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Elevated serum lactate dehydrogenase to albumin ratio is a useful poor prognostic predictor of nivolumab in patients with non-small cell lung cancer

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Abstract. – OBJECTIVE: This study aimed to evaluate the prognostic significance of the LDH-to-albumin ratio (LAR) in patients with non-small cell lung cancer (NSCLC) receiving nivolumab monotherapy. We comprehensively analyzed the associations between LAR and clinical parameters, progression-free survival (PFS), and overall survival (OS) to identify reliable biomarkers for treatment selection.

PATIENTS AND METHODS: A total of 144 patients with metastatic NSCLC treated with nivolumab were included. Patient characteristics, including demographic data, smoking history, albumin, lactate dehydrogenase (LDH) levels, and LAR were recorded. Univariate and multivariate analyses were conducted to determine the associations between these factors and PFS/OS. The LAR cut-off value was determined using receiver-operating characteristics (ROC) curve analysis.

RESULTS: The median overall survival was 14.2 months, and the median progression-free survival was 5.28 months. Univariate analysis showed that smoking, ECOG performance score, brain metastasis, PD-L1 level, nivolumab treatment line, albumin, hemoglobin, LDH levels, platelet count, monocyte count, lymphocyte count, and LAR were associated with PFS. In the multivariate analysis, only LAR remained significantly associated with PFS. For overall survival, smoking, ECOG performance score, albumin level, LDH level, platelet count, monocyte count, lymphocyte count, brain metastasis, LAR, nivolumab treatment line, and PD-L1 level were significant in the univariate analysis. Albumin level, ECOG performance score, and LAR were independently associated with overall survival in the multivariate analysis.

CONCLUSIONS: The LAR, reflecting tumor burden, tumor hypoxia, immune response, nutritional status, and systemic inflammation, emerged as a potential prognostic biomarker in NSCLC receiving nivolumab monotherapy. This study highlights the importance of considering multiple factors in treatment decisions and supports the need for personalized approaches in NSCLC immunotherapy. Further research is needed to validate the utility of LAR as a predictive biomarker in this patient population.

Key Words:
Lactate dehydrogenase-to-albumin ratio, Non-small cell lung cancer, Nivolumab, Programmed cell death-ligand 1.

Introduction

Programmed Death-1 (PD-1) inhibitors are a class of immunotherapy drugs that target the PD-1 receptor on T-cells, enhancing the immune system's ability to recognize and attack cancer cells. PD-1 inhibitors work by blocking the interaction between PD-1, which is expressed on activated T-cells, and its ligands, PD-L1 and PD-L2, which are expressed on cancer cells and immune cells[1]. This interaction dampens the immune response, allowing cancer cells to evade destruction. By inhibiting PD-1, the immune response is unleashed, leading to enhanced T-cell activity against cancer cells[2]. Nivolumab (Opdivo, Bristol-Myers Squibb, Italy) is among the most known and used anti-PD-1 drugs. Nivolumab is approved for several indications, such as melanoma, NSCLC, renal cell carcinoma, Hodgkin lymphoma, and others[3-5].

Nivolumab is used as a monotherapy or combined with other advanced NSCLC therapies. It can be used in the first-line setting for NSCLC patients with high PD-L1 expression (tumor proportion score ≥50%) or in subsequent lines of treatment regardless of PD-L1 expression. Its efficacy has been shown in both squamous and non-squamous histologies of NSCLC[6,7].

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PD-L1 expression on tumor cells is an important biomarker for selecting patients who are more likely to respond to PD-1 inhibitors. However, it is not a perfect predictor, as some patients with low or invisible PD-L1 expression still drive clinical benefit[8]. Other biomarkers, such as tumor mutational burden (TMB) and microsatellite instability (MSI), are also being investigated[9,10] for their predictive value. While PD-L1 expression remains a widely used biomarker, TMB and MSI also offer complementary information on the tumor's immunogenicity and potential responsiveness to PD-1 inhibitors.

Indeed, all these biomarkers have limitations as perfect predictors of immunotherapy efficacy in NSCLC. Various studies[11] have explored additional potential biomarkers for assessing the effectiveness of immune checkpoint inhibitors (ICIs) in NSCLC to overcome this situation. Serum inflammatory markers have been investigated[11] as potential biomarkers.

Lactate and lactate dehydrogenase (LDH) have been found[12] to contribute to immunosuppression within the tumor microenvironment, potentially affecting the response to ICI treatment. Elevated LDH levels before treatment correlate with poorer progression-free survival (PFS) and overall survival (OS) in NSCLC patients undergoing ICIs[12].

Albumin, a protein synthesized in the liver, is a negative acute phase reactant that reflects both inflammatory and nutritional status. Inflammation and the release of cytokines in conditions like malnutrition and cachexia can impact albumin levels. Therefore, in some studies[13], albumin levels have been investigated as potential biomarkers reflecting the inflammatory, immune status, and nutritional status of NSCLC patients.

Evaluating LDH and albumin levels together provides a comprehensive assessment of the immune system, inflammation, and nutritional status. The LDH-to-albumin ratio (LAR) has been proposed[12-14] as a biomarker that encompasses tumor burden, tumor hypoxia, immune response, nutritional status, and systemic inflammation. Analyzing LAR can provide better information about the prognosis in NSCLC patients receiving ICIs. However, limited research[11-14] specifically evaluates the LAR and its association with immunotherapy efficacy, particularly in NSCLC patients. To address this knowledge gap, our study aimed to comprehensively analyze patients with NSCLC who received nivolumab as monotherapy, regardless of the treatment line. The goal was to identify reliable and easily accessible biomarkers that could assist in treatment selection for these patients.

Patients and Methods

A study was conducted at Manisa City Hospital, involving 144 patients diagnosed with metastatic NSCLC and treated with nivolumab between 2019 and 2023. The patients received intravenous nivolumab at a dose of 3 mg/kg every 2 weeks. The inclusion criteria were: being diagnosed with NSCLC and receiving at least one cycle of ICIs. Patients having a second primary malignancy, insufficient clinical or laboratory data, NSCLC with epidermal growth factor receptor (EGFR) gene mutation, or anaplastic lymphoma kinase (ALK) gene rearrangement or those treated with a tyrosine kinase inhibitor were excluded. Chronic liver disease was also an exclusion criterion.

The patients' demographic characteristics, such as age and sex, sites of metastasis, Eastern Cooperative Oncology Group (ECOG) performance score, date of diagnosis, location of metastasis (liver, lung, distant lymph node, adrenal, brain, and bone), hematologic and biochemical parameters, PFS and OS were recorded for analysis.

We assessed PD L1 expression using Dako's 22C3 anti-PD-L1 primary antibody with Ventana's detection systems BenchMark XT platform. We then calculated the tumor proportion score (TPS) by dividing the number of PD-L1 positive tumor cells by the total number of all tumor cells and multiplying by 100. The patients were divided into two groups based on their tps (TPS>50 and LAR≤50).

The correlation between OS and other parameters was retrospectively analyzed. The LDH to albumin ratio (LAR) was calculated by dividing LDH levels by albumin levels. The patients were divided into two groups based on their LAR values (LAR>62.82 and LAR≤62.82), using the best cut-off value determined by ROC analysis.

The primary endpoints of the study were OS and PFS. OS is defined as the initial ICI treatment to death or the last follow-up. PFS is measured from the first ICI treatment to disease progression, death, or the last follow-up. The objective response rate (ORR) and disease control rate (DCR) were also assessed. Response Evaluation Criteria in Solid Tumors (RECIST) was used to evaluate treatment response.

Statistical Analysis

In the study's statistical analysis, descriptive statistics were presented for numerical variables, including mean, standard deviation, median, minimum, and maximum values. For categorical variables, numbers and percentages were reported.

Survival analyses were conducted using the Kaplan-Meier estimate, allowing survival probabilities to be estimated over time. Determinative factors influencing survival were examined using Cox regression analysis. To determine the cut-off value for the LDH to albumin ratio (LAR), receiver-operating characteristics (ROC) curve analysis was performed. A significance level of $p<0.05$ was considered to determine statistical significance in all statistical analyses.

Ethics Approval

The study was conducted following the principles of the Declaration of Helsinki and reviewed and approved by the Health Sciences Ethics Committee of Manisa Celal Bayar University (Decision No.: 20.478.486/1569, Date: 02.11.2022). All authors confirm these methods were carried out according to the relevant guidelines and regulations, and written informed consent was obtained from each patient.

Results

A total of 144 patients were included in the study, divided into 96 (66.7%) males and 48 (33.3%) females, respectively. The median age of the patients was 61 years, ranging from 35 to 78. Among the patients, 108 (75%) were smokers, and the median number of cigarettes smoked was 30 pack-years. Table I shows the demographic characteristics of the patients, including sex distribution and smoking status (Table I). All other laboratory parameters are shown in Table II.

Regarding treatment, the patients received nivolumab ranging from the second line to the fourth line of therapy. The median OS for all patients was 14.2 months (95% CI, 10.85-17.56), and the median PFS was 5.28 months (95% CI, 3.46-7.53).

Progression-Free Survival Analysis

Univariate and multivariate analyses assessed the factors affecting progression-free survival in the study cohort (Table III).

In the univariate analysis, smoking habit (HR: 1.431, 95% CI: 1.021-1.921, $p=0.005$), ECOG score of 0-1 (HR: 1.415, 95% CI: 1.016-2.039, $p=0.041$) and ECOG score of 1-3 (HR: 3.683, 95% CI: 2.149-6.311, $p<0.001$), brain metastasis (HR: 1.121, 95% CI: 1.015-1.089, $p=0.033$) showed a significant association with progression-free survival.

Table I. Demographic characteristics of the patients.

Parameters		Number (n), median (min-max)	Percentage (%), (min-max)
Age	Median (minimum- maximum)	61	35-78
Sex	Male	96	66.7
	Female	48	33.3
Smoking habit	Positive	108	75
	Negative	36	25
ECOG performance score	≤1	74	51.4
	1<	70	49.6
Metastaz site	Brain	34	23.6
	LN	75	52.1
	Bone	70	48.6
	Liver	40	23.8
	Adrenal	52	36.1
	Lung	61	42.4
Histology	Adenocarcinoma	88	61.1
	Squamous cell carcinoma	56	38.9
Blood group	A	66	45.8
	0	40	37.8
	B	22	15.3
	AB	11	11.1
Nivolumab Line	=2 Line	31	21.5
	>2 Line	113	78.5
PD-L1	<50	70	0.49
	50≤	74	0.51

ECOG=Eastern cooperative oncology groub, LN=Lymph node, PD-L1=Programmed cell death ligand-1, Min=minimum, Max=maximum.

Low albumin levels (HR: -0.543, 95% CI: 0.371-0.802, $p<0.0001$) and low hemoglobin levels (HR: -0.579, 95% CI: 0.670-0.850, $p<0.0001$) were associated with poorer progression-free survival. High LDH/albumin ratio (HR: 1.866, 95% CI: 1.010-3.161, $p<0.0001$) was significantly associated with worse progression-free survival.

In the multivariate analysis, after adjusting for other variables, smoking habit ($p=0.514$), ECOG score ($p=0.245$), brain metastasis ($p=0.47$), and LDH/albumin ratio (HR: 1.114, 95% CI: 1.023-1.377, $p=0.007$) remained as significant factors affecting progression-free survival (Figure 1).

Table II. Laboratory parameters of the patients.

Parameters	Median (minimum-maximum)
Albumin (g/dL)	4 (2.2-4.5)
Hemoglobin (g/dL)	13.1 (10.3-15)
LDH (U/L)	223 (158-366)
Uric acide (mg/dL)	4 (3-9)
Platelet (10^3/μL)	273 (157-640)
Neutrophil (10^3/μL)	6.9 (3.9-18)
Lymphocyte (10^3/μL)	1.61 (1-3.2)
White blood cell (10^3/μL)	8.4 (5.4-13.9)
Monocyte (10^3/μL)	0.6 (0.5-1)

LDH=lactate dehydrogenase

Table III. Univariate and multivariate analyses of progression-free survival.

	Univariate analysis (HR, 95% CI)	*p*-value	Multivariate analysis (HR, 95% CI)	*p*-value
Sex	1.023 (0.892-1.036)	0.53		
Age	1.138 (0.871-1.522)	0.47		
Smoking habit	1.431 (1.021-1.921)	0.005	1.231(0.743-1.123)	0.514
ECOG	1.623 (1.004-5.687)	0.0001	1.285 (.892-1.623)	0.245
0-1	1.415 (1.016-2.039)	0.041		
1-3	3.683 (2.149-6.311)	<0.001		
Brain metastasis	1.121 (1.015-1.089)	0.033	1.110 (0.874-1.372)	0.47
LN metastasis	1.030 (0.874-1.215)	0.725		
Bone metastasis	1.113 (0.960- 1.336)	0.139		
Liver metastasis	1.049 (0.873-1.260)	0.610		
Adrenal metastasis	1.141 (0.961-1.354)	0.132		
Lung metastasis	-0.993 (0.841-1.173)	0.936		
Histology	1.291 (0.913-1.825)	0.149		
PDL-1		0.0001	1.391 (0.930-1.725)	0.267
<50	4.425 (1.869-5.235)	<0.0001	1.295 (0.786-1.765)	0.670
≥50	3.232 (1.241-4.762)	<0.0001	1.953 (0.837-1.875)	0.540
Albumin	-0.543 (0.371-0.802)	0.0001	1.482(0.743-1.828)	0.241
Hemoglobin	-0.579 (0.670-0.850)	<0.0001	0.794 (0.456-1.239)	0.642
LDH	1.723 (1.024-4.648)	<0.0001	0.647 (0.644-1.568)	0.574
Uric acide	0.996 (0.857-1.158)	0.960		
Platelet	1.005 (1.000-1.009)	0.010	1.123 (0.901-1.171)	0.534
White blood cell	1.000 (1.000-1.000)	0.617		
Monocyte	-0.540 (0.436-0.894)	<0.0001	1.037 (0.761-1.581)	0.389
Lymphocyte	-0.599 (0.245-0.804)	<0.0001	1.143 (0.536-1.482)	0.764
Neutrophil	1.000 (1.000-1.000)	<0.0001		
LDH/Albumin	1.866 (1.010-3.161)	<0.0001	1.114 (1.023-1.377)	0.007
LDH/Hb	2.581(0.540-3.400)	0.171		
LDH/UA	1.320 (0.880-1.970)	0.193		
LDH/Plt	1.081 (0.710-1.641)	0.710		
LDH/WBC	1.423 (0.672-2.712)	0.055		
LDH/monocyte	1.623 (0.410-1.905)	0.257		
LDH/lymphocyte	1.011 (0.941-1.085)	0.761		
LDH/neutrophil	1.293 (0.892-1.692)	0.541		
Blood group		0.65		
A-0	1.536 (0.875-2.698)	0.135		
A-B	1.235 (0.750-1.565)	0.516		
A-AB	1.401 (0.723-2.718)	0.318		
Nivolumab Line		0.001		0.234
<3	1.532 (1.259-3.346)	0.001	1.497 (0.827-1.514)	0.453
3≤	1.695 (1.347-3.245)	0.001	1.568 (0.769-1.896)	0.538

HR=hazard ratio, ECOG=Eastern cooperative oncology group, LN=Lymph node, LDH=lactate dehydrogenase, Hb=hemoglobin, Alb=albumin, UA=Uric acide, WBC=white blood cell, PNL=neutrophil, PD-L1=Programmed cell death ligand-1.

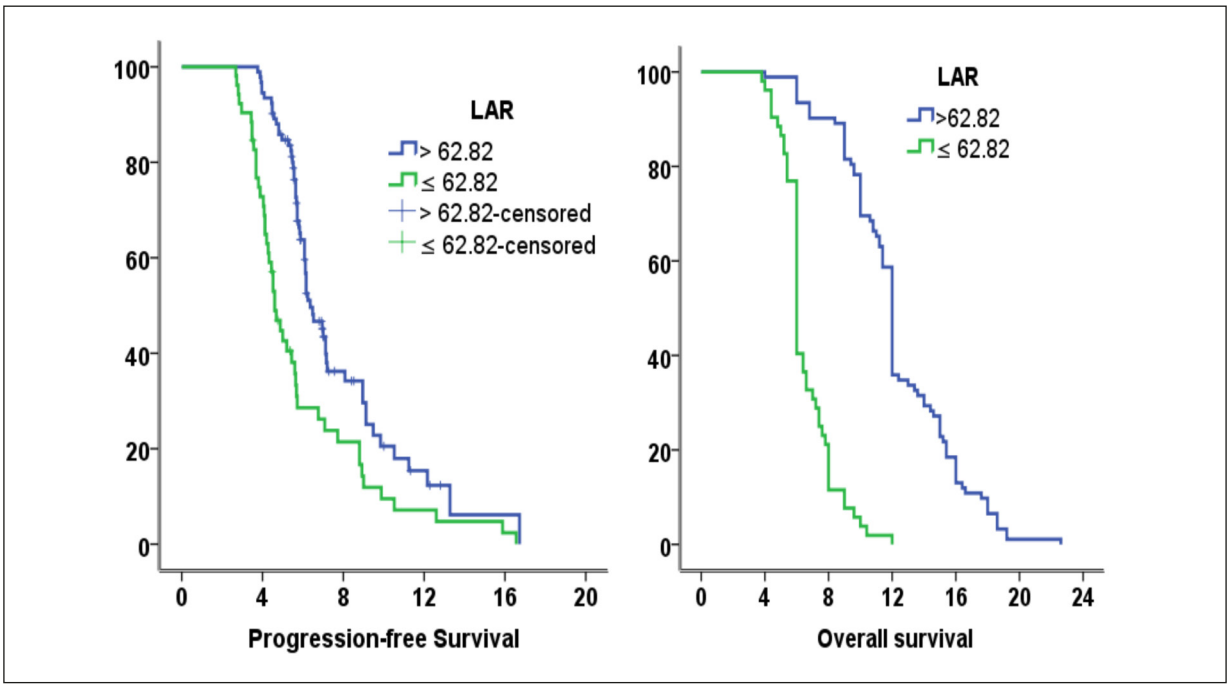

Figure 1. Kaplan-Meier curves of LAR (lactate dehydrogenase to albumin ratio) for progression-free survival and overall survival.

Overall Survival Analysis

Univariate and multivariate analyses were also performed to evaluate the factors influencing OS in the study population. Smoking status (HR: 1.321, 95% CI: 1.003-1.819, p=0.004), ECOG score (HR: 1.223, 95% CI: 1.006-4.487, p<0.0001), low albumin levels (HR: -0.453, 95% CI: 0.289-0.700, p=0.013) were associated with poorer OS. LDH/albumin ratio (HR: 1.166, 95% CI: 1.013-1.071, p<0.0001) remained a significant factor affecting OS after multivariate analysis (Table IV and Figure 1).

Discussion

In this study, encompassing a cohort of 144 patients diagnosed with NSCLC and treated with nivolumab monotherapy, receiving at least one cycle, a comprehensive exploration of clinical and laboratory parameters about patient outcomes has been undertaken. This research uniquely advances the field by investigating the significance of the LDH/LAR in NSCLC patients, independently from PD-L1 levels, thus filling a critical knowledge gap.

Our findings underscore the relevance of well-established biomarkers, notably low serum albumin levels and elevated LDH concentrations, as prognostic indicators of adverse outcomes in cancer immunotherapy, particularly in the context of NSCLC. These markers, indicative of systemic inflammation and overall health status, have been linked to treatment response variations in cancer patients, reflecting the complicated interplay between immune function and tumor microenvironment.

A central finding of our investigation is the robust association between the LDH/albumin ratio and both PFS and OS. This notable association was consistently observed across univariate and multivariate analyses, underscoring its independent prognostic capacity. Specifically, a high LDH/albumin ratio was found to be significantly correlated with diminished PFS (HR: 1.866, 95% CI: 1.010-3.161, p<0.0001) and OS (HR: 1.166, 95% CI: 1.013-1.071, p<0.0001), even following adjustment for pertinent confounding factors.

The prognostic potential of the LDH/albumin ratio has been evidenced in previous research across various tumor types[14-17]. Shen et al[18] highlighted the association between an elevated LAR and reduced OS in metastatic renal cell carcinoma patients treated with targeted therapy. Similarly, Xie et al[19] revealed the adverse impact of higher preoperative LAR on PFS and OS in glioblastoma patients, suggesting its utility as a prognostic marker in this aggressive brain malignancy. Moreover, Wu et al[20] demonstrated the prognostic relevance of LAR in stage II/III colorectal cancer patients receiving adjuvant

Table IV. Univariate and multivariate analyses of overall survival.

	Univariate analysis (HR, 95% CI)	*p*-value	Multivariate analysis (HR, 95% CI)	*p*-value
Sex	1.007 (0.984-1.018)	0.627		
Age	1.167 (0.902-1.590)	0.221		
Smoking habit	1.321 (1.003-1.819)	0.004	1.002 (0.993-1.012)	0.604
ECOG	1.223 (1.006-4.487)	<0.0001	1.185 (1.082-1.515)	0.002
0-1	1.415 (1.016-2.039)	0.041		
1-3	3.683 (2.149-6.311)	<0.001		
Brain metastasis	1.031 (1.003-1.019)	0.044	1.151 (0.971-1.254)	0.134
LN metastasis	1.236 (0.932-1.638)	0.144		
Bone metastasis	1.282(0.943-1.756)	0.115		
Liver metastasis	1.225 (0.769-1.945)	0.249		
Adrenal metastasis	1.017 (0.831-1.362)	0.954		
Lung metastasis	1.376 (0.7952-2.136)	0.161		
Histology	1.034 (0.726-1.458)	0.751		
PDL-1		<0.0001	1.391 (0.930-1.725)	0.159
<50	3.517 (1.979-6.25)	<0.0001		
≥50	2.34 (1.534-3.560)	<0.0001		
Albumin	-0.453 (0.289-0.700)	0.013	1.289 (1.143-1.626)	0.001
Hemoglobin	-0.759 (0.670-0.850)	0.013	0.896 (0.857-1.158)	0.850
LDH	1.523 (1.003-5.897)	<0.0001	0.743 (0.643-1.276)	0.614
Uric acid	1.000 (0.670-1.345)	0.455	0.455	
Platelet	1.002 (1.000-1.003)	<0.0001	1.051 (0.931-1.194)	0.434
WBC	1.000 (0.987-1.044)	0.507	0.607	
Monocyte	-0.015 (0.004-0.059)	<0.0001	1.037 (0.761-1.581)	0.334
Lymphocyte	-0.019 (0.0459-0.804)	<0.0001	1.143 (0.536-1.482)	0.567
Neutrophil	1.011 (0.984-1.021)	0.359		
LDH/Albumin	1.166 (1.013-1.071)	<0.0001	1.124 (1.004-1.340)	0.007
LDH/Hemoglobin	1.413 (0.922-2.183)	0.12		
LDH/Uric acide	1.282 (.0733-2.729)	0.39		
LDH/Platelet	1.234 (0.744-2.072)	0.41		
LDH/WBC	1.153 (0.957-1.371)	0.12		
LDH/monocyte	1.152 (0.626-2.110)	0.66		
LDH/lymphocyte	1.0391 (0.886-1.152)	0.891		
LDH/neutrophil	1.493 (0.692-1.698)	0.691		
Blood group		0.72		
A-0	2.88 (0.47-10.17)	0.32		
A-B	2.16 (0.447-3.32)	0.66		
A-AB	1.01 (0.98-1.06)	0.252		
Nivolumab Line		0.014		0.348
<3	2.132 (1.359-3.346)	0.001	1.397 (0.936-1.726)	0.512
3≤	3.195 (1.947-5.245)	0.001	1.810 (0.854-1.892)	0.562

HR=hazard ratio, ECOG=Eastern cooperative oncology group, LN=Lymph node, LDH=lactate dehydrogenase, Hb=hemoglobin, Alb=Albumin, UA=Uric acide, WBC=white blood cell, PNL=neutrophile, PD-L1=Programmed cell death ligand-1.

chemotherapy, reinforcing the potential of this biomarker across a spectrum of malignancies.

The finding that smoking status was significantly associated with both PFS and OS is also consistent with previous studies[21-23]. Smoking is a well-known risk factor for developing lung cancer, and it has been suggested that smoking-related genetic alterations may influence response to immunotherapy[21,22]. Several studies[21-23] have shown that current or former smokers have higher response rates and improved survival outcomes with immunotherapy compared to non-smokers.

A higher ECOG indicates poorer performance and is associated with worse outcomes in various cancer types, including NSCLC. Brain metastases are known to be associated with a poor prognosis in NSCLC patients[24,25]. The blood-brain barrier restricts the entry of systemic treatments, including immunotherapies, into the brain. In our study, these factors were also associated with worse survival.

The significant association between PD-L1 level and PFS/OS aligns with previous studies[8,9] evaluating the predictive role of PD-L1 expression in NSCLC patients treated with immunotherapy.

Higher PD-L1 expression has been associated with improved response rates and survival outcomes in NSCLC, receiving PD-1/PD-L1 inhibitors. However, it is important to note that PD-L1 expression is not a perfect predictor, and patients with low or invisible PD-L1 expression can still respond to immunotherapy[26,27].

Limitations

This study has certain limitations, as conducting the study in a single center may introduce potential biases and limit the generalizability of the results. The patient population and treatment protocols may not be representative of the broader NSCLC population. Multi-center studies with larger sample sizes are generally more robust in providing reliable conclusions. With a sample size of 144 cases, there is a possibility of limited statistical power and the potential for random variation to affect the results. Larger sample sizes are typically preferred to increase the validity and generalizability of the findings. Assessing LAR at a single time point before immunotherapy may not capture the dynamic changes in this biomarker throughout the entire treatment cycle. Considering LAR dynamics over time could provide a more comprehensive understanding of its prognostic value and its potential as a predictive biomarker for immunotherapy efficacy.

Overall, our study's findings are in line with existing literature on the associations between smoking, performance status, brain metastasis, PD-L1 expression, albumin, LDH, and patient outcomes in NSCLC treated with immunotherapy. The inclusion of LAR as a novel biomarker adds to the growing body of evidence suggesting its potential utility in predicting prognosis and treatment response. These results emphasize the importance of considering multiple factors in treatment decision-making and support the need for personalized approaches in NSCLC immunotherapy.

Conclusions

We found that the LAR ratio can be used as an independent adverse prognostic factor in NSCLC patients receiving nivolumab as treatment. For these patients, prognosis can lead to multi-dimensional risk stratification. The results suggest that the follow-up interval of patients should be adjusted according to the LAR ratio. Also, we claim that the follow-up interval of patients with a high LAR value should be shortened to extend their PFS and OS.

Conflict of Interest

The authors declare no conflict of interest.

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Ethics Approval

The study was conducted following the principles of the Declaration of Helsinki and reviewed and approved by the Health Sciences Ethics Committee of Manisa Celal Bayar University (Decision No.: 20.478.486/1569, Date: 02.11.2022).

Informed Consent

Written informed consent was obtained from each patient.

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