ORIGINAL RESEARCH

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Association of the Immune-Inflammation-Nutritional Parameters with Immune Checkpoint Inhibitor Outcomes in Patients with Advanced Non-Small Cell Lung Cancer

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ABSTRACT Objective: Patient prognosis is determined not only based on tumor characteristics, host inflammation and the immune-nutritional index are also important. The aim of the study was to investigate the prognostic and predictive role of pretreatment immune-inflammation-nutritional biomarkers in patients with advanced non-small cell lung cancer who were treated with immune checkpoint inhibitors (ICIs). **Material and Methods:** All consecutive patients aged over 18 years who were treated with at least one cycle of ICIs at our centers were retrospectively reviewed. We evaluated modified Glasgow Prognostic Score (mGPS), Lung Immune Prognostic Index, serum C-reactive protein (CRP) and lactate dehydrogenase (LDH) as candidate predictors for response and survival. **Results:** A total of 102 patients who were treated with ICIs between March 2017 and October 2021 were reviewed. Among the patient cohort, 46.1% and 53.9% were treatment-naive and platinum pretreated, respectively. Programmed death ligand-1 positivity (p=0.048), presence of bone metastasis (p=0.048), increasing serum CRP levels (p=0.018), and mGPS 1 (p=0.040) were independently associated with inferior progression-free survival. Presence of liver metastasis (p=0.036), serum LDH level>upper level of normal (p=0.048), Eastern Cooperative Oncology Group Performance Status (ECOG PS)≥2 (p=0.026), and increasing CRP levels (p<0.001) were independently associated with poorer overall survival. ECOG PS≥2 (p=0.001), the presence of bone metastasis (p=0.049), and mGPS 1 (p=0.016) were independently associated with poorer disease control rate. **Conclusion:** We found that immune-inflammation-nutritional parameters were reliable prognostic and predictive biomarkers to select patients with a greater likelihood of benefiting from ICIs.

Keywords: Immune checkpoint inhibitors; non-small cell lung cancer; C-reactive protein; lactate dehydrogenase; Lung Immune Prognostic Index; Modified Glasgow Prognostic Index

Immune evasion is one of the hallmarks of cancer development and progression.[1] The discovery of harnessing the immune system by using anti-programmed death-1 (PD-1) or anti-programmed death ligand-1 (PD-L1) blockade has revolutionized cancer treatment. Immune checkpoint inhibitors (ICIs) have now been integrated into the treatment of patients with advanced non-small cell lung cancer (NSCLC) whose tumors do not harbor genomic alterations. Several clinical trials have shown that treatment with ICIs significantly improved overall survival (OS) as compared to chemotherapy. Consequently, ICIs became the standard of care, initially for patients who received platinum-based chemotherapy, and it was then used either alone or in combination with chemotherapy for treatment-naive patients with advanced NSCLC.[2-9]

Although ICIs are a revolutionary treatment option, they do not induce a response in every patient. The response rate of ICIs is 14-20% for patients who are platinum-refractory and 44.8-57.9% for patients who are treatment-naïve.[2-4,9] Treatment with ICIs also

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leads to a serious financial burden. Hence, it is important to determine the predictive and prognostic biomarkers for ICI treatment. PD-L1 level has become a companion diagnostic assay for the initial choice of treatment for patients with advanced NSCLC who lack a driver mutation.[10] However, it remains controversial whether the determination of PD-L1 is an optimal assay. Patients who are PD-L1 negative may show objective responses, while those who test positive for PD-L1 may not respond adequately. Heterogeneity is also observed in the expression of PD-L1 between serial sections of the whole tumor tissue from the same patient. PD-L1 expression is dynamic in nature and may be affected by chemotherapy and radiotherapy. Moreover, there are no reliable and practical biomarkers for pretreated patients with NSCLC.[2-4,6,11-14]

Patient prognosis is determined not only based on tumor characteristics, but host inflammation status and the immune-nutritional index are also important prognostic markers. Recently, some studies have demonstrated that immune-nutritional biomarkers are prognostic and predictive for ICI treatment.[15-19] In this context, the present study aimed to investigate the prognostic and predictive role of pretreatment immune-inflammation-nutritional biomarkers in patients with unresectable or advanced NSCLC who were treated with ICIs.

MATERIAL AND METHODS

PATIENTS

All consecutive patients aged over 18 years who were diagnosed to have unresectable/advanced stage NSCLC and were treated with at least one cycle of ICIs at the Medical Oncology Departments of Dr. Burhan Nalbantoğlu State Hospital (Nicosia, Cyprus) and Near East University Hospital (Nicosia, Cyprus) were included in the study, and their medical records were retrospectively reviewed from patient files, the center's databases, and chemotherapy unit files. Ethical approval for the study was obtained from the individual institutional Ethics Review Committees (Dr. Burhan Nalbantoğlu State Hospital 21/21, March 4, 2021), and a consent waiver was granted because of the retrospective nature of the study. All study procedures that involved human participants were performed in accordance with the ethical standards of the institutional and/or national research committee, and the procedures also complied with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

STUDY DESIGN AND VARIABLES

The following patient demographics were recorded for analysis: Eastern Cooperative Oncology Group Performance Status (ECOG PS) at the time of initiating ICI treatment; smoking history; histology; molecular profiling for the *EGFR*, *ALK*, *ROS1*, and *BRAF* genes when available; PD-L1 status (Dako; Carpinteria, CA, USA) when available; sites of metastatic spread at the time of initiating ICI treatment; response status; date of death or last follow-up; immune-related adverse events (irAEs); and baseline complete blood count and serum albumin, lactate dehydrogenase (LDH), and C-reactive protein (CRP) levels (defined as the most recent drawn sample within 2 weeks before the initiation of ICI treatment).

Response assessment was performed mostly by using computed tomography (CT) or fluorodeoxyglucose positron emission tomography-CT every 3 months. The best radiographic response, i.e., complete remission (CR), progressive disease, partial response (PR), and stable disease (SD), and the time to achieve the best response were recorded using the response evaluation criteria in solid tumors criteria V 1.1.[20] The irAEs were determined, characterized, and graded by 2 investigators (O.D. and P.O.) according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0.

We evaluated immune-inflammation-nutritional biomarkers as candidate predictors for response and survival. The modified Glasgow Prognostic Score (mGPS) is based on serum CRP and albumin levels.[21] Patients with elevated CRP (>1.0 mg/dL) and hypoalbuminemia (<3.5 g/dL) are assigned an mGPS of 2. Patients with serum CRP<1.0 mg/dL with or without hypoalbuminemia receive a score of 0. Patients with only elevated CRP levels receive an mGPS of 1. The Lung Immune Prognostic Index (LIPI) is developed based on a derived neutrophil-lymphocyte

ratio (dNLR) higher than 3 and LDH level greater than the upper level of normal (ULN); it is classified into 3 groups: good, 0 factors; intermediate, 1 factor; poor, 2 factors. The dNLR is calculated as neutrophil count/(white blood cell count-neutrophil count).[16,17]

STATISTICAL ANALYSIS

Statistical analyses were conducted using SPSS version 22 software (IBM Corp., Chicago, IL). Demographic characteristics were described using frequencies and percentages for categorical variables and medians and ranges for continuous variables. Progression-free survival (PFS) was defined as the number of months between the first ICI treatment and death or tumor progression, whichever occurred first (censored at the date of the last patient contact). OS was defined as the number of months between the first ICI treatment and death or censored at the date of the last patient follow-up. The objective response rate (ORR) was calculated as the percentage of patients achieving PR and CR among all the treated patients. The disease control rate (DCR) was defined as the percentage of patients achieving CR, PR, and SD. The OS and PFS curves were drawn using the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate analyses were performed using a logistic regression model. A Cox proportional hazards model was used to identify independent predictive and prognostic factors. The multivariate models were fitted with covariates that yielded statistically significant results in the univariate model. A p-value of <0.05 was considered to be statistically significant in all analyses.

RESULTS

PATIENT AND TUMOR CHARACTERISTICS

A total of 102 patients who were treated with ICIs between March 2017 and October 2021 were retrospectively reviewed. The baseline clinical and tumor characteristics at the initiation of ICI treatment are presented in Table 1. The median age of the patients was 66.50 (range, 35-88) years. The majority of patients were male (n=89, 87.3%) and former or current smokers (n=97, 95.1%). More than half (57.8%) of the patients had an ECOG PS≥2, 35.3% of the patients were diagnosed to have squamous cell carcinoma, and 21.6% of patients had liver metastasis.

TABLE 1: Baseline patient and tumor characteristics.

Age at the start (years)	
Median	66.50
Range	35-88
Sex n (%)	
Male	89 (87.3)
Female	13 (12.7)
Smoking status n (%)	
Current or former smoker	97 (95.1)
Never smoked	5 (4.9)
Histology-no (%)	
Adenocarcinoma	62 (60.8)
Squamous cell carcinoma	36 (35.3)
Adenosquamous	1 (1.0)
NSCLC, NOS	3 (2.9)
PD-L1 n (%)	
Negative	26 (25.5)
1-49%	7 (6.9)
≥50%	10 (9.8)
Unknown	59 (57.8)
Driver mutations	
EGFR mutation	1 (1.0)
ALK translocation	1 (1.0)
Not assessed	40 (39.2)
EGFR-ALK wild type	60 (58.8)
ECOG performance status score n (%)	
0-1	43 (42.2)
2-4	59 (57.8)
CNS metastasis n (%)	
Yes	10 (9.8)
No	92 (90.2)
Liver metastasis n (%)	
Yes	22 (21.6)
No	80 (78.4)
Bone metastasis n (%)	
Yes	40 (39.2)
No	62 (60.8)
Malignant pleural effusion n (%)	
Yes	21 (20.6)
No	81 (79.4)
Adrenal gland metastasis n (%)	
Yes	25 (24.5)
No	77 (75.5)

NSCLC: Non-small cell lung cancer; NOS: Not otherwise specified; PD-L1: Programmed death ligand-1; ECOG: Eastern Cooperative Oncology Group; CNS: Central nervous system.

Two patients were found to have driver mutations, and PD-L1 results were available in 42.2% of the patients.

Among the patient cohort, 46.1% and 53.9% of the patients were treatment-naive, and platinum pretreated, respectively. The median duration of follow-up (defined as the time from the initiation of ICI treatment to death or the date of data cutoff for surviving patients) was 8.4 (range, 0.03-49.53) months. At the time of database closure (October 25, 2021), 13.7% of the patients were continuing ICI treatment. The treatment characteristics are shown in Table 2.

The median serum LDH and CRP levels were 248 IU/L and 1.98 mg/dL, respectively. A total of 17.6% of the patients were in the poor LIPI group, and 22.5% of patients had an mGPS of 2. The baseline immune-inflammation-nutritional parameters are shown in Table 3. Seventy-seven (75.5%) patients died, and the median OS was 11.6 months [95% confidence interval (CI), 8.4-14.8] (Figure 1A). The OS rate at 24 months was 21%. The ORR and median PFS were 41.2% and 5.2 (95% CI: 2.9-7.4) months, respectively (Figure 1B).

PROGNOSTIC AND PREDICTIVE FACTORS

We evaluated the prognostic and predictive role of the clinicopathological factors and immune-inflammation-nutritional parameters (Table 4). In the univariate analysis, ECOG PS≥2 (p=0.050), ≥2nd-line ICI treatment (p=0.001), presence of bone metastasis (p=0.006), malignant pleural effusion (p=0.001), liver metastasis (p=0.004), LDH level >ULN (p<0.001), elevated CRP levels (p<0.001), and mGPS (p=0.002) were associated with poor PFS. Patients who developed irAEs and PD-L1 positivity (p=0.001) showed better PFS (p=0.002). In the final multivariate analysis, presence of bone metastasis (p=0.048), elevated serum CRP levels (p=0.018), and an mGPS of 1 (p=0.040) were independently associated with poor PFS, whereas PD-L1 positivity (p=0.048) was associated with better PFS. The Kaplan-Meier survival curves are shown in Figure 2.

ECOG PS≥2 (p=0.044), ≥2nd-line ICI treatment (p=0.004), presence of bone metastasis (p=0.026), liver metastasis (p=0.003), LDH level >ULN (p<0.001), LIPI status (p<0.001), elevated CRP levels (p<0.001), and mGPS (p=0.005) were associated with worse OS in the univariate analysis.

TABLE 2: Treatment characteristics of the patients.

Variables	Patients (n=102)
First-line ICIs n (%)	47 (46.1)
Single-agent pembrolizumab	12 (11.8)
Pembrolizumab plus chemotherapy	32 (31.4)
Nivolumab plus ipilimumab	3 (2.9)
≥2nd-line ICIs n (%)	55 (53.9)
Single-agent pembrolizumab	5 (4.9)
Single agent nivolumab	50 (49.0)
Reasons of discontinuation for ICIs n (%)	
Progressive disease or death	79 (77.5)
irAEs	4 (3.9)
No evidence of disease >1 year with ICI	5 (4.9)

ICIs: Immune checkpoint inhibitors; irAEs: Immune related adverse events.

TABLE 3: Baseline immune-inflammation-nutritional parameters.

Variables	
LDH (U/L)	
Median	248
Range	136-1,335
>ULN (%)	54.9
Albumin (g/dL)	
Median	3.90
Range	2.20-5.30
≥3.5 g/dL (%)	75.5
dNLR	
Median	2.21
Range	0.38-22.05
>3 (%)	28.4
CRP (mg/dL)	
Median	1.98
Range	0.07-36.20
≥1.0 mg/dL (%)	63.7
LIPI n (%)	
Good	39 (38.2)
Intermediate	45 (44.1)
Poor	18 (17.7)
mGPS n (%)	
0	35 (34.3)
1	44 (43.1)
2	23 (22.6)

LDH: Lactate dehydrogenase; ULN: Upper level of normal; dNLR: Derived neutrophil-lymphocyte ratio; CRP: C-reactive protein; LIPI: Lung Immune Prognostic Index; mGPS: Modified Glasgow Prognostic Score.

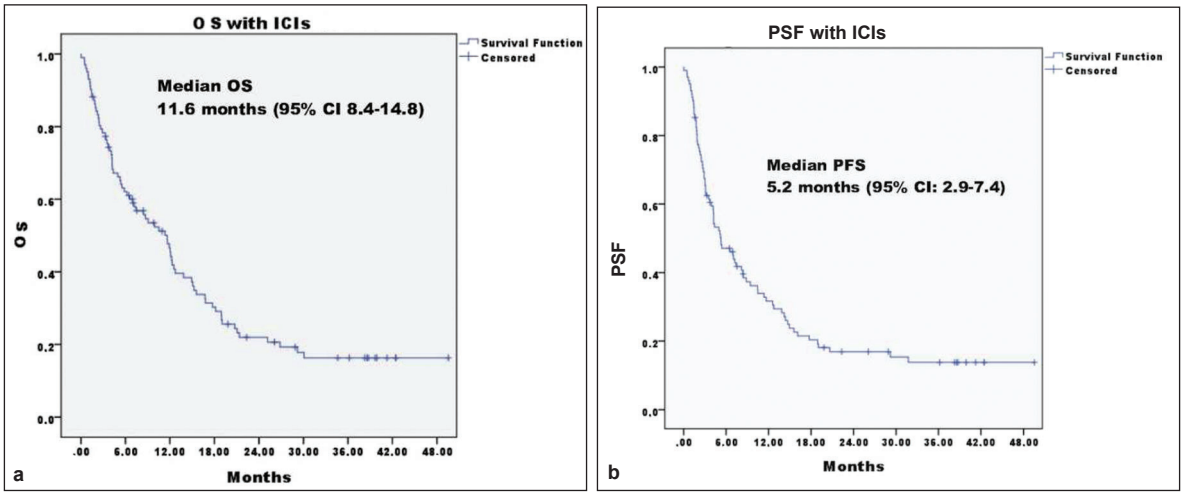

FIGURE 1: Kaplan-Meier plot for **a)** OS and **b)** PFS (95% CI). OS: Overall survival; ICIs: Immune checkpoint inhibitors; PFS: Progression-free survival; CI: Confidence interval.

TABLE 4: Univariable and multivariable analyses of OS and PFS.

	PFS		OS	
Variables	Unadjusted HR (95% CI); p value	Adjusted HR (95% CI); p value	Unadjusted HR (95% CI); p value	Adjusted HR (95% CI); p value
ECOG PS≥2	1.55 (1.00-2.41); **0.050**	2.33 (0.90-6.02); 0.080	1.60 (1.01-2.54); **0.044**	1.82 (1.07-3.10); **0.026**
Squamous cell carcinoma	0.68 (0.43-1.07); 0.099	-	0.69 (0.43-1.12); 0.137	-
Anti-PD-L1	N/A, **0.001**	N/A, 0.052	N/A, 0.115	-
Negative	1 (reference)	1 (reference)	1 (reference)	
1-49%	0.24 (0.09-0.64); **0.004**	0.29 (0.08-0.99); **0.048**	0.57 (0.24-1.34); 0.203	
≥50%	0.23 (0.09-0.55); **0.001**	0.32 (0.10-0.99); **0.048**	0.47 (0.21-1.01); 0.055	
≥2nd-line ICIs treatment	0.48 (0.31-0.75); **0.001**	0.60 (0.18-1.99); 0.405	0.51 (0.32-0.80); **0.004**	0.72 (0.43-1.20); 0.213
Presence of brain metastasis	1.32 (0.63-2.76); 0.448	-	1.36 (0.62-2.97); 0.440	-
Presence of bone metastasis	1.86 (1.19-2.91); **0.006**	2.77 (1.01-7.61); **0.048**	1.67 (1.06-2.63); **0.026**	1.34 (0.81-2.24); 0.249
Presence of adrenal gland metastasis	1.13 (0.68-1.88); 0.620	-	1.17 (0.69-2.00); 0.546	-
Presence of malignant pleural effusion	2.41 (1.43-4.05); **0.001**	1.86 (0.78-4.45); 0.161	1.65 (0.97-2.81); 0.063	-
Presence of liver metastasis	2.05 (1.25-3.36); **0.004**	1.04 (0.44-2.45); 0.919	2.15 (1.28-3.59); **0.003**	1.85 (1.04-3.30); **0.036**
irAEs	0.39 (0.21-0.71); **0.002**	1.91 (0.55-6.56); 0.302	0.44 (0.23-0.81); **0.010**	0.73 (0.37-1.43); 0.366
dNLR>3	1.54 (0.96-2.46); 0.072	-	1.49 (0.91-2.43); 0.107	-
LDH>ULN	2.77 (1.75-4.40); **<0.001**	2.25 (0.74-6.81); 0.148	2.89 (1.79-4.66); **<0.001**	2.00 (1.00-3.98); **0.048**
LIPI status	N/A, **<0.001**	N/A, 0.643	N/A, **<0.001**	N/A, 0.836
Good	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Intermediate	2.42 (1.47-3.99); **0.001**	1.23 (0.38-3.99); 0.726	2.37 (1.40-3.99); **0.001**	0.88 (0.40-1.89); 0.746
Poor	3.72 (1.97-7.03); **<0.001**	1.91 (0.47-7.68); 0.361	3.70 (1.91-7.15); **<0.001**	1.08 (0.41-2.85); 0.869
CRP level	1.12 (1.08-1.16); **<0.001**	1.08 (1.01-1.15); **0.018**	1.12 (1.08-1.16); **<0.001**	1.09 (1.04-1.14); **<0.001**
Albumin level ≥3.5 g/dL	0.69 (0.41-1.16); 0.164	-	0.66 (0.39-1.12); 0.125	-
mGPS	N/A, **0.002**	N/A, 0.063	N/A, **0.005**	N/A, 0.600
0	1 (reference)	1 (reference)	1 (reference)	1 (reference)
1	2.44 (1.46-4.06); **0.001**	2.94 (1.05-8.25); **0.040**	2.26 (1.32-3.88); **0.003**	1.38 (0.71-2.68); 0.333
2	2.37 (1.27-4.44); **0.007**	4.00 (0.88-18.01); 0.071	2.43 (1.28-4.64); **0.007**	1.12 (0.49-2.55); 0.786

OS: Overall survival; PFS: Progression-free survival; HR: Hazard ratio; CI: Confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; PD-L1: Programmed death ligand-1; N/A: Not applicable; ICIs: Immune checkpoint inhibitors; irAEs: Immune related adverse events; dNLR: Derived neutrophil-lymphocyte ratio; LDH: Lactate dehydrogenase; ULN: Upper level of normal; LIPI: Lung Immune Prognostic Index; CRP: C-reactive protein; mGPS: Modified Glasgow Prognostic Score.

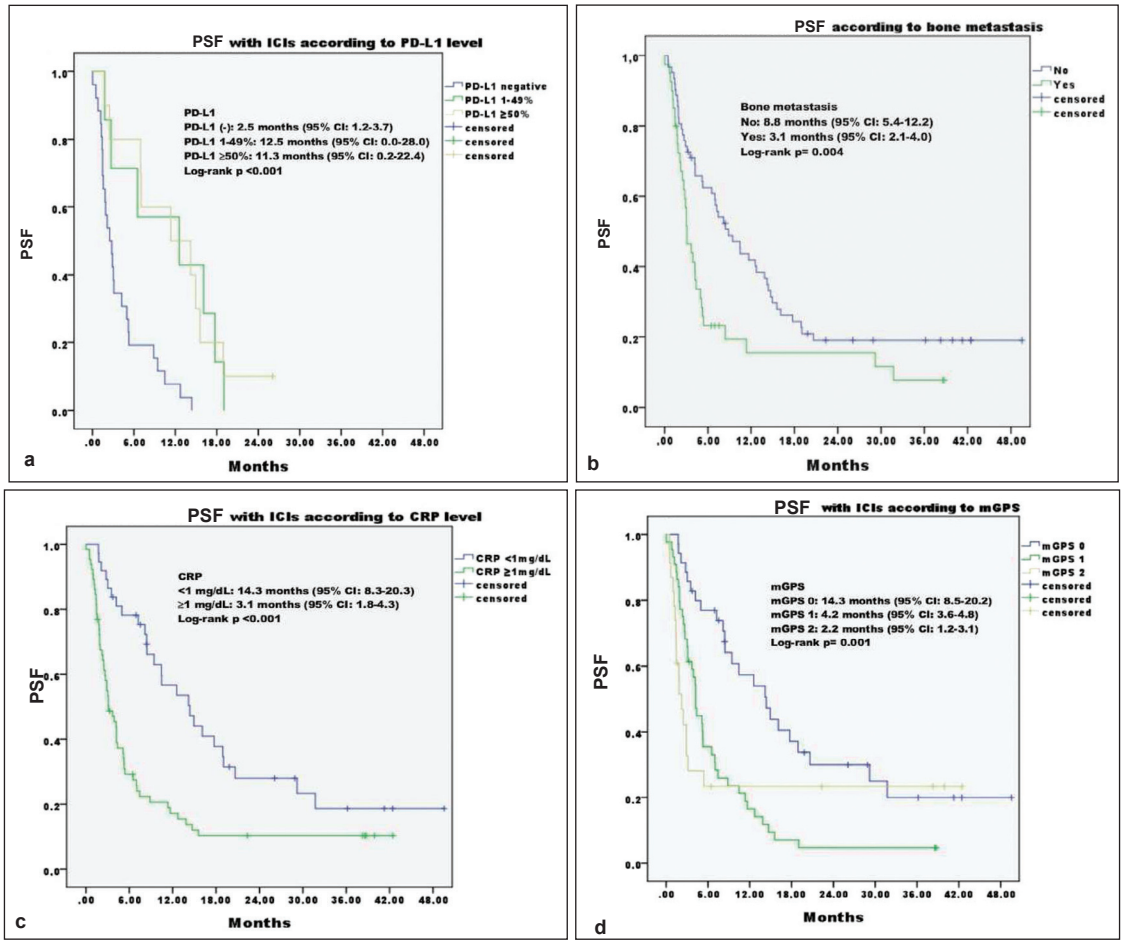

FIGURE 2: Kaplan-Meier plot for the PFS stratified by **a)** Anti-PD-L1 level, **b)** Bone metastasis, **c)** Serum CRP level and **d)** mGPS (95% CI). PFS: Progression-free survival; ICIs: Immune checkpoint inhibitors; PD-L1: Programmed death ligand-1; CI: Confidence interval; CRP: C-reactive protein; mGPS: Modified Glasgow Prognostic Score.

Presence of liver metastasis (p=0.036), serum LDH level >ULN (p=0.048), ECOG PS≥2 (p=0.026), and elevated serum CRP levels (p<0.001) were independently associated with poor OS in the final multivariate model. As shown by representative Kaplan-Meier curves, presence of liver metastasis, serum LDH level >ULN, ECOG PS≥2, and elevated serum CRP levels were associated with poor median OS (Figure 3).

None of the clinicopathological factors and immune-inflammation-nutritional parameters were independently associated with ORR. However, the multivariate analysis revealed that ECOG PS≥2 (p=0.001), presence of bone metastasis (p=0.049), and an mGPS of 1 (p=0.016) were independently associated with poor DCR (Table 5).

DISCUSSION

Immune-inflammation-nutritional parameters have been proven to be appropriate prognostic markers in the pre-ICI era.[22-24] In the present study, we focused on the role of host inflammation status and immune-nutritional biomarkers in patients with advanced NSCLC who were treated with ICIs.

In our study, pretreatment serum CRP levels were independently associated with poor PFS and OS, and this finding was consistent with the report of several studies in the literature.[15,19,25] We performed Cox regression analysis using serum CRP levels as a continuous variable. However, to perform Kaplan-Meier analysis, we categorized serum CRP levels in two groups as ≥1 mg/dL and <1 mg/dL. A strong biological relationship exists between elevated CRP

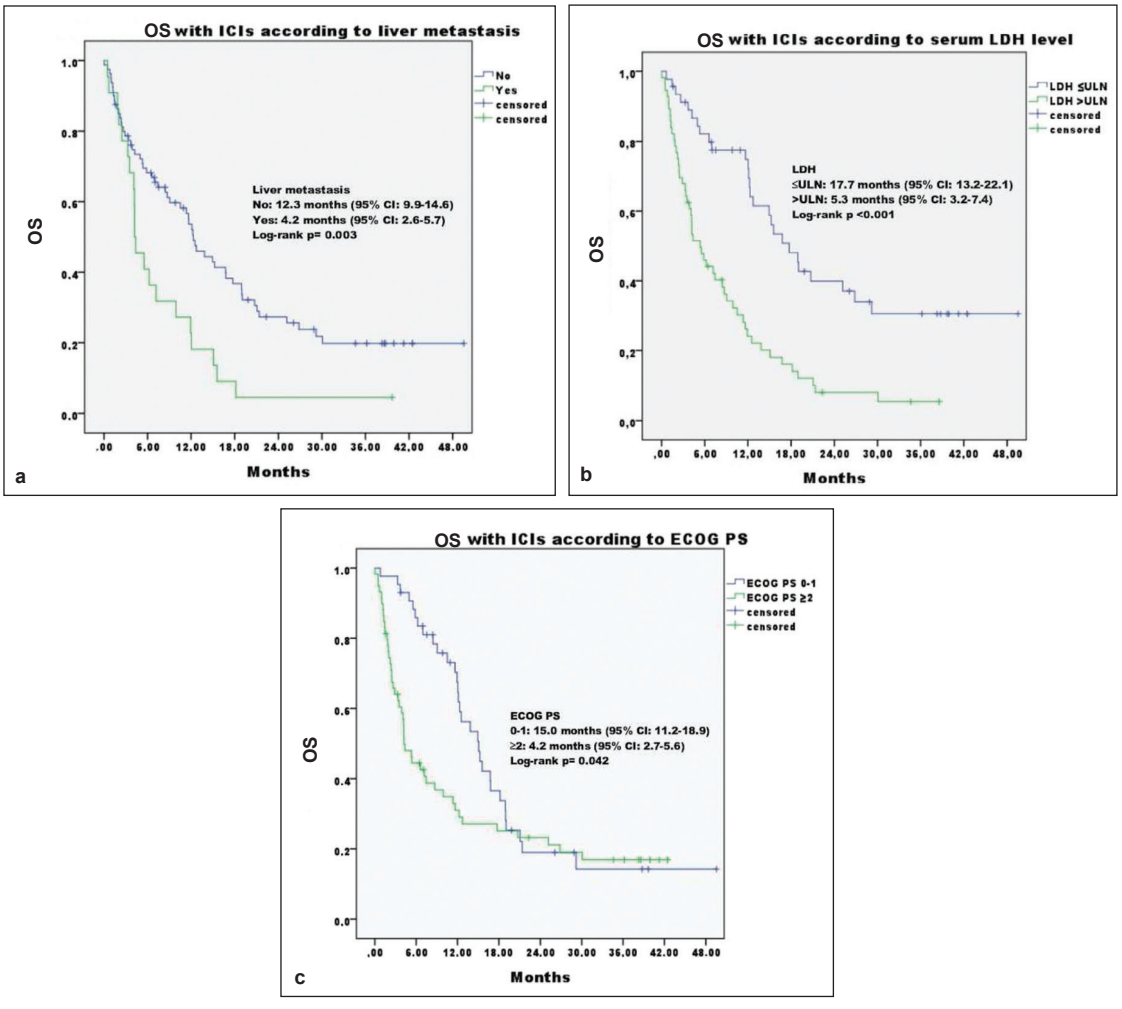

FIGURE 3: Kaplan-Meier plot for the overall survival (OS) stratified by **a)** liver metastasis, **b)** serum lactate dehydrogenase (LDH) level, **c)** Eastern Cooperative Oncology Group Performance Status (ECOG PS) and 3d: serum C-reactive protein (CRP) level (95%CI, 95% confidence interval)."

levels and adverse clinical outcomes in patients with cancer. Serum CRP levels are an indicator of systemic inflammation, as CRP is released by hepatocytes in response to proinflammatory cytokines, particularly interleukin 1 (IL)-1, IL-6, and tumor necrosis factor. Inflammation is recognized as a hallmark of cancer development and progression and ICI resistance.[1,26,27] IL-1 promotes cancer progression by enhancing the recruitment of immunosuppressor cells.[28] IL-6 is associated with cancer progression and therapeutic resistance.[29,30]

mGPS is a composite biomarker that reflects both host-related systemic inflammatory response and nutritional status. Some studies have shown that mGPS is an independent prognostic factor for PFS and OS in patients with advanced NSCLC treated with anti-PD1 treatment.[18,31] In our study cohort, mGPS 1 was observed to be an independent prognostic and predictive biomarker for PFS and DCR; this finding agreed with the results of these studies. Inflammation was a more prominent biomarker in our study cohort. This result might be explained by the fact that mGPS 0 and 2 were not associated with PFS, OS, and response status.

LDH is a glycolytic enzyme that catalyzes the transformation of pyruvate to lactate. Elevated serum LDH level is associated with poor prognosis in patients with cancer, which is consistent with the results of our study.[32,33] A strong biological relationship exists between LDH level and poor clinical outcomes in patients with cancer. Gene expression and LDH activity are increased in patients with cancer.[19,34,35]

TABLE 5: Univariable and multivariable analyses of the objective response and disease control.

	Objective response		Disease control	
Variables	Unadjusted HR (95% CI); p value	Adjusted HR (95% CI); p value	Unadjusted HR (95% CI); p value	Adjusted HR (95% CI); p value
ECOG PS≥2	0.22 (0.09-0.51); **<0.001**	0.19 (0.01-2.53); 0.214	0.18 (0.07-0.43); **<0.001**	0.12 (0.03-0.44); **0.001**
Squamous cell carcinoma	1.64 (0.72-3.72); 0.238	-	1.78 (0.78-4.06); 0.166	-
Anti-PD-L1	N/A **0.007**	N/A, 0.331	N/A **0.005**	N/A 0.224
Negative	1 (reference)	1 (reference)	1 (reference)	1 (reference)
1-49%	7.33 (1.16-46.05); **0.034**	3.03 (0.19-46.90); 0.426	8.33 (1.27-54.42); **0.027**	7.17 (1.39-47.42); 0.197
≥50%	12.83 (2.29-71.79); **0.004**	7.44 (0.45-121.67); 0.159	13.33 (2.20-80.51); **0.005**	11.27 (1.83-57.49); 0.133
≥2nd-line ICI treatment	1.34 (0.60-2.96); 0.466	-	1.62 (0.73-3.55); 0.228	-
Presence of brain metastasis	0.55 (0.13-2.29); 0.417	-	0.41 (0.10-1.68); 0.217	-
Presence of bone metastasis	0.42 (0.18-0.99); 0.048	0.06 (0.00-1.06); 0.055	0.27 (0.11-0.63); **0.003**	0.30 (0.09-0.99); **0.049**
Presence of adrenal gland metastasis	0.56 (0.21-1.46); 0.240	-	0.39 (0.15-1.01); 0.054	-
Presence of malignant pleural effusion	0.47 (0.16-1.35); 0.163	-	0.33 (0.11-0.95); **0.041**	0.56 (0.13-2.47); 0.451
Presence of liver metastasis	0.57 (0.21-1.55); 0.271	-	0.40 (0.14-1.09); 0.073	-
irAEs	5.21 (1.70-15.92); **0.004**	1.10 (0.05-21.27); 0.946	7.68 (2.07-28.44);**0.002**	2.18 (0.40-11.81); 0.364
dNLR>3	0.78 (0.32-1.89); 0.586	-	0.79 (0.33-1.87); 0.594	-
LDH>ULN	0.47 (0.21-1.04); 0.065	-	0.35 (0.15-0.78); **0.011**	0.29 (0.06-1.44); 0.133
LIPI status	N/A, 0.173		N/A, 0.060	N/A, 0.736
Good	1 (reference)	-	1 (reference)	1 (reference)
Intermediate	0.47 (0.19-1.13); 0.094		0.37 (0.15-0.90); **0.029**	1.31 (0.24-7.08);0.748
Poor	0.42 (0.13-1.37); 0.154		0.35 (0.11-1.12); 0.079	2.39 (0.23-24.51); 0.463
CRP level	0.77 (0.65-0.90); **0.002**	0.69 (0.39-1.23); 0.217	0.81 (0.71-0.92); **0.002**	0.90 (0.79-1.01); 0.096
Albumin level ≥3.5 g/dL	2.92 (1.05-8.13); **0.039**	0.80 (0.00-103.39); 0.931	3.25 (1.21-8.68); **0.019**	0.97 (0.07-13.24); 0.982
mGPS	N/A, **0.001**	N/A, 0.972	N/A, **<0.001**	N/A, 0.055
0	1 (reference)	1 (reference)	1 (reference)	1 (reference)
1	0.21 (0.08-0.55); **0.002**	0.67 (0.02-17.36); 0.812	0.18 (0.06-0.50); **0.001**	0.15 (0.03-0.70); **0.016**
2	0.12 (0.03-0.43); **0.001**	NE, 0.999	0.10 (0.03-0.35); **<0.001**	0.55 (0.03-9.26); 0.681

OR: Odds ratio; CI: Confidence interval; ECOG PS: Eastern Cooperative Oncology Group Performance Status; PD-L1: Programmed death ligand-1; N/A: Not applicable; ICIs: Immune checkpoint inhibitors; irAEs: Immune related adverse events; dNLR: Derived neutrophil-lymphocyte ratio; LDH: Lactate dehydrogenase; ULN: Upper level of normal; LIPI: Lung Immune Prognostic Index; CRP: C-reactive protein; mGPS: Modified Glasgow Prognostic Score; NE: Not estimated.

Response to ICIs is mediated by activated T cells. Glycolysis is the main energy source of both T cells and cancer cells, and it induces the secretion of a large amount of lactate into the extracellular area.[36] Because T cells are unable to eliminate lactate, the increased production of lactate inhibits T cell proliferation and cytokine production. Consequently, tumor cells escape from immune surveillance.[19,37]

ECOG PS≥2 was associated with poor OS and DCR in our study cohort. These findings were expected and consistent with several previous studies.[38-40] Poor ECOG PS is an indicator of greater disease burden and aggressive tumor biology. Previous randomized controlled trials included only patients with ECOG PS 0-1, which is significantly different from the trend observed in routine clinical practice. In our study cohort, 57.8% of the patients had ECOG PS≥2.

The tumor microenvironment differs across various organ sites, and it may affect the activity of ICIs.[41] Bone and bone marrow are immunoregulatory organs. Therefore, it is expected that response to ICI treatment will be influenced by bone metastasis. In our study cohort, bone metastasis was associated with worse PFS and DCR; this finding is consistent with the results of some studies.[42-44] The liver possesses immunomodulatory properties and can induce immune tolerance.[45,46] Liver metastasis is a well-known negative prognostic factor in patients with NSCLC,

and our results were consistent with the findings reported in the literature.[47-49]

The univariate analysis showed an association of LIPI with PFS and OS. This result agreed with the findings of several LIPI trials.[16,17,50] LIPI is based on dNLR and LDH levels. In our study, elevated pretreatment serum LDH levels were associated with poor outcomes, as mentioned above. The NLR is a well-known prognostic factor in patients with NSCLC.[51,52] dNLR is a novel parameter based on the neutrophil count and white blood cell count, including monocytes and other granulocytes. Some studies have demonstrated that dNLR is also associated with survival outcomes.[53,54] Thus, in our study, it was not surprising that LIPI groups were associated with survival outcomes.

Our present study has several limitations. PD-L1 levels were not available in more than 50% of the patients, which restricted the significance of the analysis based on PD-L1 level. Some variables were analyzed by dividing them into the ULN cutoff instead of using them as continuous variables. In addition, there were other limitations due to the retrospective nature of the study.

CONCLUSION

In the present study, we found that immune-inflammation-nutritional parameters are reliable prognostic biomarkers to select patients with a greater likelihood of benefiting from ICI treatment. In light of these results, in future research studies, we plan to develop a scoring system based on immune-inflammation-nutritional biomarkers combined with clinicopathological factors to predict the benefits of treatment with ICIs.

Source of Finance

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

Conflict of Interest

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

Authorship Contributions

Idea/Concept: *Ömer Diker;* ***Design:*** *Ömer Diker;* ***Control/Supervision:*** *Ömer Diker, Polat Olgun;* ***Data Collection and/or Processing:*** *Ömer Diker, Polat Olgun;* ***Analysis and/or Interpretation:*** *Ömer Diker;* ***Literature Review:*** *Ömer Diker;* ***Writing the Article:*** *Ömer Diker, Polat Olgun;* ***Critical Review:*** *Ömer Diker, Polat Olgun;* ***References and Fundings:*** *Ömer Diker, Polat Olgun.*

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