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Özgün Araştırma / *Research Article*

Prognostic Value of Diffuse Cancer Inflammation Index (ALI), Serum Neutrophil/Lymphocyte Ratio (NLR) and Platelet/lymphocyte Ratio (PLR) in Advanced Stage Lung Cancer

İleri Evre Akciğer Kanserinde; Yaygın Kanser İnflamasyon İndeksi (ALI), Serum Nötrofil/Lenfosit Oranı (NLR), Trombosit/Lenfosit Oranının (PLR) Prognostik Değeri

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ABSTRACT

Objective: Lung cancer (Ca) is the most common type of cancer that causes death worldwide. Systemic inflammation has been shown to play a role in cancer etiopathogenesis and can be activated from oncogenic changes in cancer cells. In lung cancer, although there are studies showing that systemic inflammatory parameters may have a role in determining prognosis and risky cases, the results are still controversial. In our study, the prognostic effects of inflammatory parameters calculated from serum were investigated in lung Ca.
Method: One hundred fifteen patients with locally advanced and advanced lung cancer who were diagnosed in our chest diseases clinic between 2013 and 2015 were retrospectively analyzed. The relationship between advanced lung cancer inflammation index (ALI index), serum neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) levels at the time of diagnosis were calculated, and their relationship with overall survival (OS), disease-free survival (PFS) and the treatment response and their effect on predicting prognosis were investigated.
Results: In our study, when advanced lung cancer cases were examined regarding OS; ALI, and NLR were statistically significant ($p < 0.05$), non-small cell lung cancer cases were similar to general statistics, and ALI and NLR values were statistically significant.
Conclusion: In our study, it was concluded that NLR and ALI values at the time of diagnosis were associated with prognosis, and those values may be useful in predicting prognosis when the cut off values was used. These parameters can be useful in routine use since they can be easily calculated without additional costs.

Keywords: ALI, lung cancer, NLR, PLR, prognostic index

ÖZ

Amaç: Akciğer kanseri tüm dünyada en sık görülen ve ölüme neden olan kanser türüdür. Sistemik inflamasyon hem kanser etiyopatogenezinde rol oynadığı hem de kanser hücrelerinde onkojenik değişikliklerden aktiflenebildiği gösterilmiştir. Akciğer kanserinde, prognozunu ve riskli olguları belirlemede sistemik inflamatuar parametrelerin yeri olabileceğini gösteren çalışmalar olmakla beraber sonuçlar halen tartışmalıdır. Çalışmamızda serumdan hesaplanan inflamatuar parametrelerin, akciğer kanserinde prognostik etkisi araştırıldı.
Yöntem: Göğüs hastalıkları kliniğimizde 2013-2015 tarihleri arasında tanı alan lokal ileri ve ileri evre akciğer kanserli 115 olgu retrospektif olarak incelendi. Tüm hastaların tanı aşamasında serum örneklerinden hesaplanan; ileri akciğer kanseri inflamasyon indexi (ALI indeksi), serum nötrofil/lenfosit oranı (NLR), trombosit/lenfosit oranı (PLR) düzeyleri ile genel sağkalım (OS), hastalıksız sağkalım (PFS) ve tedaviye yanıt değerlendirmeleri arasındaki ilişki ve prognozu öngörmede ki etkisi araştırıldı.
Bulgular: Çalışmamızda ileri evre akciğer kanserli olgular da OS için incelendiğinde; ALI ve NLR de istatistiksel olarak anlamlı ($p < 0.05$) iken, küçük hücreli dışı akciğer kanserli olgularda da genel istatistikle benzer olup ALI ve NLR değerleri istatistiksel olarak anlamlı saptandı.
Sonuç: Çalışmamızda ileri evre akciğer kanserli tüm olgularda, tanı aşamasında NLR ve ALI değerlerinin prognoz ile ilişkili olduğu, belirtilen cut off değerlerinin kullanıldığında hastanın prognozunu öngörmede yararlı olabileceği sonucuna varıldı. Bu parametrelerin ek maliyet gerektirmeden, kolayca hesaplanabilir olması nedeniyle rutin kullanımda yararlı olabilir.

Anahtar kelimeler: Akciğer kanseri, ALI, NLR, PLR, prognostik indeks

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INTRODUCTION

Lung cancer is the most common cancer in the world. Despite the newly developed treatment modalities in advanced lung cancer, 5-year survival is still 10-15% [1].

It is crucial to determine the prognosis, to predict high/low-risk patients, to determine more major toxicity risks in the treatment in lung cancer patients in order to manage the appropriate treatment plan for the patient.

It has been shown in some studies that systemic inflammatory markers can be useful both in identifying high-risk patients and in demonstrating the progression of the disease [2]. Although cancer itself may occur as a result of an inflammatory cause, inflammation may also occur as a result of cancer's oncological changes [2,4].

In our study, advanced lung cancer inflammation index (ALI index), serum neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) were calculated in patients with advanced-stage lung Cancer and relationship between treatment response parameters and prognosis were aimed to be investigated.

MATERIAL and METHOD

One hundred sixty patients with locally advanced and advanced lung cancer (2013-2015) who were diagnosed at the chest disease clinic in our hospital were retrospectively analyzed. Ethics approval was obtained for the study from our local scientific committee.

Cases with a history of malignancy, and cases who were diagnosed in another facility/center and whose data were not available, were excluded from the study. Cases scanned by PET-CT, cranial CT / cranial MRI, abdominal USG, and bone scintigraphy were staged according to the 7th TNM. Absolute neutrophil, absolute lymphocyte, platelet, and serum albumin levels at the time of diagnosis were recorded from the patient's medical records. Data belonged to pretreatment were within +/- 4 weeks of the diagnosis time. Height and weight values before the treatment were recorded retrospectively. Calculations were as follows:

BMI: Weight/ (L)2, NLR: Neutrophil / Lymphocyte ratio, PLR: Platelet / Lymphocyte ratio and ALI value: BMI x (Albumin / NLR) formula. Considering the previous studies, 18 cut off values were taken for ALI, 5 for NLR, and 250 for PLR.

The planned treatment protocols (chemotherapy, radiotherapy and/or surgery), post-treatment radiological response, and progression history were recorded retrospectively from medical records. Progression-free survival (PFS) was calculated as between the date of diagnosis and the date radiological progression was determined, while survival was calculated as the time from the date of diagnosis to death. The date of death was obtained from the death notification system (Mernis) and medical records. For the patients who were still alive, the time between the diagnosis until the termination of the study was taken as a lifetime (minimum one year was followed).

The data obtained in the study were entered into the database created in SPSS 18 program. The Kaplan-Meier method was used for survival analysis, and the survival process comparisons of independent groups were performed by using the Log-Rank test. The results were evaluated in the 95% confidence interval, and the significance level was considered as $p < 0.05$.

RESULTS

One hundred sixty patients diagnosed with advanced-stage lung cancer were examined. Forty-five cases whose exact diagnosis and stage were not known and whose data were not available were excluded from the study. Of the 115 cases included in the study, 15 (13%) were female, and 100 (87%) were male. The mean age was 61.51 + 9.69 and was similar in men and women.

Table 1. Height, weight, and serum base values of the patients included in the study.

Characteristics	Mean	STD	Mean	Min	Max
HEIGHT (cm)	168,83	8,03	170	150	188
WEIGHT (kg)	69,61	14,26	69	43	136
BMI	24,43	4,72	23,84	15,43	39,31
ALBUMIN (g/dL)	3,60	0,58	3,60	2,00	4,80
PROTEIN (g/dL)	6,91	0,63	7,00	5,40	8,60
WBC	10800,87	3880,51	10300	3700	28300
NEUTROPHILS	7781,04	3711,53	6700	1570	25100
LYMPHOCYTE	1906,09	705,22	1900	300	3800

BMI: Body Mass Index

WBC: White Blood Cell

Pretreatment, ALI, NLR, and PLR values of 115 Lung Ca cases were calculated. Overall survival and progression-free survival times were calculated, and statistical analysis was performed for their effects in predicting prognosis.

113 of 115 patients in the study died during their follow-up. For the patients who were alive, the time between the diagnosis and the termination of the study was taken as a lifetime (June 2017). The period from the date of diagnosis until the death of cases was calculated in months.

In our study, no statistically significant difference was observed in NLR, PLR, and ALI values for the PFS time ($p>0.05$).

For overall survival (OS), there were 77 (67%) patients who were over the NLR 5.00, and 38 (33%) patients were below NLR 5.00 value. The average time for OS for NLR below 5.00 was 9.67 months, and for NLR above 5.00, it was 5.95 months. A statistically significant difference was observed in the NLR value up to OS time ($p:0.026$; $p<0.05$).

For OS, there were 44 (38%) patients below the ALI value of 18.00, and 71 (62%) patients had a value of above 18.00. The average time for OS under ALI 18.00 was 4.24 months, and above 18.00, it was 10.13 months. A statistically significant difference was observed for the time up to the OS of the ALI value.

However, in our study, no statistically significant difference was observed for PLR value for OS ($p>0,05$).

The two groups were statistically evaluated as subgroups for NLR, PLR, and ALI values due to differences between SCLC and NSCLC in staging, treatment, and follow-up. When evaluated as SCLC subgroup, in terms of OS and PFS, no statistically significant difference was observed regarding ALI, NLR, PLR value ($p>0.05$). In our statistical study of NSCLC, no statistically significant difference was observed in ALI, NLR, and PLR values for PFS and PLR for OS.

There were 58 (66%) patients under the NLR value of 5.00, and 30 (34%) patients were above this value for OS. The average time for OS under NLR 5.00 was 8.7 months, and above the value of 5.00, it was 4.2 months. For NSCLC, a statistically

Table 1. Height, weight, and serum base values of the patients included in the study.

Characteristics		#	%
SCLC		27	23.47%
NSLC	**Adenocarcinoma**	43	37.39%
	With Squamous Cell Carcinoma	37	32.17%
	NSCLC subtype can not be determined	8	6.95%
Stage	**Stage 3B**	38	33.04%
	Stage 4:	77	66.95%
Treatment	**CT**	73	63.47%
	Concomitant CRT	7	6.08%
	Consecutive CT-RT	13	11.30%
	RT	2	1.73%
	Operated	1	0.86%
	Palliative	19	16.52%

SCLC: Small Cell Lung Carcinoma

NSCLC: Non - Small Cell Lung Carcinoma

CT: Chemotherapy

CRT: Chemoradiotherapy

RT: Radiotherapy

significant difference was observed in the NLR value up to OS time.

In NSCLC, there were 37 (42%) patients below the ALI value of 18.00, and 51 (58%) patients had a value above 18.00 for OS. The average time for OS below the value of 18.00 was 3.780 months, and it was 9.010 months for above. For NSCLC, a statistically significant difference was observed for the time up to OS for the ALI value (p:0.001; $p<0.05$)

DISCUSSION

Studies on various clinical and pathological factors have been conducted to determine the prognosis in lung cancer from past to present. Indexes such as ALI, NLR, GPS, and IPI, which are obtained especially from routine biochemical data, are one of the issues that keep up to date in cancer because it is easy to calculate and does not require additional costs. However, limited

data are available on the prognostic effect of inflammatory parameters in lung cancer.

It has been reported that systemic inflammation increases tumor cell proliferation, causes increased angiogenesis and metastasis, reduces the response to anti-cancer drugs, and is therefore associated with poor prognosis [3]. There are publications in some months that increased systemic inflammation in lung cancer is associated with disease progression, weakness, cancer cachexia [4].

NLR is an easily calculated parameter that reflects the severity of inflammation as neutrophil/lymphocyte in serum.

In our study, NLR value was found to be associated with overall survival in all lung cancer cases, but no relationship was found between PFS. NLR in tumor subgroups was found to be associated with OS only in the NSCLC group.

In their study, Cendes et al. found that NLR values of T4 and N3 patients with higher tumor burden were higher than T1 and N0 patients, and with our study, NSCLC was associated with NLR>5 poor prognosis [5].

Regarding the relationship between NLR and chemotherapy, Yao et al. reported that high NLR value in advanced NSCLC patients receiving platinum-based chemotherapy responded worse to first-line platinum-based chemotherapy and caused shorter survival and was associated with poor prognosis [6].

In the literature, PLR is generally combined with NLR in studies; isolated prognostic data are limited. It has been shown by Hong et al. that PLR, PNI (prognostic nutritional index) (albumin + 5 * lymphocyte) and NLR are significantly associated with OS in SCLC [7].

In another study, a significant relation was found between OS and PFS rates in NSCLC and NLR and PLR, and it was mentioned in the multivariate analysis that PLR was significantly related between OS and NLR and PFS8.

However, in a study conducted by Wu et al., the prognostic effect of PLR in NSCLC was not demonstrated in all NSCLC patients [9]. In our study, no relationship was found between OS and PFS of PLR in advanced lung cancer cases and subgroups.

ALI is an index developed to evaluate the high-risk group, especially in advanced lung cancer.

Hypoalbuminemia, in its content, is not only associated with inflammation but is associated with poor prognosis in many cancers10. The ALI value may be more valuable for the OS as it combines albumin, NLR, and BMI factors, which were previously associated with prognosis.

In our study, no significant difference for PFS was detected between ALI value and all lung cancer cases and subgroups. A significant relationship was found between OS and ALI in all cases and the NSCLC subgroup.

Failure to obtain expected results in SCLC may be related to the low number of cases and limitations of our study. SCLC has different biological behavior by nature, and different cut-off values may need to be calculated, so large-scale studies are required.

In one study, it was found that the number of metastases of patients with ALI <18 in NSCLC cases was higher, their performance status was poor, they could not receive chemotherapy, and were associated with low PFS and OS [11].

In a study conducted by He et al. for SCLC, the cut-off value was taken as 19.5 for ALI. In the group with common disease ALI in a low figure, OS was found to be shortly related [12].

In the meta-analysis conducted by Hua X et al., a total of 1736 cases from 9 studies were included, and it was shown that low ALI value was associated with poor prognosis. Similar significant results were obtained in the subgroups of SCLC, NSLC, and other cancer types [13].

In the meta-analysis of 1587 lung cancer cases in which Yi Zhang et al. examined eight studies, low ALI value was found to be associated with poor OS and PFS [14].

Limitations of our study: Although we reached a high number of patients, the interval between the data used and the date of diagnosis could not

be the same since it was performed retrospectively, and especially the number of cases of SCLC cases was not sufficient. Therefore, detailed prospective studies are needed in this regard.

In our study, it was concluded that NLR and ALI values at the time of diagnosis were associated with survival in all patients with advanced lung cancer and that it may be useful in predicting survival and prognosis when the specified cut off values of the patient are used. These parameters are thought to be useful in routine use since they can be easily calculated without additional costs.

Ethics Committee Approval: Izmir Dr. Suat Seren Chest Diseases and Training and Research Hospital Ethics Committee approved (18.01.2016 / 575).

Conflict of Interest: There is no conlict interest.

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