Prognostic Value of Inflammatory and Nutritional Index in Advanced Stage Non-Small Cell Lung Cancer Patients Treated with Nivolumab in Second-Line Therapy

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ABSTRACT

This study aims to evaluate the impact of inflammatory and nutritional index on the prognosis of patients who have experienced progression with platinum-based chemotherapies and subsequently received Nivolumab treatment for non-small cell lung cancer (NSCLC). The investigation included 124 patients who underwent treatment and observation at the medical oncology clinic from February 2022 to June 2023. A retrospective analysis was conducted on the medical records of 1144 individuals diagnosed with non-small cell lung cancer (NSCLC). After applying exclusion criteria, 124 patients were included in the study. Inflammatory and nutritional index values were calculated based on the pre-treatment blood values of the patients. Our results demonstrated a relationship between decreased SII and increased PNI ratios, indicating a connection with better overall survival. Furthermore, we established that the existence of adrenal metastasis was recognized as an independent risk factor linked to overall survival. SII and PNI variables were statistically significant in terms of the risk of death ($p< 0.05$). multivariate Cox regression model, having adrenal metastasis (HR: 2.61; 95%CI: 1.15-5.90; $p= 0.021$) increased the risk of death ($p= 0.007$, -2 loglikelihood= 455,371). The data underscores the predictive value of inflammatory and nutritional indices for treatment responses. These parameters, derived from routine assessments of hemoglobin, albumin, lymphocyte, neutrophil, and platelet levels, provide accessible information compared to complex and expensive methods. Subsequent multicenter studies may set a standardized cut-off value for routine use, emphasizing the necessity for broader validation through extensive research.

Keywords: Inflammatory index, Nivolumab, Nutritional index

INTRODUCTION

Lung cancer is the most commonly diagnosed malignancy worldwide and has a significantly high mortality rate. Non-small cell lung cancer (NSCLC), constituting approximately 85% of lung cancers, is the most common primary malignancy of the lung.[1] About 16% of patients present with localized disease at diagnosis, while the majority are diagnosed at an advanced stage.[2] For patients with advanced-stage NSCLC without targetable mutations, immune checkpoint inhibitors (ICIs) are recommended as standard treatment either in combination with chemotherapy or as a standalone therapy in the first-line setting.[3] ICIs are also suggested as standard second-line treatment for patients who progress after first-line chemotherapy, due to their significant survival benefits, safety profile, and durable responses.[4] However, not all patients respond uniformly to these treatments; some may experience disease progression and fatal toxicities.[5] Given the costs and potential toxicities associated with these therapies, predictive factors for treatment response are critically important.

Although markers such as PD-L1 expression, tumor mutation burden (TMB), tumor neoantigen burden (TNB), high microsatellite instability (MSI-H), and tumor-infiltrating lymphocytes (TILs) have been identified to predict treatment response, there is a need for simpler and more cost-effective biomarkers to predict prognosis in these patients.[6]

Nivolumab is a fully human, monoclonal, programmed death-1 (PD-1) immune checkpoint inhibitor antibody recommended for second-line treatment in advanced NSCLC.[7] It has been found to be significantly superior to chemotherapy in patients with advanced NSCLC who received platinum-based chemotherapy in the first-line setting.[8]

It is known that the systemic inflammatory response is associated with tumor characteristics such as proliferation, invasion, and metastasis, and inflammation plays a significant role in tumor formation and growth.[9] Blood cells secrete various cytokines that aid in inflammatory processes and affect tumor cells via the adaptive immune response.[10] Changes in tumor-associated inflammatory cells indicate the degree of the inflammatory response to the tumor. Markers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and prognostic nutritional index have been shown to represent inflammatory changes in the tumor microenvironment. A high inflammatory response generally indicates a poor prognosis.[11]

Combining these parameters provides a much more accurate prediction of a patient's prognosis compared to using a single index. In our study, we aimed to assess the impact of inflammatory and nutritional indices on prognosis in patients who experienced progression with platinum-based chemotherapies and received Nivolumab in second-line treatment.

PATIENTS AND METHODS

This study included 124 patients treated and followed up at the medical oncology clinic between February 2022 and June 2023. Records of 1144 patients diagnosed with NSCLC were retrospectively reviewed. Patients who received targeted therapy or had positive driver mutations were excluded from the study. Additionally, patients receiving anti-inflammatory treatment, and those with serious comorbidities or inadequate organ function, were also excluded. Patients' age, demographic characteristics, stages, histological types of the tumor, Eastern Cooperative Oncology Group (ECOG) status, and sites of metastasis were recorded. Approval from the local ethical committee was obtained for the study. Laboratory data for calculating the Hemoglobin Albumin Lymphocyte Platelet (HALP) index, Neutrophil to Lymphocyte Ratio (NLR), Platelet to Lymphocyte Ratio (PLR), Systemic Inflammation Index (SII), and Prognostic Nutritional Index (PNI) were collected from patients' laboratory information systems prior to the first cycle of treatment.

HALP score was calculated according to the formula Hemoglobin (g/L) X albumin (g/L) x lymphocyte (10^3/qL)/platelet (10^3/qL). NLR was calculated as neutrophil (10^3/qL)/lymphocyte (10^3/qL), PLR as platelet (10^3/qL)/lymphocyte (10^3/qL), SII as platelet/NLR and PNI as albumin (g/L)/5 x lymphocyte (10^3/qL). Progression status of the patients was evaluated according to iRECIST criteria.

Statistical Analysis

Statistical analyses were performed using "IBM SPSS Statistics for Window. Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA)". Descriptive statistics are presented as n and % for categorical variables, and Mean±SD for continuous variables. Data normality was assessed, and since Kolmogorov-Smirnov values were $p > 0.05$, Independent t-tests and ANOVA were used to compare indices with various sociodemographic and clinical variables. The results of the ROC Curve analysis predicting mortality from various numerical parameter scores have been provided. The Kaplan Meier method was used for comparing survival durations between various clinical parameter groups. Finally, Multivariate Cox Regression results were provided for the impact of various clinical factors on the risk of death. A p-value of < 0.05 was considered statistically significant.

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Insti-

Table 1. Data on sociodemographic and clinical characteristics

		n	%
Gender	Male	110	88.7
	Female	14	11.3
Tobacco	No	16	12.2
	Yes	108	87.8
ECOG	0	44	35.5
	1	70	56.5
	2	10	8.1
Histology	Adenocarcinoma	64	51.6
	Squamous cell carcinoma	52	41.9
	Other	8	6.5
Stage	Local Advanced	23	185
	Metastatic	101	81.5
LN metastasis	No	12	9.7
	Yes	112	90.3
Bone metastasis	No	85	68.5
	Yes	39	31.5
Liver metastasis	No	99	79.9
	Yes	25	37.9
Opposite AC metastasis	No	77	62.1
	Yes	47	37.9
Brain metastasis	No	109	87.9
	Yes	15	12.1
Adrenal metastasis	No	113	91.1
	Yes	11	8.9
Mortality	Alive	67	54.0
	Deceased	57	46.0
Median Follow-up Period (min-max)		18.86 (3.93-73.67)	
Average age		62.32±8.43	

tutional Ethics Committee of Kayseri City Hospital (22.08.2023 76397871/703).

RESULTS

The demographic and clinical characteristics of the 124 patients included in the study were analyzed (Table 1). The mean age was 62.32±8.43 years. Of these patients, 110 (88.7%) were male, and 14 (11.3%) were female. The most common histopathological type was adenocarcinoma in 62 patients (51.6%). Progression was observed in 77 patients (63.6%) during follow-up. The median follow-up period was 18.86 (3.93-73.67) months. At the end of the follow-up period, 57 patients (46%) had died.

In Table 2, the estimates of NLR (p= 0.002), PLR (p= 0.006), SII (p= 0.003), PNI (p= 0.008) and HALP (p= 0.003) were statistically significant to discriminate the presence of mortality.

As seen in Table 3, the overall median overall survival (months) was 28.76 (95%CI: 20.24-37.29). 2-year survival was 57.9% and 5-year survival was 25.2%. There was no statistically significant difference between PFS and the parameters studied.

As presented in Table 4, the results of univariate analyses indicated that adrenal metastasis, SII and PNI variables were statistically significant in terms of the risk of death (p< 0.05). These variables were found to be significant in univariate analyses, but according to the results of the multivariate Cox regression model, having adrenal metastasis (HR:2.61; 95%CI: 1.15-5.90; p= 0.021) increased the risk of death (p= 0.007, -2 loglikelihood= 455,371).

Table 2. Analysis of the predictive values of various parameter values in discriminating mortality

Variables	AUC	95% CI	Cut-off	Sensitivity (%)	Specificity (%)	p
NLR	0.662	0.565-0.758	≥ 3.71	57.9	58.2	0.002
PLR	0.644	0.547-0.741	≥ 0.17	63.2	62.7	0.006
SII	0.654	0.557-0.751	≥ 1024.50	63.2	62.7	0.003
PNI	0.639	0.542-0.737	≤ 6660.50	61.4	61.2	0.008
HALP	0.657	0.561-0.753	≤ 2549.56	57.9	58.2	0.003

AUC= Area under the curve; %95CI= Confidence interval

Table 3. Comparisons of OS in patients

	OS (months)	
Variables	**Median (95% CI)**	**p**
General	28.76 (20.24-37.29)	
Adrenal		
No	33.63 (17.59-48.47)	0.047
Yes	18.93 (10.53-27.33)	
SII		
< 1024.50	49.33 (3.70-96.15)	0.015
≥ 1024.50	25.70 (17.10-34.29)	
PNI		
> 6660.50	49.93 (–)	0.032
≤ 6660.50	25.70 (19.90-31.50)	

Kaplan Meier curve, Long rank test, p< 0.05 statistically significant

Table 4. Multivariate cox regression results for various clinical variables

OS	Multivariate	
Variables	**HR (95%CI)**	**p**
Surrenal (ref: None)	2.61 (1.15-5.90)	0.021
SII (ref: < 1024,50)	1.75(0.96-3.20)	0.067
PNI (Ref: >6660.50)	1.46 (0.80-2.65)	0.213

p= 0.007; -2 Log Likelihood= 455,371

DISCUSSION

Despite the emergence of many new treatment options, including immunotherapies, advanced-stage lung cancer remains a significant cause of mortality and morbidity. In patients undergoing immunotherapy, while some exhibit excellent responses and prolonged survival, others may only survive for a few months. Predicting which patients will benefit from these treatments, which are costly and can have serious side effects, is of great importance.[12,13]

The efficacy of immunotherapies is influenced by the patients' inflammatory and nutritional status. Numerous studies have investigated the relationship between inflammatory and nutritional indices and prognosis and survival.[14] The combined assessment of these indices is much more valuable than evaluating a single index.

We evaluated simple prognostic markers using basic laboratory measurements such as hemoglobin, albumin, lymphocyte, neutrophil, and platelet levels, which are part of the routine evaluation process for every patient. We found that lower SII and higher PNI ratios were associated with better OS. While there is a scarcity of comprehensive studies evaluating nutritional and inflammatory indices together in patients treated with second-line Nivolumab, there are limited studies assessing prognostic and nutritional indices in patients receiving immune checkpoint inhibitors (ICI). Additionally, our study identified adrenal metastasis as an independent poor prognostic factor for OS. In the GETUG-AFU-26-NIVOREN study, adrenal metastasis in patients with metastatic renal cell cancer treated with Nivolumab was identified as an independent prognostic factor for poor response and survival.[15] However, there is no study demonstrating the negative impact of adrenal metastasis on OS in patients with advanced-stage lung cancer treated with Nivolumab.

Inflammation is critically important in tumor development and progression at all stages.[16] It also affects the tumor's immune microenvironment and response to treatment. Neutrophils, by producing proangiogenic chemokines and vascular endothelial growth factor, are thought to be effective in the proliferation, vascularization, and metastasis of cancer cells.[17] Lymphocytes play a significant role in the prognosis of cancer patients by participating in immunosurveillance and suppressing the proliferation, invasion, and migration of cancer cells.[18-19]

Studies have shown that hemoglobin levels are directly related to survival and tumor development in cancer patients.[20] Particularly in patients with advanced-stage cancer, low hemoglobin levels have been associated with progression and poor survival outcomes. Albumin, a negative acute phase reactant synthesized by the liver, is influenced by the patient's nutritional status. In inflammatory processes, a decrease in albumin levels is expected.[21] Numerous studies have reported that low albumin levels in cancer patients are associated with poor survival.[22-23] Platelets have been shown to play a role in tumor metastasis and in protecting tumor cells from immune detection.[24-25]

In a study by Nishihara-Kato et al. on patients with mNSCLC treated with pembrolizumab combined with carboplatin and paclitaxel, significantly higher OS was observed in the group with higher PNI values (23.4 months vs 13.9 months). Similar to our study, no significant difference in PFS was found between different PNI levels.[26]

In a study by Stares et al. evaluating patients with mNSCLC treated with first-line pembrolizumab, higher OS was observed in the group with higher PNI (28.7 months vs 9 months). Contrary to our study, this research also found a significant difference in PFS (15.0 months vs 5.1 months).[27]

Although PNI level is associated with OS in the mentioned studies, cut-off values differ. This suggests that multicenter studies should be conducted in larger populations. The scoring system created using only routine blood test parameters can be a cost-effective method to predict treatment success and may be suitable for routine use.

In a study by Qiyu Fang et al. on patients with mNSCLC receiving first-line anti-PD1-chemotherapy combinations, better OS was observed in the group with lower SII (21 months vs 18 months) and higher PNI (26 months vs 17 months). These findings are consistent with our study, although the inclusion of the driver mutation positive group and the use of chemotherapy combination with PD1 inhibitors in their study differs.[28]

In another study by Liu Jingjing et al. on 44 patients with mNSCLC treated with second-line or later nivolumab, better OS was found with lower SII values (19.8 months vs 8.9 months), aligning with our study. Our research, however, involved a broader population and excluded patients with driver mutation positivity, resulting in a more homogeneous group evaluation.[29]

Yuting Zhou et al. conducted a meta-analysis of 8 studies involving 2267 patients with mSCLC, finding that high SII values were associated with poor OS.[30] A high SII value is linked to the components of the score: high neutrophil count, high platelet count, or low lymphocyte count. These findings correlate with the roles previously discussed for these parameters in the prognosis of cancer patients.

As seen in these data, inflammatory and nutritional indices can assist in predicting treatment responses. Unlike complex and costly methods, these parameters, derived from evaluating hemoglobin, albumin, lymphocyte, neutrophil, and platelet levels – part of the routine assessment for every patient – offer easy access. Future multicenter studies could establish a standard cut-off value for routine use. Therefore, there is a need for more extensive and multicenter studies to further validate these findings.

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