Acta Medica Alanya

Research Article

Araştırma

Acta Medica Alanya 2023;7(2): 153-162
Doi: 10.30565/medalanya.1314292

Prognostic Significance of PNI, SIRI and LIPI in Non Small-Cell Lung Cancer

Küçük Hücreli Dışı Akciğer Kanserinde PBİ, SİYİ ve AİPİ'nin Prognostik Önemi

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ABSTRACT

Aim: Non-small cell lung cancer (NSCLC) is one of the 3 most common and deadly cancers. The aim of the current study is to investigate whether Prognostic Nutritional Index /PNI), Systemic Immune-Inflammation Index (SIRI), Lung Immune Prognostic Index (LIPI) has a prognostic significance in patients with metastatic NSLCL.

Methods: Patients diagnosed with pathologically confirmed metastatic NSCLC in 5 different hospitals in Turkey between 2016-2022 were included in our study and analyzed retrospectively. overall survival (OS) and progression-free survival (PFS) were recorded.

Results: The median PFS was 5.50 months, while the median OS was 16.03 months. Median OS was 14.86 months for the PNI-Low group and 17.2 months for the PNI-High group (p: <0.121). The median OS of the PNI-Low group was shorter than the PNI-High group, but there was no statistically significant difference between the groups. Median OS was 19.86 months for the SIRI-Low group and 14.23 months for the SIRI-High group (p: <0.112). Median OS was 17.76, 15.13, 13.73 months for the LIPI-Low, LIPI-intermediate group and LIPI-high group, there was no statistically significant difference between the groups (p: <0.391).

Conclusion: In conclusion, PNI and SIRI may be significant in a prospective study in a specific patient group to be performed with a larger number of patients to predict the prognosis of patients with metastatic NSCLC.

Key Words: Prognostic Nutritional Index, Systemic Immune-Inflammation Index, Lung Immune Prognostic Index, Non Small Cell Lung Cancer

ÖZET

Amaç: Küçük hücreli dışı akciğer kanseri (KHDAK) en sık görülen ve en çok ölüme sebep olan 3 kanserden birisidir. Mevcut çalışmanın amacı, metastatik KHDAK'lı hastalarda Prognostik Beslenme İndeksi (PBI), sistemik inflamatuvar Yanıt İndeksi (SİYİ), Akciğer İmmün Prognostik İndeksi (AİPİ)'nin prognostik bir öneminin olup olmadığını araştırmaktır.

Yöntem: Çalışmamıza 2016-2022 yılları arasında Türkiye'de 5 farklı hastanede patolojik doğrulanmış metastatik KHDAK tanısı almış hastalar dahil edilmiş ve retrospektif olarak incelenmiştir. Bazı hemogram parametreleri ve Idh, albumin gibi biokimyasal parametreler, ayrıca genel sağkalım (GSK) ve progresyonsuz sağkalım (PSK) kaydedilmiştir.

Bulgular: Çalışmamıza 297 hasta dahil edilmiştir. Median PSK 5,5 ay iken median GSK 16,03 ay idi. Median GSK PBİ-düşük grup için 14,86 ay, PBİ-yüksek grup için ise 17,2 ay ay idi (p: <0.121). PBİ-düşük grubunun medyan GSK'sı, PBİ-yüksek gruptan daha kısaydı, ancak gruplar arasında istatistiksel olarak anlamlı bir fark yoktu. Median GSK SİYİ-düşük grup için 19,86 ay iken, SİYİ-yüksek grup için ise 14,23 ay idi(p: <0.112). SİRİ-düşük grubunun medyan GSK'sı, SİYİ-yüksek gruptan daha uzundu, ancak gruplar arasında istatistiksel olarak anlamlı bir fark yoktu. Medyan GSK, AİPİ-Düşük grup için 17,76 (%95 GA 16,51 -19,02) ay, AİPİ- orta grup için 15,13 ay, AİPİ-yüksek grup için 13,73 ay (%95 GA 8,05 -19,41) bulundu. AİPİ -Düşük AİPİ -orta ve AİPİ -Yüksek grupları arasında istatistiksel olarak anlamlı bir fark yoktu (p: <0,391).

Sonuç: Sonuç olarak PNI ve SIRI daha çok hasta sayısıyla yapılacak spesifik bir hasta grubunda prospektif bir çalışmada KHDAK hastaların prognozunu tahmin etmek için anlamlı çıkabilir.

Anahtar Kelimeler: Prognostik Beslenme İndeksi, Sistemik İmmün İnflamasyon İndeksi, Akciğer İmmün Prognostik İndeksi, Küçük Hücreli Dışı Akciğer Kanseri

Recieved Date: 14.06.2023 / **Accepted Date:** 07.08.2023 / **Published (Online) Date:** 29.10.2023

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To cited: Balçık OY, Aytaç A, Avcı T, Demir B, İlhan Y, Karakaya G, Erdoğan AP. Prognostic significance of PNI, SIRI and LIPI in non small-cell lung cancer. Acta Med. Alanya 2023;7(2): 153-162 doi: 10.30565/medalanya.1314292

Introduction

Non-small cell lung cancer (NSCLC) is one of the 3 most common cancers and the leading cause of death. They constitute approximately 85% of newly emerging lung cancers [1]. If we classify NSCLC according to histology, adenocarcinoma (AC) is in the first place with an incidence of 32%, while squamous cell cancer (SCC) is around 29% [2]. Despite new developments in chemotherapy and surgical techniques, NSCLC survival was around 5-10%. With the introduction of immunotherapy, this rate reached around 20-40% [3,4]. However, due to the possibility of developing fast-progression and hyper progression in patients using immunotherapy, the fact that recent studies are needed has appeared [5].

Access to genetic biomarkers in developing and underdeveloped countries is financially difficult. Therefore, there is a need for useful indices that can be used in daily clinical practice.

Malnutrition plays a significant role in the prognosis of cancer in many ways, in the immune system. Substances released from the tumor have a key role in cancer prognosis because they increase systemic inflammation through cytokines. At the same time, systemic inflammatory responses such as infection and trauma increase angiogenesis and play a role in tumor development [6].

Previously, indices created by hematological parameters emerged as prognostic markers in some cancers [7,8]. The prognostic nutritional index (PNI) is calculated based on the number of lymphocytes and albumin. A low PNI appears to have a poor prognostic value in small cell lung cancer (SCLC) and metastatic laryngeal cancer [9,10]. The Systemic Inflammatory Response Index (SIRI) is a comprehensive marker of inflammation calculated from monocyte, neutrophil, and lymphocyte counts. Studies in patients with SCLC have shown that elevated SIRI has poor prognostic value [11]. High SIRI was also found to be a poor prognostic factor in a study of stage 3 NSCLC patients undergoing definitive chemotherapy (CRT) [12]. The combination of LDH, which indicates neutrophil, leukocyte, and proliferation levels, resulted in a poor prognosis for patients with locally advanced NSCLC, leading to shorter overall survival (OS) and progression-free survival (PFS). However, there is a lack of research regarding the importance of PNI, SIRI, and LIPI as prognostic indicators in patients suffering from metastatic NSLCL.

In our current study, we aimed to investigate whether PNI, SIRI, LIPI have prognostic significance in patients with metastatic NSCLC.

Material And Methods

Our study included patients who underwent surgery between 2016 and 2022. was diagnosed with pathologically confirmed metastatic NSCLC in 5 different hospitals in Turkey. We retrospectively reviewed patient records and hospital databases and recorded patient demographic and hemogram parameters such as platelet, neutrophil, monocyte and lymphocyte count and biochemical parameters such as LDH and albumin. We also recorded demographic data, metastatic sites, and tumor mutational status. Survival outcomes were also recorded. Patients with additional malignancy, known autoimmune disease, steroid use, and active infection were excluded from the study.

PNI was determined by adding together 10 times the serum albumin value (in g/dl) and 0.005 times the peripheral lymphocyte count (per mm3). The formula for calculating SIRI is (neutrophil multiplied by lymphocyte) divided by monocyte. The dNLR was calculated prior to determining the LIPI. The value of dNLR was obtained by dividing the number of neutrophils by the difference between the total number of leukocytes and the number of neutrophils. If dNLR is less than or equal to 3 and LDH is less than or equal to the upper limit of normal, then it belongs to the low group of LIPI. If dNLR is greater than 3 or LDH is greater than the ULN, then it falls into the intermediate group of LIPI. If both dNLR and LDH are greater than the ULN, then it is categorized in the high group of LIPI.

Statistical Analysis

The statistical analysis was conducted using IBM SPSS Statistics for Windows, Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA). Categorical variables are presented as n and %, while continuous variables are expressed as mean±SD in the descriptive statistics.

The study's data was assessed for normality assumptions, and comparisons between continuous variables and groups were made using the parametric tests of ANOVA and independent t-tests after analyzing the Kolmogorov-Smirnov values. To compare categorical variables, researchers employed either the chi square test or Fisher's Exact test. Patients in the high LIPI group have a dNLR score of 3 or less and LDH levels below the upper limit of normal. In the intermediate LIPI group, patients have a dNLR score greater than 3 or LDH levels above the upper limit of normal. The SIRI-high group consists of patients with both a dNLR score greater than 3 and LDH levels above the upper limit of normal.

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The Kaplan Meier method was used to compare survival time and disease-free survival according to several variables. Finally, multivariate Cox regression results based on risk of death and disease-free survival are presented. $p<0.05$ was considered statistically significant.

The research was approved by the ethics committee of Diyarbakir Gazi Yaşargil Training and Research Hospital in compliance with the Declaration of Helsinki and Good Clinical Practices. The study was carried out following these regulations and guidelines. (Approval Date-No:November 25th, 2022 - 2022/232).

Results

There were 297 patients in our study. The median mean age was 63 (53, 73). 245 (82.5%) of our patients were male. ECOG performance scale of 247 (83%) of our patients was 0 or 1. Of our patients, 174 (58.6%) were AC and 123 (41.4%) were scc. The metastasis site of 153 (51.5%) of our patients was bone, while 106 (35.7%) of them were liver. As a metastatic 1st line chemotherapy option, 100 (33.7%) patients received carboplatin + paclitaxel, 64 (21.5%) patients received a platinum regimen + gemcitabine, and 56 (18.9%) patients received a platinum regimen + pemetrexed combination.

ROC analysis results of various variables predicting death were calculated. While this value was 483.3 for PNI, it was found to be 1.8 for SIRI. There was no statistically significant difference between the group with a PNI score < 483.3 (PNI-Low) and the group with a PNI score ≥ 483.3 (PINI-High). However, a statistically significant difference was found between liver metastasis and PNI groups (p=0.014). General characteristics and demographic information of patients grouped according to PNI and SIRI are shown in Table I in detail. No statistically significant difference was found between the group with a SIRI score <1.8 (SIRI-Low) and the

Table 1. Comparison of various sociodemographic and clinical variables by SIRI group.

Variables		Total	SIRI		p	PNI		p
			LOW <1,8	HIGH ≥1,8		LOW <483,3	HIGH ≥483.3	
Age, Mean±SD		63,51±10,07				64,10±9,88	62,94±10,26	0.321
Gender, n (%)	Male	245 (82,5)	83 (78,3)	162 (84,8)	0.157	122 (83,6)	123 (81,5)	0.663[a]
	Female	52 (17,5)	23 (21,7)	29 (15,2)		24 (16,4)	28 (18,5)	
ECOG, n (%)	0	61 (20,5)	26 (24,5)	35 (18,3)	0.559	32 (21,9)	29 (19,2)	0.655
	1	186 (62,6)	65 (61,3)	121 (63,4)		91 (62,3)	95 (62,9)	
	2	44 (14,8)	13 (12,3)	31 (16,2)		19 (13)	25 (16,6)	
	3-4	6 (2,1)	2 (1,9)	4 (2,1)		4 (2,7)	2 (1,3)	
Histopathological Subtype, n (%)	Adenocarcinoma	174 (58,6)	61 (57,5)	113 (59,2)	0.787	90 (61,6)	84 (55,6)	0.293[a]
	SCC	123 (41,4)	45 (42,5)	78 (40,8)		56 (38,4)	67 (44,4)	
Smoking, n (%)	Yes	172 (57,9)	17 (16)	32 (16,8)	0.966	23 (15,8)	26 (17,2)	0.501
	No	49 (16,5)	61 (57,5)	111 (58,1)		83 (56,8)	89 (58,9)	
	Left	76 (25,6)	28 (26,4)	48 (25,1)		40 (27,4)	36 (23,8)	
COPD, n (%)	No	223 (75,1)	81 (76,4)	142 (74,3)	0.693	112 (76,7)	111 (73,5)	0.524[a]
	Yes	74 (24,9)	25 (23,6)	49 (25,7)		34 (23,3)	40 (26,5)	
Diabetes mellitus, n (%)	No	246 (82,8)	85 (80,2)	161 (84,3)	0.369	120 (82,2)	126 (83,4)	0.775[a]
	Yes	51 (17,2)	21 (19,8)	30 (15,7)		26 (17,8)	25 (16,6)	
Chronic kidney disease, n (%)	No	272 (91,6)	97 (91,5)	175 (91,6)	0.973	137 (93,8)	135 (89,4)	0.169[a]
	Yes	25 (8,4)	9 (8,5)	16 (8,4)		9 (6,2)	16 (10,6)	

PNI (Perioperative Nutritional Index), SIRI (Systemic Immune-Inflammation Index), SCC: squamous cell carcinoma, COPD: chronic obstructive pulmonary disease

Table 1. Comparison of various sociodemographic and clinical variables by SIRI group. *(continued)*

Variables		Total	SIRI LOW <1,8	SIRI HIGH ≥1,8	p	PNI LOW <483,3	PNI HIGH ≥483.3	p
Liver metastasis, n (%)	No	191 (64,3)	70 (66)	121 (63,4)	0.643	104 (71,2)	87 (57,6)	**0.014[a]**
	Yes	106 (35,7)	36 (34)	70 (36,6)		42 (28,8)	64 (42,4)	
Bone metastasis, n (%)	No	144 (48,5)	50 (47,2)	94 (49,2)	0.736	69 (47,3)	75 (49,7)	0.678[a]
	Yes	153 (51,5)	56 (52,8)	97 (50,8)		77 (52,7)	76 (50,3)	
Brain metastasis, n (%)	No	221 (74,7)	86 (81,1)	135 (71,1)	0.056	102 (70,3)	119 (78,8)	0.094[a]
	Yes	75 (25,3)	20 (18,9)	55 (28,9)		43 (29,7)	32 (21,2)	
Type of First-Line Chemotherapy, n (%)	Platinum Gemcitabine	64 (21,5)						
	Carboplatin-paclitaxel	100 (33,7)						
	Platinum-pemetrexed	56 (18,9)						
	Platinum-etoposide	3 (1,0)						
	Cisplatin-paclitaxel	8 (2,7)						
	Cisplatin-doxorubicin	15 (5,1)						
	Cisplatin-vinorelbine	5 (1,7)						
	Chemotherapy plus Immunotherapy	5 (1,7)						
	Immunotherapy	7 (2,4)						
	Single-Agent Chemotherapy	7 (2,4)						
	Target-specific	27 (9,1)						

group with a SIRI score ≥1.8 (SIRI-High). There was no statistically significant difference between LIPI-Low group, LIPI-intermediate group, and LIPI-high group (p>0.05). General characteristics and demographic information of patients grouped according to LIPI are shown in Table II in detail.

In the overall population, median PFS was 5.50 (95% CI 4.95-6.04) months and median OS was 16.03 (95% CI 14.13-17.93) months. Median PFS was 5.96 (95% CI 5.26-6.67) months in the low PNI group and 6.03 (95% CI 4.99-7.01) months in the high PNI group. The median PFS of the low PNI group was lower than that of the high PNI group, but there was no statistically significant difference between the groups (p < 0.108). Median PFS was 5.16 (95% CI 4.28-6.04) months in the SIRI-Low group and 4.80 (95%

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Table 2. Comparison of various sociodemographic and clinical variables by LIPI groups

Variables		Total	LIPI			p
			dNLR negative and LDH normal	One of the two is Positive	Both Positive	
Age, Mean±SD		63,51±10,07	62,95±9,63	64,14±10,01	63,20±11,16	0.636[c]
Gender, n (%)	Male	245 (82,5)	95 (84,1)	105 (81,4)	45 (81,8)	0.852[a]
	Female	52 (17,5)	18 (15,9)	24 (18,6)	10 (18,2)	
ECOG, n (%)	0	61 (20,5)	27 (23,9)	28 (21,7)	6 (10,9)	0.180[b]
	1	186 (62,6)	71 (62,8)	80 (62)	35 (63,6)	
	2	44 (14,8)	12 (10,6)	20 (15,5)	12 (21,8)	
	3-4	6 (2,1)	3 (2,7)	1 (0,8)	2 (3,6)	
Histopathological Subtype, n (%)	Adenocarcinoma	174 (58,6)	74 (65,5)	66 (51,2)	34 (61,8)	0.068[a]
	SCC	123 (41,4)	39 (34,5)	63 (48,8)	21 (38,2)	
Smoking, n (%)	Yes	172 (57,9)	23 (20,4)	14 (10,9)	12 (21,8)	0.132[a]
	No	49 (16,5)	67 (59,3)	76 (58,9)	29 (52,7)	
	Left	76 (25,6)	23 (20,4)	39 (30,2)	14 (25,5)	
COPD, n (%)	No	223 (75,1)	87 (77)	95 (73,6)	41 (74,5)	0.831[a]
	Yes	74 (24,9)	26 (23)	34 (26,4)	14 (25,5)	
Diabetes mellitus, n (%)	No	246 (82,8)	98 (86,7)	103 (79,8)	45 (81,8)	0.358[a]
	Yes	51 (17,2)	15 (13,3)	26 (20,2)	10 (18,2)	
Chronic kidney disease, n (%)	No	272 (91,6)	105 (92,9)	117 (90,7)	50 (90,9)	0.808[a]
	Yes	25 (8,4)	8 (7,1)	12 (9,3)	5 (9,1)	
Liver metastasis, n (%)	No	191 (64,3)	73 (64,6)	85 (65,9)	33 (60)	0.745[a]
	Yes	106 (35,7)	40 (35,4)	44 (34,1)	22 (40)	
Bone metastasis, n (%)	No	144 (48,5)	55 (48,7)	66 (51,2)	23 (41,8)	0.509[a]
	Yes	153 (51,5)	58 (51,3)	63 (48,8)	32 (58,2)	
Brain metastasis, n (%)	No	221 (74,7)	92 (81,4)	90 (70,3)	39 (70,9)	0.110[a]
	Yes	75 (25,3)	21 (18,6)	38 (29,7)	16 (29,1)	
	No-Not Viewed	245 (82,5)	93 (82,3)	108 (83,7)		
Type of First-Line Chemotherapy, n (%)	Platinum Gemcitabine	64 (21,5)				
	Carboplatin-paclitaxel	100 (33,7)				
	Platinum-pemetrexed	56 (18,9)				
	Platinum-etoposide	3 (1,0)				
	Cisplatin-paclitaxel	8 (2,7)				
	Cisplatin-doxorubicin	15 (5,1)				
	Cisplatin-vinorelbine	5 (1,7)				
	Chemotherapy plus Immunotherapy	5 (1,7)				
	Immunotherapy	7 (2,4)				
	Single-Agent Chemotherapy	7 (2,4)				
	Target-specific	27 (9,1)	62,95±9,63	64,14±10,01	63,20±11,16	

LIPI (Lung Immune Prognostic Index), dNLR: derived neutrophil lymphocyte ratio, SCC: squamous cell carcinoma, COPD: chronic obstructive pulmonary disease

CI 4.18-5.41) months in the SIRI-Low High group. The median PFS of the SIRI-Low group was longer than that of the SIRI-High group, but there was no statistically significant difference between the groups (p < 0.422). Median PFS was 5.3 (95% CI 4.39–6.20) months for the low LIPI group and 5.46 (95% CI 3.52–7.41) months for the intermediate LIPI group. For the high LIPI group, it was 5.36 (95% CI 4.64 -6.08). There was no statistically significant difference between LIPI-Low, LIPI-Intermediate and LIPI-High groups (p < 0.362). The shrinkage of the tumor in one of our patients with high PNI and low SIRI was supportive on a case-by-case basis. (Figure – 1)

If we look at the whole population, the median OS was 16.03 (95%CI: 14.13-17.93) months. The median OS was 14.86 (95% CI: 11.7 -18.03) months for the PNI-Low group and 17.2 (95% CI: 14.75-19.64) months for the PNI-High group. The median OS of the PNI-Low group was shorter than the PNI-High group, but there was no statistically significant difference between the groups (p: <0.121). Median OS was 19.86 (95% CI:16.31 -23.42) months for the SIRI-Low group and 14.23 (95% CI: 11.98-16.48) months for the SIRI-High group. The median OS of the SIRI-Low group was longer than the SIRI-High group, but there was no statistically significant difference between the groups (p: <0.112) (Figure 1). The median OS was 17.76 (95% CI 16.51 -19.02) months for the LIPI-Low group and 15.13 (95% CI: 12.15-18.11) months for the LIPI-intermediate group. For the LIPI-high group, it was found to be 13.73 (95% CI 8.05 -19.41). There was no statistically significant difference between LIPI-Low LIPI-intermediate and LIPI-High groups (p: <0.391).

Median PFS was 5.86 (95% CI: 5.34-6.38) months in those without brain metastases, and 4.70 (95% CI: 4.01-5.38) months in those with brain metastases. It was shorter in those with brain metastases than in those without PFS, and it was statistically significant (p=0.040). In patients without brain metastases, 2-year disease-free survival was 4.4%, while 5-year disease-free survival was 2.2%. In patients with brain metastases, 2-year disease-free survival was 0%.

Median OS was statistically significant according to histological subtype groups (p=0.001). The median OS was 8.06 (95%CI: 14.76-21.37) months in AC, and the median OS was 13.60 (95%CI: 10.55-16.64) months in SCC. The OS in AC is statistically significantly longer than SCC. While 2-year survival was 35.2% in AC patients, 5-year survival was 16.7%, and 2-year survival in SCC was 27.1%.

We conducted a Multivariate Cox regression analysis in order to identify factors that independently predict PFS (progression-free survival). In the group of individuals who did not have brain metastases, the duration of progression-free survival was observed to be longer, although the difference was not found to be statistically significant, in comparison to the group with brain metastases [HR (95% CI) = 1.29 (0.98-1.71), p: 0.68].

Multivariate Cox regression analysis was performed to find independent prognostic factors to determine OS). The OS was found to be longer in AC than in SCC [HR (95% CI) = 1529 (1.18-2.14), p: 0.002].

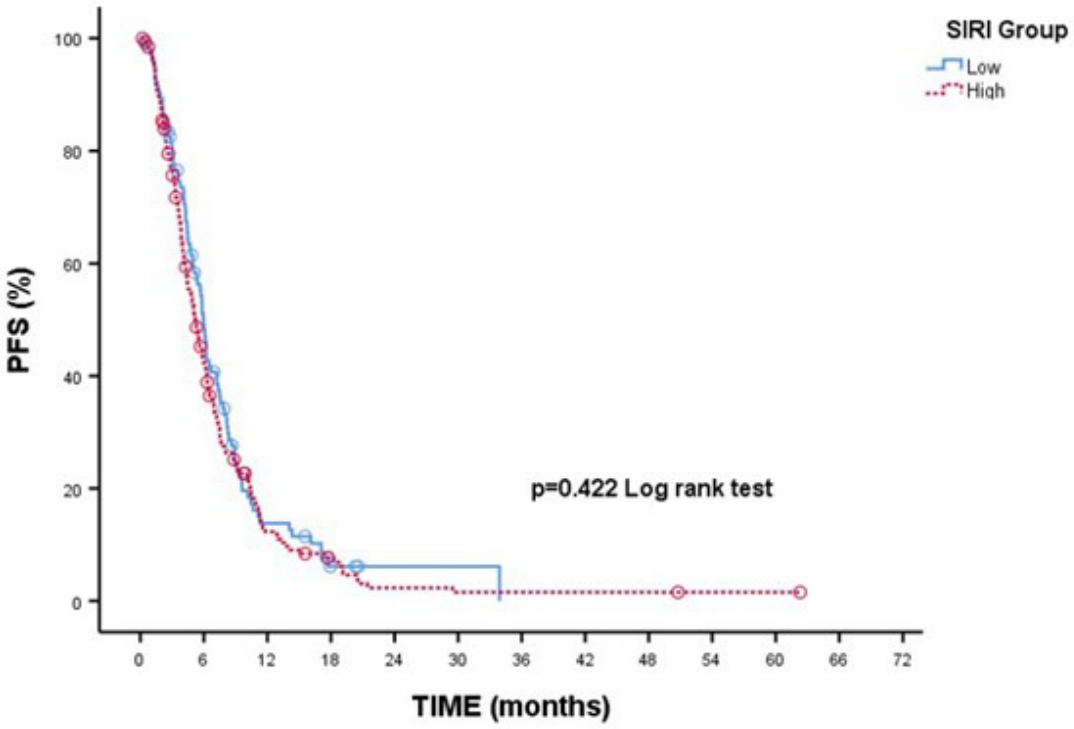

Figure 1. Progression Free Survival analysis functions by SIRI groups

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Table 3. Univariate analysis of PFS and OS

	mOS (95%CI)	p-value	mPFS (95% CI)	p-value
General	**16,03 (14,13-17,93)**		5,50 (4,95-6,04)	
Gender		**0.988**		0.093
Male	**16,00 (13,75-18,25)**		5,40 (4,72-6,07)	
Woman	**17,70 (14,48-20,91)**		5,90 (5,06-6,73)	
Histological subtype		0.001		0.315
AC	**18,06 (14,76-21,37)**		5,63 (4,94-6,32)	
SCC	**13,60 (10,55-16,46)**		5,40 (4,26-6,53)	
Liver Metastasis		**0.700**		0.018
No	**16,00 (13,67-18,32)**		5,06 (4,25-5,87)	
Yes	**16,03 (13,36-18,70)**		6,20 (5,48-6,91)	
Lung Metastasis		**0.734**		0.484
No	**16,06 (15,77-19,35)**		5,93 (4,98-6,88)	
Yes	**15,76 (13,53-18,00)**		5,30 (4,61-5,98)	
Bone Metastasis		**0.070**		0.333
No	**17,53 (13,88-21,17)**		5,80 (4,80-6,79)	
Yes	**14,60 (13,53-18,00)**		5,30 (4,59-6,01)	
Brain Metastasis		**0.540**		0.040
No	**16,06 (14,32-17,80)**		5,86 (5,34-6,38)	
Yes	**14,60 (9,84-19,35)**		4,70 (4,01-5,38)	
PDL		**0.167**		0.907
No-Not Viewed	**15,76 (13,62-17,91)**		5,63 (5,06-6,20)	
Positive	**18,06 (12,02-24,11)**		4,40 (2,94-5,85)	
SIRI		**0.112**		0.422
Low	**19,86 (16,31-23,42)**		**5,16 (4,28-6,04)**	
High	**14,23 (11,98-16,48)**		**4,80 (4,18-5,41)**	
PNI		**0.121**		0.108
Low	**14,86 (11,70-18,03)**		**5,96 (5,26-6,67)**	
High	**17,20 (14,75-19,64)**		**6,03 (4,99-7,01)**	
LIPI		**0.391**		0.362
dNLR negative and LDH normal	**17,76 (16,51-19,02)**		**5,30 (4,39-6,20)**	
One of the two is Positive	**15,13 (12,15-18,11)**		**5,46 (3,52-7,41)**	
Both Positive	**13,73 (8,05-19,41)**		**5,36 (4,64-6,08)**	
Type of First-Line Chemotherapy		**0.211**		0.787
Platinum Taxane	14,86 (11,75-17,97)		4,76 (3,80-5,73)	
Platinum-peme-trexed	18,10 (13,07-23,12)		5,36 (4,64-6,08)	

PFS: Progression-free survival, OS: Overall Survival, CI: Confidence interval, PS: performance status, LIPI (Lung Immune Prognostic Index), dNLR: derived neutrophil lymphocyte ratio, SCC: squamous cell carcinoma, COPD: chronic obstructive pulmonary disease, PNI (Perioperative Nutritional Index), SIRI (Systemic Immune-Inflammation Index)

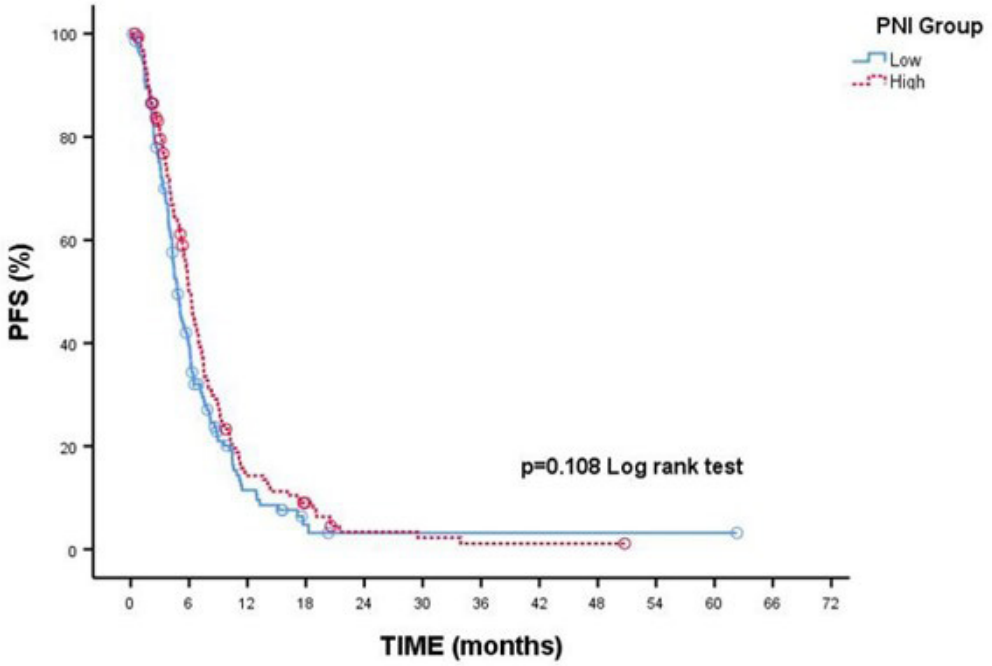

Figure 2. Progression Free Survival analysis functions by PNI groups

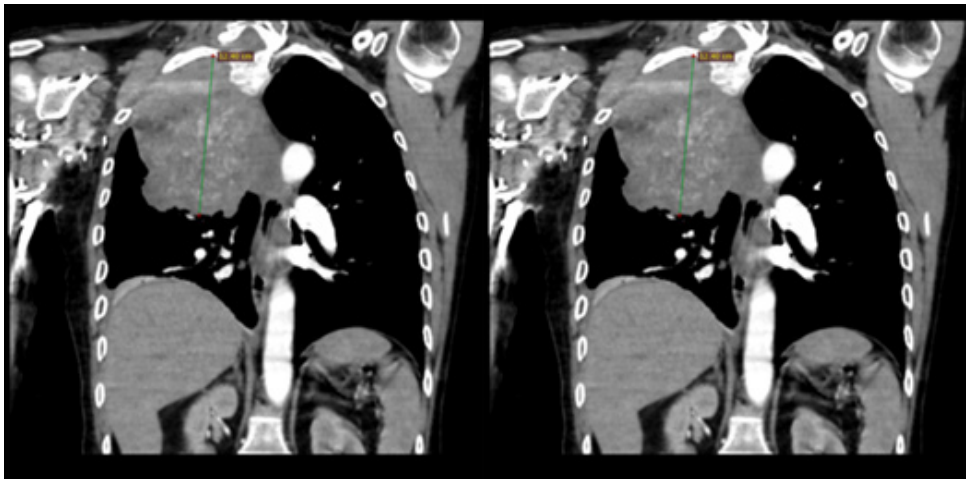

Figure 3. Coronal section computed tomography of the tumor shrinkage in a case with high PNI and low SIRI

Discussion

Many studies have been conducted to predict the prognosis of patients with metastatic NSCLC and prognostic factors have been identified. Unfortunately, no marker to be used in daily clinical practice has been found. Albumin is a negative acute phase reactant synthesized in the liver. Hypoalbuminemia can be caused by malnutrition, hyper catabolism caused by cancer cells, and increased inflammation due to cytokine release, which plays a role in the survival of cancer patients [14]. Lymphocytes contribute to prolonged survival by inhibiting apoptosis by secreting tumor necrosis factor alpha and interferon gamma, preventing tumor migration and invasion [15]. An increase in the number of neutrophils plays a role in tumoral pathogenesis by increasing the C-X-C motif chemokine ligand 8, nuclear factor kappa-B, Transforming growth factor-beta-β1 (TGF-β1) and vascular endothelial growth factor (VEGF) [16]. Meanwhile, the number of circulating monocytes is known to contribute to the tumor microenvironment by differentiation into macrophages and secreting proteases that degrade the extracellular matrix, leading to poor prognosis in various tumors [17]. We decided to conduct this study evaluating PNI, SIRI and LIPI, which we think will play a prognostic role in metastatic NSCLC.

In the study, we observed 297 patients overall, with 245 of them being men, accounting for 82.5% of the total. Out

Acta Medica Alanya 2023;7(2): 153-162
Doi: 10.30565/medalanya.1314292

of the total number of patients, 174 (58.6%) were categorized as AC, while 123 (41.4%) were classified as scc. When considering the entire population, the middle point of progression-free survival (PFS) is 5.50 months with a range of 4.95-6.04 months, whereas the middle point of overall survival (OS) is 16.03 months with a range of 14.13-17.93 months. The overall traits and average lifespan of the patients included in our research align with what is stated in the existing literature[18]. While the median PFS was 5.96 months for the PNI-Low group, it was 6.03 months for the PNI-High group. The median PFS of the PNI-Low group was shorter than the PNI-High group, but not statistically significant (p: <0.108). While the median OS was 14.86 months for the PNI-Low group, it was 17.2 months for the PNI-High group. The median OS of the PNI-Low group was shorter than the PNI-High group, but there was no statistically significant difference between the groups (p: <0.121). In a meta-analysis of 4922 patients with metastatic NSCLC, lower PNI was found with shorter OS (HR: 1.59, 95% CI: 1.28–1.96, P = 0.001) and PFS (HR = 1.52, %CI = 1.26–1.83, P = 0.002) [19]. In a study of gastrointestinal cancers recruiting 3414 patients preoperatively, low PNI was associated with low OS (HR = 1.80, CI = 1.26–1.83, P = 0.002) [20]. In a study of 319 patients with metastatic and locally limited pharyngeal cancer Stage 1-4, a low PNI score was associated with poor OS [9].

In our study, the median PFS was 5.16 (95% CI: 4.28 -6.04) months for the SIRI-Low group and 4.80 (95% CI: 4.18-5.41) months for the SIRI-High group. The median PFS of the SIRI-Low group was longer than the SIRI-High group, but not statistically significant (p: <0.422). Median OS was 19.86 (95% CI:16.31 -23.42) months for the SIRI-Low group and 14.23 (95% CI: 11.98-16.48) months for the SIRI-High group. But it was not statistically significant (p: <0.112). In a meta-analysis of 38 studies with a predominance of gastrointestinal cancers, breast cancer, and head and neck cancer involving 10,734 patients, high SIRI was associated with poor OS (HR = 2.04, 95% CI = 1.82–2.29, P < .001). and PFS (HR = 2.08, 95% CI = 1.84–2.34, P < .001). At the same time, SIRI elevation was found to be correlated with low tumor size, lymph node involvement, and TNM (Tumor, Node, Metastasis) stage [21]. In a study of 176 patients with stage 3 NSCLC undergoing definitive chemoradiotherapy, low SIRI was found to be correlated with good prognosis (HR=1.868 CI:1.016–3.436) (p:0.018) [10]. In a study of 390 patients with locally limited NSCLC, preoperative high SIRI was associated with lower OS and PFS [22].

Median PFS was 5.3 (95% CI 4.39 -6.20) months for the LIPI-Low group and 5.46 (95% CI: 3.52-7.41) months for the LIPI-intermediate group. For the LIPI-high group, it was found to be 5.36 (95% CI 4.64 -6.08). There was no statistically significant difference between the groups (p: <0.362). Median OS was 17.76 (95% CI 16.51 -19.02) months for the LIPI-Low group and 15.13 (95% CI: 12.15-18.11) months for the LIPI-intermediate group. For the LIPI-high group, it was found to be 13.73 (95% CI 8.05 -19.41). There was no statistically significant difference between the groups (p: <0.391). A higher LIPI score was associated with longer OS in a meta-analysis of 12 studies of 4883 patients, the majority of whom were patients with NSCLC receiving immunotherapy. A higher LIPI score was associated with longer OS in a meta-analysis of 191 patients, the majority of whom were patients with malignant melanoma receiving immunotherapy [23].

In our study, there were 221 (74.7%) patients with brain metastases. PFS was found to be 5.86 (95% CI: 5.34-6.38) months in the group without brain metastases, and 4.70 (95% CI: 4.01-5.38) months in the group with brain metastases (p=0.040). Although it did not reach statistical significance in multivariate analysis, it was found to be longer [HR (95% CI) = 1.29 (0.98-1.71) (p:0.68)]. Our study is compatible with the literature in terms of the poor prognosis of brain metastases [24].

OS was found to be longer in AC compared to scc [HR (95% CI) = 1.59 (1.18-2.14) (p:0.002). Our study is compatible with the literature. [25,26].

The small number of patients is one of the limitations of our study because it is retrospective. Our study found a cut-off value of 483.31 for PNI and 2.34 for SIRI using ROC analysis, but a more accurate value can be calculated using methods with higher specificity and sensitivity, but this optimal value is not known. Prospective, well-designed studies with large numbers of patients are needed.

In conclusion, PNI and SIRI are inexpensive, practical, literature contributing markers and can be used in routine clinical practice to predict the prognosis of patients with metastatic NSCLC, if confirmed by prospective studies. Although not reaching statistical significance, low PNI and high SIRI were independent predictors of poor prognosis in patients with metastatic NSCLC.

Conflict of Interest: The author declares no conflict of interest related to this article. Funding sources: The author declares that this study has received no financial support.

Funding sources: The authors declare that this study has received no financial support.

Ethics Committee Approval: Diyarbakir Gazi Yaşargil Training and Research Hospital (Approval Date-No: 25.11.2022-2022/232).

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Peer-review: Externally peer reviewed.

Acknowledgment: No

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