicting response to nivolumab in patients with metastatic non-small cell lung cancer (NSCLC).

Materials and Methods: Clinical, demographic and laboratory data of stage 4 NSCLC patients who were treated between February 2021 and November 2024 were analyzed. Before nivolumab treatment, inflammatory markers such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), prognostic nutritional index (PNI), hemoglobin-albumin-lymphocyte-platelet score (HALP), neutrophil-to-eosinophil ratio (NER) and C-reactive protein-to-albumin ratio (CAR) were calculated. Factors affecting overall survival (OS) were determined by Cox regression analysis, and ROC curve analysis was used to calculate the ideal cut-off.

Results: The study included 229 NSCLC patients and the median age of the patients was 63 years. The majority were male (84.3%) and had right lung localization (56.8%). Median overall survival was calculated as 21.2 months (95% CI: 17.4–25.0). In univariate cox-regression analysis, the presence of brain metastases (HR: 2.08; p=0.004), liver metastases (HR: 1.85; p=0.014) and adrenal metastases (HR: 1.64; p=0.045) negatively affected the treatment response. Inflammatory markers such as high NLR (HR: 2.04; p<0.001), high SII (HR: 1.96; p<0.001), high CAR (HR: 1.84; p=0.001), high PLR (HR: 1.60; p=0.009) and high SIRI (HR: 1.51; p=0.021), low PNI (HR: 0.48; p<0.001), low HALP (HR: 0.49; p<0.001) and low LMR (HR: 0.65; p=0.016) were associated with poor prognosis. In multivariate analysis, the presence of brain metastasis (HR: 2.84; p<0.001), adrenal metastasis (HR: 1.64; p=0.046) and low PNI (HR: 0.44; p<0.001) together predicted poor prognosis and formed a statistical model on treatment response.

Conclusion: In patients with metastatic NSCLC, nivolumab treatment response is predicted by inflammatory markers and the presence of brain and adrenal metastases. It was concluded that low PNI among inflammatory markers is a strong prognostic indicator in this patient group.

Keywords: immune checkpoint inhibitors, systemic inflammation index, prognostic nutritional index, overall survival

Introduction

Lung cancer is the second most common type of cancer in women and men, but it is the most important cause of cancer-related deaths.[1] Non-small-cell lung cancer (NSCLC) constitutes approximately 85% of all lung cancers.[2] Currently, immunotherapy is the main treatment modality for NSCLC cancer without driver mutation.[3]

Nivolumab is a human immunoglobulin G4 (IgG4) antibody targeting programmed death-1 (PD-1) receptors. It is an important treatment agent with demonstrated efficacy independent of PD-L1 score in chemotherapy-resistant NSCLC cancer without ALK, RET, or ROS1 mutations. In daily practice, a validated marker that will benefit from treatment in patients receiving Nivolumab has not yet been clearly established. In the Checkmate 227 and CheckMate 568 studies, ipilimumab, a CTLA-4 antibody, was found to be effective together with nivolumab in patients with advanced stage

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NSCLC patients with tumor mutation burden independent of PD-L1 score. Tumor Mutational Burden (TMB) is an important biomarker in predicting response to immunotherapy. Studies have shown that patients with a TMB greater than 10 mutations per megabase have the highest predicted objective response rate (ORR), reaching up to 38% to 42%, regardless of PD-L1 expression levels. However, despite its predictive value, TMB is not yet used as a standard test due to its high financial cost and the technical complexity of measurement.[4–6]

In the inflammatory tumor microenvironment (TME), innate immune cells such as monocytes and adaptive immune cells (eg T lymphocytes) produce various inflammatory mediators in response to abnormal signals from the tumor, creating an inflammatory response.[7,8] In this process, neutrophils stand out as both effective elements of innate immunity and cellular messengers shaping the adaptive response. They not only suppress the tumor-killing activity of cytotoxic T lymphocytes (CTLs), but also trigger angiogenesis and support tumor progression by secreting numerous growth factors and chemokines, such as TGF-β, VEGF, IL-6, IL-8, IL-12, and matrix metalloproteinases. G-CSF secreted by tumor cells reinforces this tumor-supportive cycle by increasing the number of neutrophils.[9–12] Only 15–60% of patients can achieve the expected response with CTLA-4, PD-1 and PD-L1 inhibitors developed through activation of the immune system.[13]

In this study, we aimed to investigate the prognostic importance of inflammatory and nutritional markers along with clinical parameters on treatment response in metastatic NSCLC patients who received nivolumab treatment.

Materials and Methods

Patient Characteristics

In this multicenter study, data of metastatic non-small cell lung cancer (NSCLC) patients diagnosed and treated between February 2021 and November 2024 at three oncology centers (Ankara Etlik City Hospital, Nevşehir State Hospital, and Ankara Atatürk Sanatoryum Hospital) were retrospectively analyzed. Patients who had previously received 1 line of platinum-containing chemotherapy (cisplatin or carboplatin) and progressed and received second-line immunotherapy were included. (Figure 1) Patients with pathologically confirmed NSCLC who received at least 2 cycles of nivolumab treatment at the metastatic stage with 240 mg every 2 weeks or 360 mg every 3 weeks were included in the study. Patients who had another concurrent malignancy, had active infection findings, did not have driver mutations (EGFR, ALK, ROS1), and had pre-treatment blood parameters, were over 18 years of age, and had ECOG <2 before nivolumab treatment were included. PD-L1 expression was evaluated by immunohistochemical staining using the VENTANA PD-L1 (SP263) assay (Roche, Switzerland) on the BenchMark ULTRA automated staining platform. All procedures, including antigen retrieval and detection steps, were performed in accordance with the manufacturer's protocol. The Common Terminology Criteria for Adverse Events Scoring System (CTCAE) v4.0 was used for the definition and

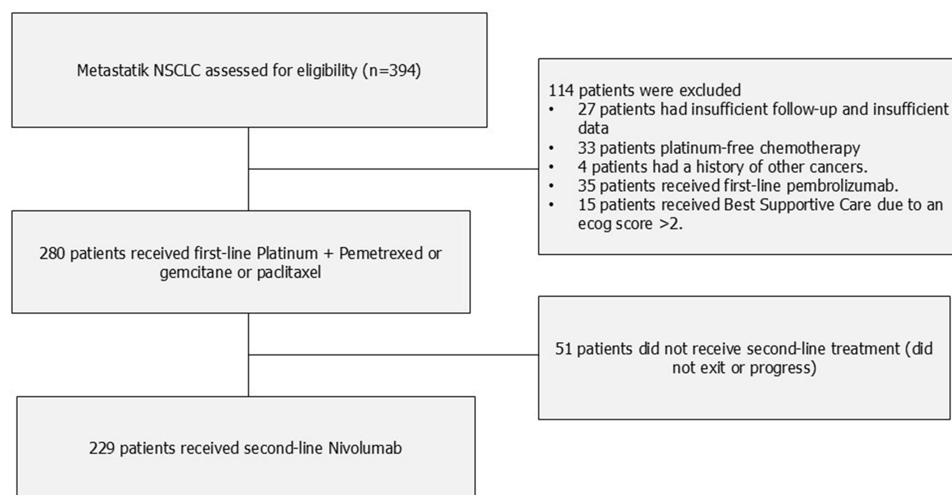

Figure 1 CONSORT Flow Diagram.

evaluation of immune-related adverse events (irAEs). The study received approval from the local ethics board (Approval no: 2500043238 / 28.05.2025, Non-Interventional Ethics Committee of Nevsehir Haci Bektas Veli University).

Calculation of Indices

In the metastatic stage, the indices were calculated as follows by taking the complete blood count and biochemistry data obtained from the blood samples collected 7 days or earlier before the start of treatment. CRP levels were quantitatively measured using the immunoturbidimetric method, while albumin levels were determined by spectrophotometric methods.

- Neutrophil-to-Lymphocyte Ratio (NLR) = Neutrophils (10^9/L) / Lymphocytes (10^9/L)
- Platelet-to-Lymphocyte Ratio (PLR) = Platelets (10^9/L) / Lymphocytes (10^9/L)
- Lymphocyte-to-Monocyte Ratio (LMR) = Lymphocytes (10^9/L) / Monocytes (10^9/L)
- Systemic Immune-Inflammation Index (SII) = (Platelets (10^9/L) × Neutrophils (10^9/L)) / Lymphocytes (10^9/L)
- Systemic Inflammation Response Index (SIRI) = (Neutrophils (10^9/L) × Monocytes (10^9/L)) / Lymphocytes (10^9/L)
- Prognostic Nutritional Index (PNI) = Albumin (g/dL) + 0.005 × Lymphocytes (10^9/L)
- Hemoglobin, Albumin, Lymphocyte, Platelet Score (HALP) = Hemoglobin (g/dL) × Albumin (g/dL) × Lymphocytes (10^9/L)) / Platelets (10^9/L)
- Neutrophil-to-Eosinophil Ratio (NER) = Neutrophils (10^9/L) / Eosinophils (10^9/L)
- C-Reactive Protein-to-Albumin Ratio (CAR): CRP (mg/L) / Albumin (g/dL).

Statistical Analysis

Statistical analyses were performed using SPSS 24 (SPSS Inc., Chicago, III) and Microsoft® Excel® 2019 (Version 2503) 32 bit and R software (R Core Team, 2024). Receiver operating characteristic (ROC) analysis was used to determine the ideal cut-off for the markers and to calculate sensitivity-specificity, and the Youden index method was used.[14] In determining the ideal cut-off, long survival was considered a predictive marker. For variables that did not reach a statistically significant p value in the ROC analysis, the median cut-off value was included in the analyses. Kaplan-Meier survival analysis was used to calculate the estimated median overall survival time. Cox-regression analysis was used to calculate the univariate overall survival Hazard Ratio, and the Forward Stepwise (Likelihood Ratio) method was used for multivariate models. In the univariate Cox regression analysis for PDL1, patients with unknown PDL1 were not included, and 3 categories (< 1 vs 1–49 vs ≥ 50) were compared. All patients were included in the other univariate analyses. The proportional hazards assumption was tested using Schoenfeld residuals. The Schoenfeld residuals test was evaluated using the survival library in the R program (R Core Team, 2024).[15,16] Variables demonstrating a p-value below 0.05 were deemed statistically significant and consequently included in the final model based on the predetermined retention criteria. Situations where the P value was below 0.05 and the Type 1 error level was below 5% were interpreted as statistically significant.

Results

The study included 229 patients with metastatic non-small cell lung cancer who received nivolumab treatment. The median age of the patients was 63 (min: 41, max: 83). 84.3% (n=193) of the patients were male and 56.8% (n=130) of the tumorswere localized to the right lung. 51.1% (n=117) patients had adenocarcinoma, 40.6% had squamous histology and 8.3% (n=19) had "not otherwise specified (nos) histology". The PDl-1 score of 49 patients (21.4%) was unknown. More than half of them (43.2%, n=122) were metastatic at the time of diagnosis and the most common metastatic site was bone metastasis (31.4%, n=72). Other clinical and pathological data are shown in Table 1.

The ideal cut-off values for inflammatory and nutrient markers to predict long survival were calculated separately. The ideal cut-off value for SII was determined as 1224 (AUC: 0.564, P=0.094), for PNI as 45.1 (AUC: 0.591, P=0.018), for HALP score as 2.0 (AUC: 0.576, P=0.046) and for CAR as 8.5 (AUC: 0.598, P=0.010) and the median values for other parameters were included in the analyses. Sensitivity and specificity are given in Table 2 with AUC 95% Confidence interval.

Table 1 Clinical and Laboratory Characteristics of the Patients (n = 229)

Variable	Category	n	%
Age (years)	< 60	78	34.1
	≥ 60	151	65.9
Gender	Female	36	15.7
	Male	193	84.3
Histological subtype	Adenocarcinoma	117	51.1
	Squamous-cell carcinoma	93	40.6
	Not otherwise specified (NOS)	19	8.3
PD-L1 expression (%)	Unknown	49	21.4
	< 1	86	37.6
	1 – 49	49	21.4
	≥ 50	45	19.7
Stage at diagnosis	≤ III	107	46.7
	IV	122	53.3
Tumour laterality	Left lung	99	43.2
	Right lung	130	56.8
Liver metastasis	No	201	87.8
	Yes	28	12.2
Bone metastasis	No	157	68.6
	Yes	72	31.4
Brain metastasis	No	203	88.6
	Yes	26	11.4
Pleural effusion	No	181	79.0
	Yes	48	21.0
Contralateral-lung metastasis	No	158	69.0
	Yes	71	31.0
Extramediastinal lymph-node metastasis	No	204	89.1
	Yes	25	10.9
Adrenal metastasis	No	197	86.0
	Yes	32	14.0
Hepatitis B prophylaxis	No	199	86.9
	Yes	30	13.1
Hyper-progression	No	156	68.1
	Yes	46	20.1
Death during progression	–	27	11.8
Pseudo-progression	No	204	89.1
	Yes	25	10.9
Immune-related adverse event	No	176	76.9
	Yes	53	23.1

Table 2 ROC-Curve Analysis for Long-Term Survival and Derived Optimal Cut-off Values

Variable	AUC	AUC 95% CI	P value	Cut-off	Sensitivity (%)	Specificity (%)
NLR	0.443	0.369–0.518	0.139	4.3 (median)	–	–
PLR	0.440	0.366–0.515	0.118	213.2 (median)	–	–
LMR	0.562	0.488–0.636	0.105	2.32 (median)	–	–
SII	0.564	0.489–0.639	0.094	1,224	60.2	55.4
SIRI	0.441	0.367–0.516	0.124	2.38 (median)	–	–
PNI	0.591	0.517–0.664	0.018	45.1	58.7	56.5
HALP	0.576	0.502–0.651	0.046	2.0	59.5	53.7

(*Continued*)

Table 2 (Continued).

Variable	AUC	AUC 95% CI	P value	Cut-off	Sensitivity (%)	Specificity (%)
NER	0.454	0.379–0.529	0.233	43.1 (median)	–	–
CAR	0.598	0.525–0.671	0.010	8.5	57.4	57.0

Abbreviations: NLR: Neutrophil-to-Lymphocyte Ratio; PLR: Platelet-to-Lymphocyte Ratio; LMR: Lymphocyte-to-Monocyte Ratio; SII: Systemic Immune-Inflammation Index; SIRI: Systemic Inflammation Response Index; PNI: Prognostic Nutritional Index; HALP: Hemoglobin, Albumin, Lymphocyte, Platelet Score; NER: Neutrophil-to-Eosinophil Ratio; CAR: C-Reactive Protein-to-Albumin Ratio.

The estimated median survival time of the patients was calculated as 21.2 months (95% CI: 17.4–25.0 months). The factors affecting survival were evaluated according to Univariate Cox regression analysis. Having brain metastasis at the time of diagnosis (HR: 2.08, 95% CI: 1.26–3.44, p=0.004), detection of liver metastasis (HR: 1.85, 95% CI: 1.13–3.03, p=0.014) and presence of adrenal metastasis (HR: 1.64, 95% CI: 1.01–2.66, p=0.045) were detected as negative prognostic findings. High neutrophil-lymphocyte ratio (NLR), which indirectly indicates inflammation (HR: 2.04, 95% CI: 1.42–2.92, p<0.001), high systemic immune-inflammation index (SII) (HR: 1.96, 95% CI: 1.37–2.79, p<0.001), high C-reactive protein-albumin ratio (CAR) (HR: 1.84, 95% CI: 1.29–2.61, p=0.001), high platelet-lymphocyte ratio (PLR) (HR: 1.60, 95% CI: 1.13–2.26, p=0.009) and high systemic inflammation response index (SIRI) (HR: 1.51, 95% CI: 1.07–2.15, p=0.021) were found to be poor prognostic markers predicting survival. Low prognostic nutritional index (PNI) (HR: 0.48, 95% CI: 0.34–0.69, p<0.001), low hemoglobin-albumin-lymphocyte-platelet score (HALP) (HR: 0.49, 95% CI: 0.35–0.70, p<0.001) and low lymphocyte-monocyte ratio (LMR) (HR: 0.65, 95% CI: 0.46–0.92, p=0.016) was found to be a predictive marker indicating poor prognosis. Clinically, the presence of immune-related adverse events was associated with prolonged overall survival (OS) (HR: 0.63, 95% CI: 0.41–0.97, p=0.034). Other investigated markers were tumor histological type (HR: 1.18, 95% CI: 0.98–1.41, p=0.075), disease stage at diagnosis (HR: 1.38, 95% CI: 0.97–1.97, p=0.076), PLD1 (HR: 0.88, 95% CI: 0.74–1.05, p=0.146), presence of pleural effusion (HR: 1.36, 95% CI: 0.90–2.05, p=0.145), use of hepatitis B prophylaxis (HR: 1.31, 95% CI: 0.83–2.09, p=0.250), presence of contralateral lung metastases (HR: 0.82, 95% CI: 0.55–1.20, p=0.298), tumor localization (HR: 0.84, 95% CI: 0.59–1.18, p=0.318), age group (HR: 1.18, 95% CI: 0.82–1.70, p=0.375), presence of bone metastases (HR: 0.87, 95% CI: 0.61–1.26, p=0.474), presence of extramediastinal lymphadenopathy (HR: 0.84, 95% CI: 0.50–1.43, p=0.527), gender (HR: 1.04, 95% CI: 0.64–1.68, p=0.873) and high neutrophil-eosinophil ratio (HR: 1.00, 95% CI: 0.71–1.42, p=0.986) and no statistically significant difference was found between survival (Table 3, Figure 2).

Table 3 Univariate Cox Proportional-Hazard Analysis for Overall Survival

Variable	Category	HR (95% CI)	p
Age	< 60 vs ≥ 60	1.18 (0.82–1.70)	0.375
Gender	Female vs Male	1.04 (0.64–1.68)	0.873
Histological subtype	Adenocarcinoma vs SCC vs NOS	1.18 (0.98–1.41)	0.075
PD-L1 expression	< 1 vs 1–49 vs ≥ 50	0.88 (0.74–1.04)	0.146
Stage at diagnosis	≤ III vs IV	1.38 (0.97–1.97)	0.076
Tumour location	Left vs Right	0.84 (0.59–1.18)	0.318
Liver metastasis	No vs Yes	1.85 (1.13–3.02)	**0.014**
Bone metastasis	No vs Yes	0.87 (0.60–1.26)	0.474
Brain metastasis	No vs Yes	2.08 (1.26–3.44)	**0.004**
Pleural effusion	No vs Yes	1.36 (0.90–2.05)	0.145
Contralateral-lung metastasis	No vs Yes	0.81 (0.55–1.20)	0.298
Extramediastinal lymph-node metastasis	No vs Yes	0.84 (0.50–1.43)	0.527
Adrenal metastasis	No vs Yes	1.64 (1.01–2.66)	**0.045**
Hepatitis B prophylaxis	No vs Yes	1.31 (0.83–2.09)	0.250

(*Continued*)

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Table 3 (Continued).

Variable	Category	HR (95% CI)	p
Immune-related adverse event	No vs Yes	0.63 (0.41–0.97)	**0.034**
NLR	< 4.3 vs ≥ 4.3	2.04 (1.42–2.92)	**< 0.001**
PLR	< 213.2 vs ≥ 213.2	1.60 (1.13–2.26)	**0.009**
LMR	< 2.32 vs ≥ 2.32	0.65 (0.46–0.92)	**0.016**
SII	< 1,224 vs ≥ 1,224	1.96 (1.37–2.79)	**< 0.001**
SIRI	< 2.38 vs ≥ 2.38	1.51 (1.07–2.15)	**0.021**
PNI	< 45.1 vs ≥ 45.1	0.48 (0.34–0.69)	**< 0.001**
HALP	< 2.0 vs ≥ 2.0	0.49 (0.34–0.70)	**< 0.001**
NER	< 43.1 vs ≥ 43.1	1.00 (0.71–1.42)	0.986
CAR	< 8.5 vs ≥ 8.5	1.84 (1.29–2.61)	**0.001**

Notes: Statistically significant p values are marked in bold.
Abbreviations: CI, Confidence Interval; HR, Hazard Ratio; NLR, Neutrophil-to-Lymphocyte Ratio; PLR, Platelet-to-Lymphocyte Ratio; LMR, Lymphocyte-to-Monocyte Ratio; SII, Systemic Immune-Inflammation Index; SIRI, Systemic Inflammation Response Index; PNI, Prognostic Nutritional Index; HALP, Hemoglobin, Albumin, Lymphocyte, Platelet Score; NER, Neutrophil-to-Eosinophil Ratio; CAR, C-Reactive Protein-to-Albumin Ratio.

In the multivariate Cox regression analysis, the presence of brain metastasis (HR: 2.84, 95% CI: 1.68–4.79, p<0.001), the presence of adrenal metastasis (HR: 1.64, 95% CI: 1.01–2.67, p=0.046) and low PNI value (HR: 0.44, 95% CI: 0.30–0.63, p<0.001) prognosis showed the characteristic of being a prognostic model (Table 4). The findings obtained from the Cox regression analysis were tested for the proportional hazards assumption using Schoenfeld residuals. It was determined that the p-values for all variables in the model were above 0.05, indicating that the proportional hazards assumption was met. The multivariate model created in Table 4 is statistically significant (χ^2= 31.93, p<0.001). To assess the fit of the model, the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values were calculated and were obtained as 1183.73 and 1192.35, respectively. These values indicate that the overall fit of the model is acceptable VIF values were examined for multicollinearity, and no significant multicollinearity was detected (VIF<5).

Discussion

In this study, 229 patients with metastatic non-small cell (NSCLC) who received nivolumab immunotherapy were analyzed. In the study, in univariate analysis, the presence of brain metastasis, liver and adrenal metastasis were associated with poor prognosis. Patients who developed immune-related side effects during treatment had better treatment responses. Except for NER, the investigated inflammation markers (PLR, LMR, SII, SIRI, PNI, HALP, NER, CAR) predicted prognosis. In multivariate analysis, brain metastasis, adrenal metastasis and Prognostic nutritional index (PNI) formed a strong prognostic model.

While immunotherapy treatments for lung cancer are rapidly advancing, it is still unclear in which patients the treatment will be effective. Although the PDL-1 score is the most basic marker in clinical studies, immunotherapy treatments can be effective in patients with negative PDL-1 scores, while immunotherapy is not effective in some groups with high PDL1 scores.[17,18] With the investigation of tumor mutation burden and microsatellite instability, MSI was detected positive in only 0.33% of small cell lung cancers.[19] TMB is a high-cost test and is not a routinely recommended test.[20] Therefore, a cheap, easily applicable marker is needed to predict immunotherapy response. In the study conducted by Lin et al, PDL-1 score did not statistically predict treatment response in patients receiving nivolumab.[21] Phase 3 study data for nivolumab demonstrated that treatment efficacy was independent of PD-L1 levels. When we excluded the subgroup with unknown PD-L1 levels from our study analysis, there was no association between PD-L1 levels and survival (p=0.146), and these results were consistent with the literature.[22]

Immune-Related Adverse Events (irAEs) are the definition of side effects caused by autoimmune or inflammatory toxins that develop due to excessive activation of the immune system in patients treated with immune checkpoint inhibitors.[23] irAEs are seen when the immune system is not limited to tumor cells but also invades normal tissues. In the study conducted by Ebi et al, it was

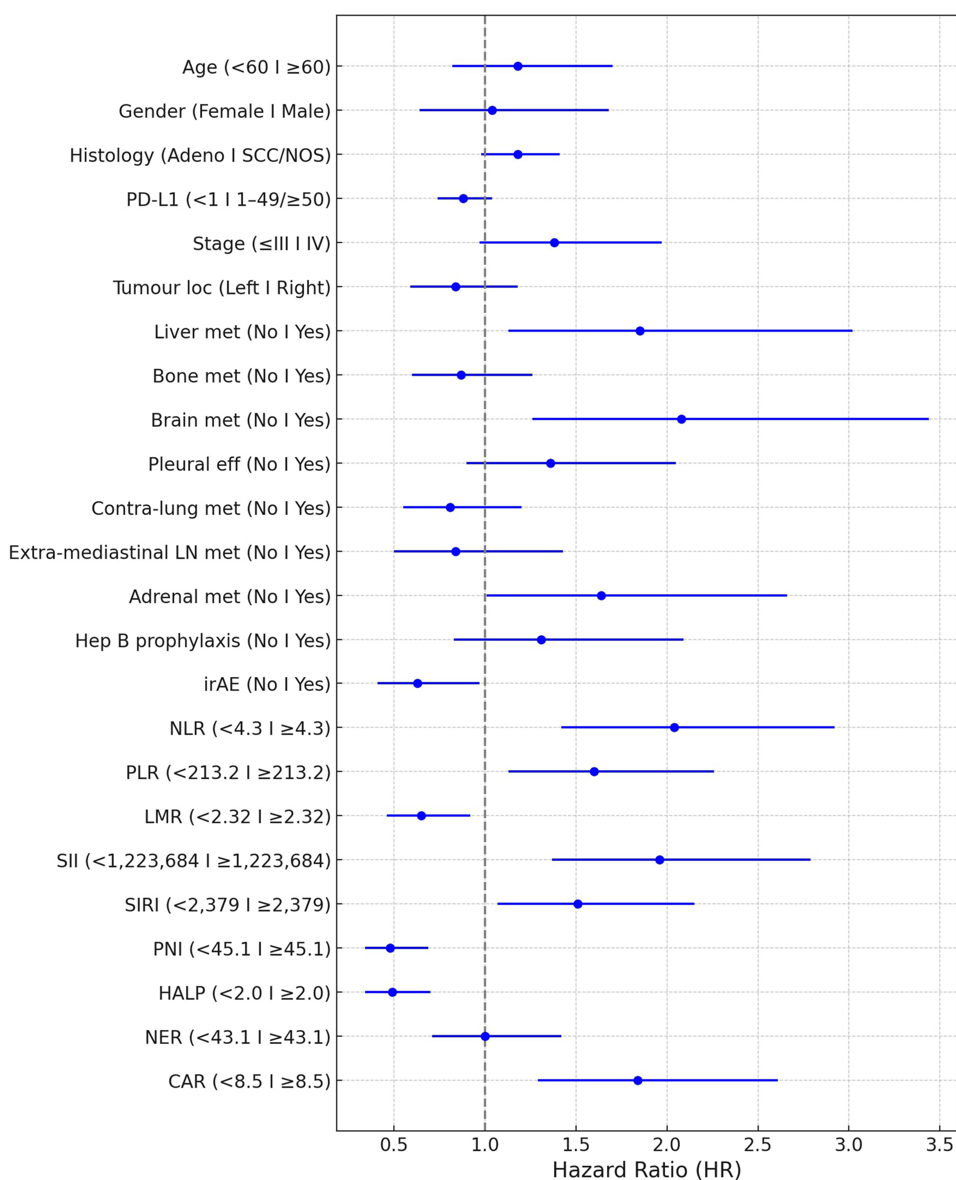

Figure 2 Hazard ratios for clinical, pathological, and inflammatory markers in patients with metastatic non-small cell lung cancer (NSCLC) receiving nivolumab therapy. (Blue dots represent hazard ratio estimates, and horizontal lines indicate 95% confidence intervals.).

seen to be associated with good prognosis in patients receiving ipilimumab together with nivolumab.[24] Zhou et al. The meta-analysis revealed that immunotherapy responses were better in patients who developed irAEs.[25] In our study, patients who developed irAEs had better survival, consistent with the results of the mentioned studies.

Table 4 Multivariate Cox Proportional-Hazard Analysis for Overall Survival

Variable*	Category	HR (95% CI)	p	VIF
Brain metastasis	No/Yes	2.84 (1.68–4.79)	<0.001	1.070
Adrenal metastasis	No/Yes	1.64 (1.01–2.67)	0.046	1.019
PNI	45.1</≥45.1	0.44 (0.30–0.63)	<0.001	1.065

Notes: *Variables that were found to be statistically significant in the univariate analysis (11 variable) were included in the multivariate analysis and investigated with the forward-LR method. χ^2=31.93, p<0.001, AIC=1183.73, BIC: 1192.35.
Abbreviation: PNI, Prognostic Nutritional Index.

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For a clearer understanding of immunotherapy biomarkers, it would be helpful to focus on neoantigen formation and presentation, the tumor microenvironment, changes in certain gene signaling pathways, MHC molecules, and T-cell receptors.[26] Among these pathways, the IL-6/STAT3 axis has been implicated in mediating resistance to checkpoint blockade by intrinsically impairing CD8+ T-cell differentiation and function, with elevated circulating IL-6 levels correlating with poor responses to anti-PD-L1 therapy.[12,27,28] Although it is technically not possible to measure these markers directly, indirectly looking at inflammation markers in the blood seems to be an easily accessible and inexpensive method. Recent studies suggest that increased lymphocytes and decreased neutrophils are associated with better prognosis in NSCLC patients treated with nivolumab. Russo et al. In their study, they demonstrated that increased neutrophil levels are poor prognostic in NSCLC patients.[29] The same study demonstrated that increased NLR and increased PLR are poor prognostic in nivolumab treatment.[29] Cao et al. In a pooled analysis of 14 retrospective studies, increased NLR was found to be a poor prognostic marker and determined the ideal cut-off value as 5.[30] In our study, the median cut-off was 4.3, and patients above this cut-off were considered to have poor nivolumab responses.

As a result of the immune system response that occurs together with inflammation, an increase in C-reactive protein (CRP), neutrophils, and a decrease in albumin and lymphocytes in the blood are expected results.[31] The C-reactive protein/albumin ratio (CAR), which reflects high CRP and low albumin scores, has been suggested to be prognostic in lung cancer. Dai et al found that patients with high CAR scores had shorter OS and PFS.[32] Prognostic nutritional index (PNI) is a score that evaluates serum albumin level and lymphocyte count together, and Wang et al found a 57% decrease in the risk of death in patients with low prognostic index compared to those with high prognostic index (HR:0.43).[33] HALP Score, which evaluates the combination of Hemoglobin, Albumin, Lymphocyte, Platelet, is an immune-nutritional index defined in recent years. Akgül et al found that patients with low HALP scores in lung cancer patients treated with nivolumab in the second line had a poor prognosis.[34] Our study is consistent with the literature, and when each was evaluated independently, high CAR (HR:1.84), low PNI (HR:0.48), and low HALP (HR:0.49) were found to be associated with poor prognosis in patients receiving nivolumab.

There were some limitations regarding our study. The retrospective nature of our study design was an important limitation. Other limitations were the small percentage of patients with brain metastases (11.4%) and the high percentage of patients with unknown pdl1 (21.4%). In addition, the inability to calculate the ideal cut-off using Roc-Curve analysis for hematological parameters that were significant in the survival analysis was a statistical weakness of our study. The evaluation of immunotherapy results in brain metastatic patients, which is an exclusion criterion in most clinical studies, and the data of a homogeneous center make the study strong.

Conclusion

In conclusion, when evaluated separately in our study, NSCLC patients treated with nivolumab had poor response to treatment in liver, brain and adrenal metastatic patients and markers (NLR, PLR, LMR, SII, SIRI, PNI, HALP, CAR) which are indirect indicators of inflammation were prognostic on their own, and PNI formed a prognostic model with brain metastasis and adrenal metastasis among these markers. Prospective data are needed in further studies.

Abbreviations

ANC, Absolute Neutrophil Count; AUC, Area Under the Curve; CAR, C-Reactive Protein-to-Albumin Ratio; CI, Confidence Interval; CRP, C-Reactive Protein; CTLA-4, Cytotoxic T-Lymphocyte Antigen-4; ECG, Eastern Cooperative Oncology Group; HALP, Hemoglobin, Albumin, Lymphocyte, Platelet Score; HR, Hazard Ratio; irAEs, Immune-related Adverse Events; LMR, Lymphocyte-to-Monocyte Ratio; NER, Neutrophil-to-Eosinophil Ratio; NLR, Neutrophil-to-Lymphocyte Ratio; NOS, Not Otherwise Specified; NSCLC, Non-Small Cell Lung Cancer; PD-1, Programmed Death-1; PD-L1, Programmed Death Ligand-1; PLR, Platelet-to-Lymphocyte Ratio; PNI, Prognostic Nutritional Index; ROC, Receiver Operating Characteristic; SCC, Squamous Cell Carcinoma; SII, Systemic Immune-Inflammation Index; SIRI, Systemic Inflammation Response Index; TMB, Tumor Mutational Burden; VEGF, Vascular Endothelial Growth Factor.

Ethics Approval and Consent to Participate

This study was reviewed and approved by the Ethics Committee of Nevsehir Haci Bektas Veli University.All participants provided written informed consent prior to treatment. The study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Disclosure

The authors declare that they have no conflicts of interest related to this work.

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