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The predictive and prognostic value of the Advanced Lung Cancer Inflammation Index in metastatic NSCLC receiving second-line nivolumab: a multicenter retrospective cohort study

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ABSTRACT

Aims: The Advanced Lung Cancer Inflammation Index (ALI)—calculated from body-mass index (BMI), serum albumin, and neutrophil-to-lymphocyte ratio (NLR)—is an accessible composite biomarker of systemic inflammation and nutritional status. Its prognostic value in second-line immune checkpoint inhibitor (ICI) therapy in an ICI-naive population remains undefined.

Methods: This multicenter retrospective cohort study included 249 metastatic non-small cell lung cancer (NSCLC) patients treated with second-line single-agent nivolumab without prior immunotherapy exposure. ALI was categorized using a receiver operating characteristic (ROC)-derived cut-off of 27.27. Treatment response was assessed by RECIST 1.1. Progression-free survival (PFS) and overall survival (OS) were analyzed using Kaplan-Meier and Cox regression models.

Results: High baseline ALI (≥27.27) was associated with significantly longer median PFS (10.05 vs. 6.01 months; p=0.012) and OS (13.89 vs. 6.27 months; p<0.001). In multivariable analyses, high ALI remained independently associated with improved PFS (HR 0.688; p=0.011) and OS (HR 0.585; p=0.002). The overall objective response rate (ORR) was 35.3% and disease control rate (DCR) was 43.0%; both were numerically higher in the high-ALI group but did not reach statistical significance, and no significant differences were observed in ORRs.

Conclusion: Baseline ALI is an independent prognostic biomarker for PFS and OS in ICI-naive metastatic NSCLC patients receiving second-line nivolumab, representing a cost-effective tool for pre-treatment risk stratification. Prospective validation is warranted.

Keywords: Non-small cell lung cancer, Advanced Lung Cancer Inflammation Index, nivolumab, immunotherapy, prognosis, biomarker

INTRODUCTION

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality worldwide, with the majority of patients presenting with advanced or metastatic disease at diagnosis,[1] where long-term survival outcomes remain poor despite recent therapeutic advances.[2] The introduction of immune checkpoint inhibitors (ICIs) targeting the programmed cell death protein 1 (PD-1)/PD-L1 axis has substantially transformed the treatment landscape of metastatic NSCLC.[3,4] Pivotal trials including CheckMate 017 and CheckMate 057 established nivolumab as a standard second-line option in this setting.[4,5] Nevertheless, despite improvements in first-line outcomes with immunotherapy-based regimens, a substantial proportion of patients develop primary or acquired resistance and require subsequent systemic treatment. In this context, the identification of reliable, readily available biomarkers to predict benefit from second-line immunotherapy represents a critical and currently unmet clinical need.

Systemic inflammation and nutritional status have been increasingly recognized as key determinants of cancer progression, treatment response, and survival. Tumor-related inflammation contributes to immunosuppression, tumor proliferation, angiogenesis, and resistance to therapy.[6,7] Among several inflammation-based prognostic scores, the Advanced Lung Cancer Inflammation Index (ALI)—calculated as body-mass index (BMI)×serum albumin/neutrophil-to-lymphocyte ratio (NLR)—has emerged as a simple and reproducible composite biomarker integrating both host nutritional and inflammatory status.[8]

Several studies have demonstrated the prognostic relevance of ALI in lung cancer. In metastatic NSCLC, low ALI has been consistently associated with poor overall survival (OS) and adverse clinical features, including higher tumor burden and impaired performance status. Moreover, ALI has been identified as an independent prognostic factor for OS, outperforming several conventional inflammatory markers in retrospective analyses.[9] Similarly, ALI has also shown prognostic significance in early-stage NSCLC, surgical cohorts, and patients receiving radiotherapy, further supporting its robustness across different disease stages and treatment modalities.[10,11]

More recently, emerging evidence has suggested that ALI may also be associated with outcomes in patients receiving ICIs. In a multicenter cohort of advanced NSCLC patients treated with PD-1/PD-L1 inhibitors, higher ALI values were correlated with improved survival, particularly in the immunotherapy monotherapy setting, suggesting a potential role of ALI in reflecting tumor-immune interaction and host immunocompetence.[12] However, most available data are derived from first-line immunotherapy settings, and there is a paucity of evidence regarding the predictive value of ALI in patients undergoing second-line immunotherapy after progression on prior systemic treatment.

Given the increasing use of immunotherapy beyond first-line treatment in metastatic NSCLC, identifying reliable and easily accessible biomarkers that can predict response in the second-line setting is clinically important. Inflammation-based indices such as ALI are particularly attractive due to their cost-effectiveness, routine availability, and reflection of both tumor biology and host systemic condition.

To address this gap, we conducted a multicenter retrospective cohort study evaluating the prognostic and predictive value of baseline ALI in patients with metastatic NSCLC receiving second-line nivolumab. A key methodological strength of this study is the restriction of the cohort to ICI-naive patients—those who had not received immunotherapy in the first-line setting—thereby eliminating prior ICI exposure as a confounding variable and allowing a cleaner assessment of ALI's independent role. We hypothesized that higher baseline ALI would be independently associated with improved progression-free survival (PFS) and OS in this population.

METHODS

Ethics

Ethical approval for this multicenter non-interventional clinical study was obtained from the Non-interventional Clinical Researches Ethics Committee of Aydın Adnan Menderes University (Date: 13.03.2026, Decision No: E-53043-469-050.04-831562). The study was conducted in accordance with the Declaration of Helsinki. As this was a retrospective study based on existing medical records, individual patient informed consent was waived by the ethics committee.

Study Design and Patient Population

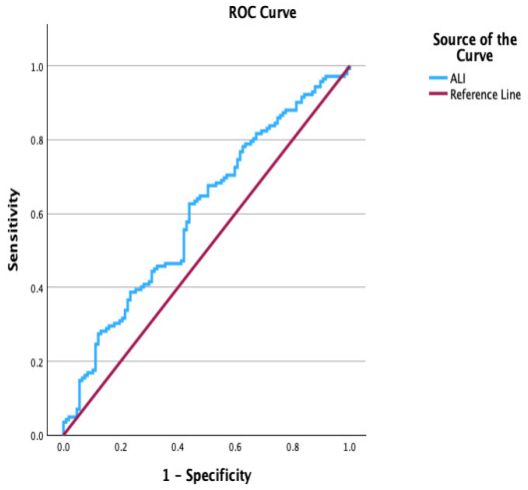
This multicenter retrospective cohort study included patients with metastatic NSCLC treated with second-line single-agent nivolumab at two centers in Turkiye. Eligible patients were adults with histologically confirmed metastatic NSCLC who had received at least one cycle of nivolumab in the second-line setting. Medical records from both centers were retrospectively reviewed for eligibility and data extraction. Patients were excluded if they had received prior ICI therapy, had incomplete medical records precluding data extraction, had active autoimmune disease requiring systemic treatment, had severe hepatic or renal impairment, or had an ECOG performance status of 3-4.

Data Collection

Demographic, clinical, pathological, and laboratory data were collected from electronic medical records at both centers. Variables included age, gender, smoking status, Eastern Cooperative Oncology Group (ECOG) performance status, histological subtype, metastatic sites, comorbidities, and prior treatment regimens. Laboratory parameters required for calculation of ALI—including BMI, serum albumin, and NLR—were recorded prior to nivolumab initiation. Tumor response and survival outcomes were retrieved from medical records at both institutions. Radiologic evaluations performed in routine clinical practice were used to assess treatment response according to RECIST 1.1 criteria.

Definition of ALI

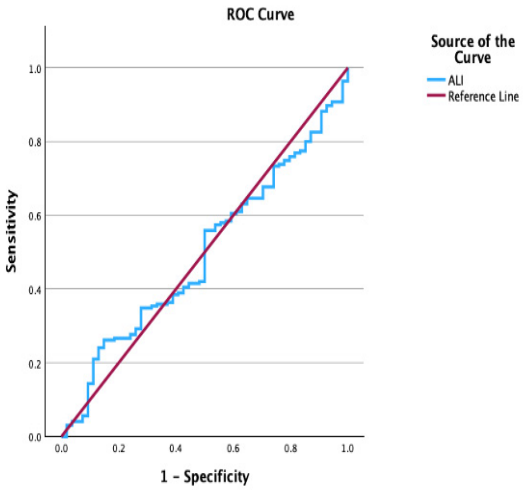
ALI was calculated using the following formula: ALI=BMI×serum albumin/NLR. ALI was evaluated both as a continuous variable and as a categorical variable. Receiver operating characteristic (ROC) analysis was performed to identify the optimal cut-off value for mortality, and the cut-off with the highest Youden index was selected (**Supplementary Figures S1.1** and **S1.2**). Based on this analysis, patients were classified into low-ALI (<27.27) and high-ALI (≥27.27) groups. Although the discriminatory ability of ALI for progression was limited, the same threshold was retained across all efficacy analyses to ensure consistency and clinical interpretability.



Supplementary Figures S1.1. Receiver operating characteristic (ROC) curve for overall survival (OS) showing the optimal ALI cut-off value (27.27)
ALI: Advanced Lung Cancer Inflammation Index

Treatment Response and Survival Outcomes

All patients received nivolumab at a dose of 3 mg/kg administered intravenously every two weeks. Tumor response to nivolumab was assessed according to RECIST 1.1 criteria. Best overall response was categorized as complete response



Supplementary Figures S1.2. Receiver operating characteristic (ROC) curve for progression-free survival (PFS) showing the optimal ALI cut-off value (27.27)
ALI: Advanced Lung Cancer Inflammation Index

(CR), partial response (PR), stable disease (SD), or progressive disease (PD). Objective response rate (ORR) was defined as the proportion of patients achieving CR or PR; disease control rate (DCR) was defined as the proportion achieving CR, PR, or SD. PFS was defined as the time from nivolumab initiation to documented disease progression or death from any cause. OS was defined as the time from nivolumab initiation to death from any cause. Patients without events at last follow-up were censored on the date of last contact.

Statistical Analysis

The data analyses were performed using IBM SPSS Statistics v29 (IBM Corp., Armonk, NY, USA) and R v4.5 (R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were summarized as number (percentage) and continuous variables as median (range). Baseline characteristics were compared between ALI groups using the Chi-square test or Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables. ROC analysis was used to evaluate the discriminatory performance of ALI and to determine the optimal cut-off value using Youden's index. Survival curves were estimated using the Kaplan-Meier method and compared with the log-rank test. Median follow-up was estimated separately for each endpoint using the reverse Kaplan–Meier method. As this estimate is driven by the timing of censored observations rather than their absolute number, median follow-up values may differ between PFS and OS analyses depending on the distribution of censoring times for each endpoint. Cox proportional hazards regression analyses were performed to identify prognostic factors for PFS and OS; variables significant in univariate analyses were entered into multivariable models. Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported. A two-sided $p<0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

A total of 249 patients with metastatic NSCLC who received second-line single-agent nivolumab were included. The median age was 66 years (range, 37-87), and 226 patients (90.8%) were male. Histologically, 126 patients (50.6%) had non-squamous NSCLC and 123 (49.4%) had squamous NSCLC. Most patients were active/former smokers (236/247, 95.5%) and had an ECOG performance status of 0-1 (220, 88.4%). Baseline patient characteristics are summarized in **Table 1**.

Determination of ALI Cut-off

ROC analysis identified 27.27 as the optimal ALI cut-off. For mortality, the area under the curve (AUC) was 0.601, with a Youden index of 0.188, sensitivity of 62.7%, and specificity of 56.1%. For progression, the AUC was 0.495, with a Youden index of 0.059, suggesting limited discriminatory performance. Using this cut-off, 136 patients (54.6%) were classified as low ALI and 113 (45.4%) as high ALI. Patients in the high-ALI group had significantly higher BMI and albumin levels (both $p\leq0.001$); other baseline characteristics were generally balanced between the groups (**Table 1**).

Treatment Response

The ORR was 35.3% and the DCR was 43.0% in the overall cohort. ORR and DCR were numerically higher in the high-ALI group than in the low-ALI group (41.6% vs. 30.1%, p=0.064; 49.6% vs. 37.5%, p=0.072, respectively) (**Figure 1**). Best overall response distribution did not significantly differ between the two groups (p=0.275) (**Figure 2**).

All patients who discontinued nivolumab did so due to disease progression. No treatment discontinuations attributable to immune-related adverse events or other toxicities were recorded.

Progression-free Survival

At a median follow-up of 25.5 months, the median PFS in the overall cohort was 7.58 months (95% CI, 6.10-9.06). Patients with low ALI had a median PFS of 6.01 months (95% CI, 4.92-7.10), whereas those with high ALI had a median PFS of 10.05 months (95% CI, 8.02-12.07; log-rank p=0.012; **Figure 3**). In multivariable analysis, high ALI remained independently associated with improved PFS (HR 0.688, 95% CI 0.516-0.918; p=0.011), while older age, ECOG performance status 2-4, liver metastasis, and adrenal metastasis remained independently associated with worse PFS (**Table 2**).

Overall Survival

At a median follow-up of 15.01 months, the median OS in the overall cohort was 9.29 months (95% CI, 7.09-11.49). Median OS was 6.27 months (95% CI, 4.56-7.98) in the low-ALI group and 13.89 months (95% CI, 10.39-17.40) in the high-ALI group (log-rank p<0.001; **Figure 4**). High ALI remained independently associated with improved OS in multivariable analysis (HR 0.585, 95% CI 0.414-0.827; p=0.002). Older age (HR 1.026; p=0.028), ECOG performance status 2-4 (HR 1.729; p=0.041), and chronic obstructive pulmonary disease (COPD) (HR 1.489; p=0.036) were independently associated with worse OS (**Table 3**).

Sensitivity Analyses

Using a literature-based ALI cut-off of 18, high ALI was associated with improved OS in univariate analysis (HR 0.696, 95% CI 0.498-0.973; p=0.034), but this association did not remain statistically significant in the multivariable model (HR 0.734, 95% CI 0.521-1.036; p=0.078). Similarly, the association between ALI and PFS was not statistically significant with this cut-off (HR 0.829, 95% CI 0.618-1.112; p=0.210).

Table 1. Baseline characteristics of the patients according to ALI group

Variable	Total (n=249)	Low ALI (n=136)	High ALI (n=113)	p value
Age, years, median (range)	66 (37-87)	66 (37-87)	66 (47-84)	0.536
Gender, male, n (%)	226 (90.8)	124 (91.2)	102 (90.3)	0.805
Histology, n (%)				0.764
Non-squamous	126 (50.6)	70 (51.5)	56 (49.6)	
Squamous	123 (49.4)	66 (48.5)	57 (50.4)	
Smoking status, n (%)*				0.549
Never smoker	11 (4.5)	5 (3.7)	6 (5.3)	
Active/former smoker	236 (95.5)	129 (96.3)	107 (94.7)	
Smoking exposure, pack-years†	40 (0-150)	38 (0-150)	40 (0-135)	0.449
ECOG performance status, n (%)				0.210
0-1	220 (88.4)	117 (86.0)	103 (91.2)	
2-4	29 (11.6)	19 (14.0)	10 (8.8)	
First-line treatment, n (%)				0.459
Platinum-pemetrexed	47 (18.9)	22 (16.2)	25 (22.1)	
Platinum-gemcitabine	76 (30.5)	42 (30.9)	34 (30.1)	
Platinum-taxane	118 (47.4)	66 (48.5)	52 (46.0)	
Other	8 (3.2)	6 (4.4)	2 (1.8)	
PD-L1 status, n (%)				0.059
Unknown	118 (47.4)	74 (54.4)	44 (38.9)	
<1%	56 (22.5)	25 (18.4)	31 (27.4)	
1-49%	48 (19.3)	26 (19.1)	22 (19.5)	
≥50%	27 (10.8)	11 (8.1)	16 (14.2)	
Metastatic sites, n (%)				
Lung	120 (48.2)	64 (47.1)	56 (49.6)	0.694
Liver	40 (16.1)	25 (18.4)	15 (13.3)	0.274
Bone	88 (35.3)	53 (39.0)	35 (31.0)	0.189
Adrenal	38 (15.3)	21 (15.4)	17 (15.0)	0.931
Brain	28 (11.2)	14 (10.3)	14 (12.4)	0.602
Distant lymph node	98 (39.4)	50 (36.8)	48 (42.5)	0.358
Comorbidities, n (%)				
COPD	66 (26.5)	37 (27.2)	29 (25.7)	0.784
Hypertension	83 (33.3)	46 (33.8)	37 (32.7)	0.857
Diabetes mellitus	45 (18.1)	24 (17.6)	21 (18.6)	0.848
Coronary artery disease	51 (20.5)	29 (21.3)	22 (19.5)	0.718
Hyperlipidemia	10 (4.0)	4 (2.9)	6 (5.3)	0.519
Nivolumab cycles, median (range)	6 (1-120)	6 (1-80)	8 (1-120)	<0.001
BMI, kg/m², median (range)	24.2 (15.2-39.1)	23.9 (15.2-37.1)	24.9 (15.6-39.1)	0.001
Albumin, g/dl, median (range)	3.8 (2.1-4.9)	3.6 (2.1-4.6)	4.0 (2.4-4.9)	<0.001
ALI, median (range)	24.1 (1.6-176.4)	14.4 (1.6-27.2)	43.9 (27.3-176.4)	<0.001

ALI: Advanced Lung Cancer Inflammation Index, BMI: Body-mass index, COPD: Chronic obstructive pulmonary disease, ECOG: Eastern Cooperative Oncology Group performance status, PD-L1: Programmed death-ligand 1, NSCLC: Non-small cell lung cancer. *n=247; †n=245. Values are median (range) unless otherwise stated.

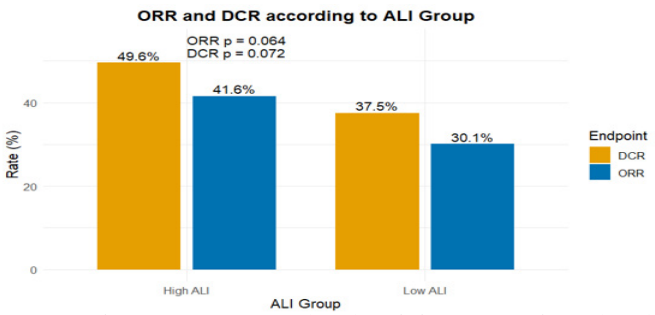


Figure 1. Objective response rate (ORR) and disease control rate (DCR) according to baseline ALI groups in patients treated with nivolumab

p-values were calculated using the Chi-square test. ALI: Advanced Lung Cancer Inflammation Index, DCR: Disease control rate, ORR: Objective response rate

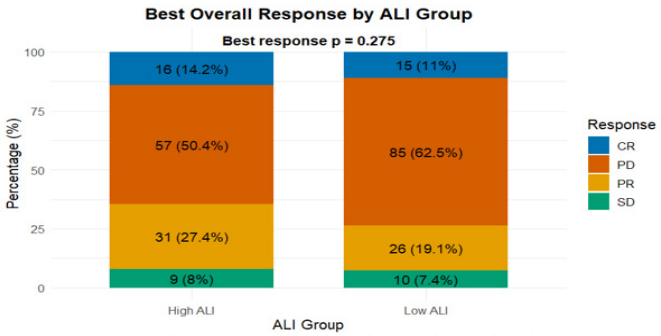


Figure 2. Best overall response to nivolumab according to baseline ALI groups

ALI: Advanced Lung Cancer Inflammation Index, CR: Complete response, PD: Progressive disease, PR: Partial response, SD: Stable disease

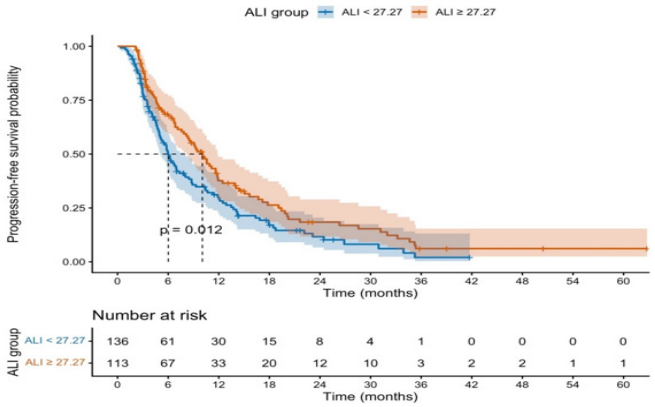


Figure 3. Kaplan-Meier curves for progression-free survival according to baseline ALI group

High ALI (≥27.27) vs. low ALI (<27.27); log-rank p=0.012. ALI: Advanced Lung Cancer Inflammation Index, CI: Confidence interval, PFS: Progression-free survival

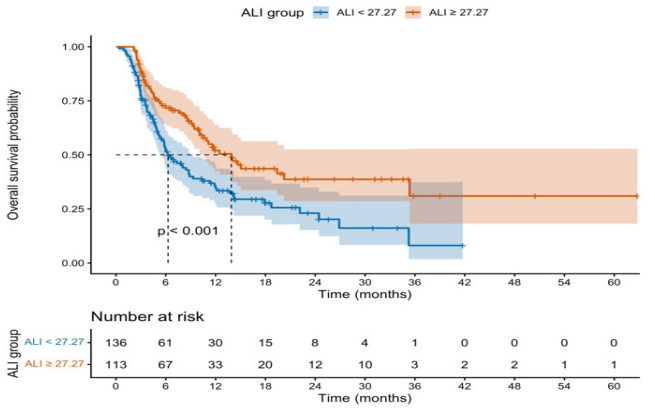


Figure 4. Kaplan-Meier curves for overall survival according to baseline ALI group

High ALI (≥27.27) vs. low ALI (<27.27); log-rank p<0.001. ALI: Advanced Lung Cancer Inflammation Index, CI: Confidence interval, OS: Overall survival

DISCUSSION

In this multicenter retrospective cohort study, we evaluated the prognostic and potential predictive role of ALI in patients with metastatic NSCLC treated with second-line nivolumab. Higher baseline ALI was independently associated with improved PFS and OS, while no significant association was observed between ALI and radiological response outcomes. These findings suggest that ALI may function primarily as a prognostic rather than a direct predictive biomarker of tumor response in this setting.

Systemic inflammation plays a central role in cancer progression and treatment outcomes. In the landmark study by Jafri et al.,[8] involving 173 patients with metastatic NSCLC, a lower ALI (<18) was associated with significantly worse survival outcomes (median OS 3.4 vs. 8.3 months). That study included a heterogeneous population treated predominantly

Table 2. Univariate and multivariable Cox regression analyses for progression-free survival

Variable	Univariate HR (95% CI)	p value	Multivariable HR (95% CI)	p value
Gender (female vs. male)	1.299 (0.825-2.045)	0.259	-	-
Age, years	1.035 (1.016-1.053)	<0.001	1.033 (1.014-1.052)	<0.001
Histology (SCC vs. non-SCC)	1.252 (0.943-1.663)	0.121	-	-
Smoking (active/former vs. never)	0.982 (0.483-1.994)	0.959	-	-
ECOG PS (2-4 vs. 0-1)	2.054 (1.309-3.223)	0.002	1.721 (1.069-2.771)	0.025
Lung metastasis	1.005 (0.758-1.333)	0.972	-	-
Liver metastasis	1.514 (1.032-2.220)	0.034	1.504 (1.015-2.228)	0.042
Bone metastasis	1.288 (0.957-1.733)	0.094	-	-
Adrenal metastasis	1.469 (1.003-2.150)	0.048	1.677 (1.141-2.466)	0.009
Brain metastasis	1.228 (0.792-1.904)	0.358	-	-
COPD	1.321 (0.961-1.817)	0.087	-	-
ALI ≥27.27 vs. <27.27	0.694 (0.522-0.923)	0.012	0.688 (0.516-0.918)	0.011

ALI: Advanced Lung Cancer Inflammation Index, CI: Confidence interval, COPD: Chronic obstructive pulmonary disease, ECOG PS: Eastern Cooperative Oncology Group performance status, HR: Hazard ratio, SCC: Squamous cell carcinoma. First-line treatment group was not significant in univariate analysis and was excluded.

Table 3. Univariate and multivariable Cox regression analyses for overall survival

Variable	Univariate HR (95% CI)	p value	Multivariable HR (95% CI)	p value
Gender (female vs. male)	1.091 (0.616-1.931)	0.765	-	-
Age, years	1.034 (1.013-1.056)	0.002	1.026 (1.003-1.049)	0.028
Histology (SCC vs. non-SCC)	1.447 (1.037-2.018)	0.029	1.228 (0.866-1.742)	0.249
Smoking (active/former vs. never)	1.437 (0.532-3.885)	0.475	-	-
ECOG PS (2-4 vs. 0-1)	2.291 (1.402-3.743)	<0.001	1.729 (1.023-2.920)	0.041
Liver metastasis	1.791 (1.186-2.702)	0.006	1.493 (0.971-2.297)	0.068
Bone metastasis	1.419 (1.009-1.997)	0.045	1.349 (0.948-1.918)	0.096
COPD	1.501 (1.048-2.150)	0.027	1.489 (1.026-2.160)	0.036
ALI (continuous)	0.991 (0.982-0.999)	0.031	-	-
ALI ≥27.27 vs. <27.27	0.560 (0.398-0.788)	<0.001	0.585 (0.414-0.827)	0.002

ALI: Advanced Lung Cancer Inflammation Index, CI: Confidence interval, COPD: Chronic obstructive pulmonary disease, ECOG PS: Eastern Cooperative Oncology Group performance status, HR: Hazard ratio, SCC: Squamous cell carcinoma

with chemotherapy, reflecting the pre-immunotherapy era. Ozyurek et al.[13] similarly reported that ALI <18 was associated with shorter OS in 112 stage IV NSCLC patients, with a negative correlation between ALI and systemic inflammatory markers such as C-reactive protein, reinforcing the biological link between ALI and systemic inflammation.

In contrast, our study focused exclusively on a homogeneous cohort receiving second-line ICI therapy with nivolumab. We observed a stronger association between ALI and long-term survival outcomes, particularly for OS (HR 0.585). Unlike chemotherapy-based cohorts where ALI may primarily reflect tumor burden and cachexia-related systemic decline, in immunotherapy-treated populations ALI may more specifically reflect host immune competence and systemic inflammatory balance, both of which are closely linked to ICI efficacy.

A notable finding was the higher optimal ALI cut-off value (27.27) compared with those reported in previous studies (approximately 18-23). This likely reflects differences in patient populations and treatment eras. Earlier studies by Jafri et al.[8] and Bacha et al.[14] included more heterogeneous patients with higher systemic inflammatory burden and poorer nutritional status. Patients selected for immunotherapy often have better baseline performance status and more favorable metabolic profiles, shifting the distribution of ALI values toward higher levels. Variation in optimal cut-off values across cohorts is expected and likely reflects biological heterogeneity rather than methodological inconsistency. Despite these differences, the direction of the association remains highly consistent across studies, with lower ALI uniformly indicating poorer survival outcomes.

Our findings also align with earlier inflammation-based prognostic models such as the C-reactive protein-albumin score described by Forrest et al.,[15] which demonstrated that systemic inflammatory status strongly influences survival in advanced NSCLC. While such earlier models were developed in the pre-immunotherapy era, ALI may provide a broader biological assessment by incorporating both nutritional status and immune cell dynamics—particularly relevant in patients receiving ICIs, where therapeutic efficacy depends on host immune competence.

Limitations

Several limitations should be acknowledged. The retrospective design may introduce selection bias and limits causal inference. Although multicenter, the study population was relatively limited in size and derived from a single country, which may affect generalizability. ALI was assessed only at baseline, and dynamic changes during treatment were not evaluated. Information on PD-L1 expression and molecular alterations was not uniformly available and could not be incorporated into the analysis.

Nevertheless, our study has important strengths. To our knowledge, this is one of the largest homogeneous real-world cohorts specifically evaluating ALI in patients receiving second-line nivolumab, with a critical methodological distinction: all patients were ICI-naive at enrollment, ensuring that the observed associations reflect ALI's prognostic role in the context of de novo ICI exposure. This design significantly reduces confounding and strengthens internal validity. The consistency of results across both PFS and OS endpoints further supports the robustness of ALI as a prognostic marker. Additionally, the use of a data-driven ROC-derived cut-off supported by sensitivity analyses with a literature-based threshold enhances reproducibility and clinical applicability.

CONCLUSION

This multicenter study demonstrates that baseline ALI is an independent prognostic biomarker for both PFS and OS in ICI-naive patients with metastatic NSCLC receiving second-line nivolumab. As an accessible, low-cost composite of nutritional and inflammatory host status, ALI holds promise as a practical stratification tool in routine oncological practice. These findings provide a rationale for prospective evaluation of ALI-guided patient selection strategies in the second-line immunotherapy setting.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethical approval for this multicenter non-interventional clinical study was obtained from the Non-interventional Clinical Researches Ethics Committee of Aydın Adnan Menderes University (Date: 13.03.2026, Decision No: E-53043-469-050.04-831562).

Informed Consent

This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

Concept: AA; Design: AA; Control: AA, BD, KC; Resources: AA, BD, KC; Materials: AA, KC, BD, HİE, YAC; Data Collection and/or Processing: AA, KC, BD, HİE, YAC; Analysis and/or Interpretation: AA, KC; Literature Review: All Authors; Writing the Article: AA, KC; Critical Review: All Authors.

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