



## ARAŞTIRMA / RESEARCH

### Prognostic value of basal neutrophil lymphocyte ratio in patients with extensive stage small cell lung cancer

İleri evre küçük hücreli akciğer kanseri olan hastalarda bazal nötrofil lenfosit oranının prognostik değeri

Ali Murat Sedef<sup>1</sup>, Züleyha Calıküşu<sup>2</sup>, Aykut Bahçeci<sup>3</sup>, Serkan Gökçay<sup>1</sup>, Ali Ayberk Beşen<sup>4</sup>, Ahmet Taner Sümbül<sup>4</sup>

<sup>1</sup> Department of Medical Oncology, Sanliurfa Mehmet Akif Inan Education and Research Hospital, Sanliurfa, Turkey,

<sup>2</sup> Department of Medical Oncology Acıbadem Mehmet Ali Aydınlar University, Adana, Turkey

<sup>3</sup> Department of Medical Oncology, Ersin Arslan Training and Research Hospital, Gaziantep, Turkey.

<sup>4</sup> Department of Medical Oncology, Baskent University Medical School, Adana, Turkey, Turkey.

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#### Abstract

**Purpose:** The neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and lymphocytopenia are markers of poor prognosis in lung cancer patients. The aim of this trial is evaluate the prognostic significance of basal NLR, PLR and lymphocytopenia in patients with extensive stage (ES) small cell lung cancer(SCLC).

**Materials and Methods:** This study was designed as a hospital-based retrospective observational case-series study. A total of 117 patients with extensive stage small cell lung cancer have been treated at four different oncology centers in Turkey between 2011 and 2017. Laboratory results and demographic data were collected.

**Results:** The median follow-up time was 12 months and 95 (81%) patients died. Progression-free survival (PFS) and overall survival (OS) were estimated, respectively, as 8 and 13 months. 65 (55.6 %) patients had complete response at the end of first line platin-etoposide combination treatment. The cut-off value for NLR and PLR were determined for whole group and patients were dichotomized into high ( $\geq 3.28$ ) and low ( $< 3.28$ ) NLR groups and high ( $\geq 139.8$ ) and low ( $< 139.8$ ) PLR groups.. Median OS was lower in patients who had high neutrophil lymphocyte ratio (NLR) (14 versus 12 months respectively).

**Conclusion:** This study showed that basal NLR may have prognostic biological value in patients with ES SCLC treated with cisplatin + etoposide.

**Key words:** Small cell lung cancer, NLR, lymphocytopenia

#### Öz

**Amaç:** Nötrofil lenfosit oranı (NLR) akciğer kanseri tanımlı hastalarda kötü prognostic bir belirteçtir. Bu çalışmanın amacı yaygın evre küçük hücreli akciğer kanseri (KHAK) tanısı ile tedavi edilen hastaların NLR'leri ile genel sağkalım ve tedavi sonuçları ile ilişkisinin incelenmesidir.

**Gereç ve Yöntem:** Bu çalışma, hastane tabanlı retrospektif gözlemsel olgu serisi bir çalışma olarak tasarlanmıştır. 2011 ile 2017 yılları arasında yaygın evre KHAK tanısı ile tedavi edilen 117 hasta çalışmaya dahil edilmiştir. Hastalar tedavi sonrası tam yanıt alınan ve alınmayan hastalar olmak üzere 2 gruba ayrıldılar. NLR oranları ve demografik veriler hesaplandı.

**Bulgular:** Ortalama izlem süresi 12 aydı ve 95 (%81) hasta öldü. Progresyonsuz sağkalım (PFS) ve genel sağkalım (OS) sırasıyla 8 ve 13 ay olarak hesaplandı. İlk sırada platin-etoposid kombinasyon tedavisinin sonunda 65 (% 55.6) hasta tam yanıt aldı (grup 1). NLR ve PLR için cut-off değeri tüm grup için belirlenmiş ve hastalar yüksek ( $\geq 3.28$ ) ve düşük ( $< 3.28$ ) NLR gruplarına ve yüksek ( $\geq 139.8$ ) ve düşük ( $< 139.8$ ) PLR gruplarına dikotomize edilmiştir. Medyan OS yüksek nötrofil lenfosit oranı (NLR) olan hastalarda daha düşüktü (sırasıyla 14'e karşı 12 ay).

**Sonuç:** Bu çalışma bazal NLR'nin cisplatin + etoposide ile tedavi edilen ES SCLC'li hastalarda prognostik biyolojik değere sahip olabileceğini göstermiştir..

**Anahtar kelimeler:** Küçük hücreli akciğer kanseri, NLR, lenfositopeni

Yazışma Adresi/Address for Correspondence: Dr. Ali Murat Sedef, Department of Medical Oncology, Sanliurfa Mehmet Akif Inan Education and Research Hospital, Sanliurfa, Turkey, E-mail: alimuratsedef@gmail.com  
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## INTRODUCTION

Small cell lung cancer (SCLC) constitutes approximately 15% of all lung cancers and the estimated number of cases in SCLC is about 29,000 in 2016 1,2. SCLC is distinguished from other tumors by rapid growth with early development of metastases. Most of patients presented at the extensive stage and could not be treated with curative treatment modalities like chemoradiotherapy. Patients have short symptom duration. Prognostic factors include ECOG performance status, gender, stage, number and location of metastases, SIADH and treatment response<sup>2</sup>. Management of ESCLC is nearly same over forty years though despite enormous effort on SCLC none of targeted treatment strategies or investigational immunotherapeutic agents did not result with significant improvement of survival parameters. Besides, the factors that can predict which patients will receive more response to treatment are not sufficient.

Inflammation is closely associated with tumorigenesis. Several laboratory markers associated with systemic inflammatory responses, including plasma C-reactive protein, albumin, hemoglobin, the absolute white blood cell count. White cell count or its components, NLR<sup>3</sup> and platelet-lymphocyte ratios (PLR)<sup>4</sup> have been investigated as prognostic and predictive markers in patients with different types of cancer<sup>5</sup>. NLR has been used not only as a marker of inflammation but also as a prognostic index for malignancies<sup>6</sup>. NLR was not an independent prognostic factor<sup>4</sup> and was not associated with cancer-specific survival<sup>7</sup>. Although there are various studies in the literature, the prognostic role of basal NLR, PLR and lymphocytopenia in ES SCLC is still unclear. The aim of the present study was to evaluate the prognostic role of basal NLR, PLR and lymphocytopenia in ES SCLC treated with cisplatin + etoposide.

## MATERIALS AND METHODS

We designed this study to evaluate the prognostic role of basal NLR, PLR and lymphocytopenia in ES-SCLC patients treated with cisplatin-based combination regimen. In a 6-year-period (Between September 2011-December 2017) among 1500 newly diagnosed lung cancer patients, 117 patients with stage 4 Small Cell Lung Cancer were enrolled

into the study from different four oncology center (Sanliurfa Mehmet Akif Inan Education and Research Hospital, Acibadem Mehmet Ali Aydinlar University, Ersin Arslan Training and Research Hospital and Baskent University Departments of Medical Oncology). Patients were histologically diagnosed as SCLC by invasive biopsy from main lung tumors or metastatic sites of patients. Conventional tomography and PET CT was used for staging and treatment response evaluation of the patients. Ethical approval was sought and granted by the institutional ethics committee in Baskent University Hospital, Adana, Turkey. Informed consent was obtained from all individual participants included in the study.

The clinical and laboratory information of the patients was transferred safely from the electronic records to the SPSS form. Demographic and clinicopathologic variables of the patients were determined by considering the disease characteristics and follow-up criteria included in the international guidelines. Neutrophil, lymphocyte, platelet and other laboratory levels of the patients were measured at the time of diagnosis before the initiation of systemic chemotherapy. Blood samples were drawn as a part of diagnostic evaluation at the time of diagnosis and were studied at the same time with other parameters of serum biochemistry. Venous blood samples were put into anticoagulant-free test tubes for measurement of blood laboratory levels. Neutrophil lymphocyte ratio (NLR) was calculated as the ratio of the absolute neutrophil count to the absolute lymphocyte count and platelet-lymphocyte ratios (PLR) was calculated as the ratio of the absolute thrombocyte count to the absolute lymphocyte count. Cut-off values were calculated using cox regression analysis for NLR and PLR. The effect of NLR and PLR on survival parameters were examined.

## Statistical analysis

All results were presented as the rate for categorical values or mean and median for continuous variables. Clinical and statistical significant correlation between continuous variables was calculated by Spearman's rank correlation test,  $r_s$  (spearman's correlation coefficient) and  $p$  value (2-tailed) were noted. Overall Survival (OS) was defined by the time from the date of death and last control minus the first day of the chemotherapy. Survival curves were estimated according to the Kaplan-Meier

method, and log-rank tests were used for univariate statistical comparisons. Adjusted Hazard Ratio (HR) and 95% confidence interval (95% CIs) were used for estimation. Receiver operating characteristic curve analysis was performed to determine the NLR cut-off. All statistical data were analyzed using the SPSS version 17.0, and a p value of <0.05 was considered statistically significant.

## RESULTS

### Patients

Patient characteristics are shown in Table 1. The median age of the patients was 61 (range 38-81) years and 105 (89.7%) patients were male. All of the patients (n:117) were stage 4 and 86 (73,5 %) patients had oligometastatic disease. Twenty one (17,9 %) patients had cranial metastases and 43 (368%) patients had liver metastases.

**Table-1. Patient and tumor characteristics**

Variable	
Median age (years) (min-max)	61 (39-83) years old
Gender	n (%)
Men	105 (89.7)
Women	12 (10.3)
Oligometastatic disease	86 (73.5)
Cranium Metastases	21 (17.9)
Liver Metastases	43 (36.8)
NLR	
≥3.28	56 (47.9)
<3.28	61 (52.1)
PLR	
≥139.8	67 (57.3)
<139.8	50 (42.7)
Lymphocytopenia	31 (26.5)

All patients were treated with the platinum etoposide combination regimen and 111 patients (94,9 %) received cisplatin in combination. The cut-off value for NLR and PLR were determined for whole group and patients were dichotomized into high (≥3.28) and low (<3.28) NLR groups and high (≥139.8) and low (<139.8) PLR groups. Besides, the patients were divided into 2 groups according to the presence of lymphocytopenia.

### Treatment and outcomes

The median follow-up time was 12 months and 95 (81%) patients died. Progression-free survival (PFS) and overall survival (OS) were estimated, respectively, as 8 and 13 months (Figure 1, 2). Sixty

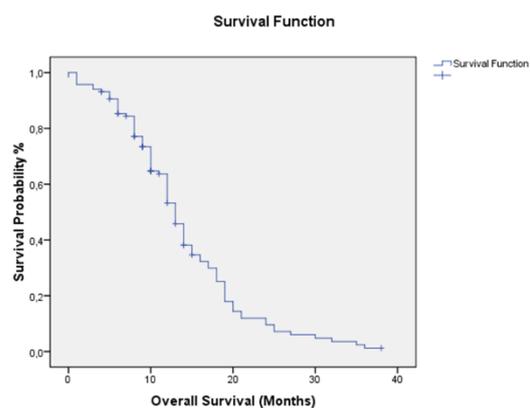
five (55.6 %) patients had complete response (CR) with radiological assesment at the end of first line platin-etoposide combination treatment. Forty seven (72,3 %) patients had CR at the end of treatment and 18 (27,7 %) patients had CR at the first analysis (after 3 cycle chemotherapy).

**Table 2. Relationship between systemic inflammatory response markers with survival analysis**

Variables (median)	OS	p	PFS	p
NLR		a		
High (≥3.28)	12	<b>0.013<sup>a</sup></b>	8	0.97
Low (<3,28)	14		8	
PLR				
High (≥139.8)	13	0.66	8	0.47
Low (<139,8)	13		8	
Lymphocytopenia				
Yes	12	0.29	8	0.44
No	13		9	

a Statistically significant; OS: Overall survival, PFS: Progression free survival

Patients in the low NLR group had better overall survival than those with high NLR (14 versus 12 months respectively and p=0.013) (Figure-3). There was no statistically significant difference in median PFS between patients with high NLR and those with low NLR (8 versus 8 months respectively and p=0.97).



**Figure 1. Kaplan–Meier estimates of overall survival (OS) of whole patients in the study**

There was no statistically significant relationship between PLR groups (<139.8 and >139.8) and OS (13 versus 13 months respectively and p=0.66). Similarly, there was no statistically significant relationship between PLR groups (<139.8 and

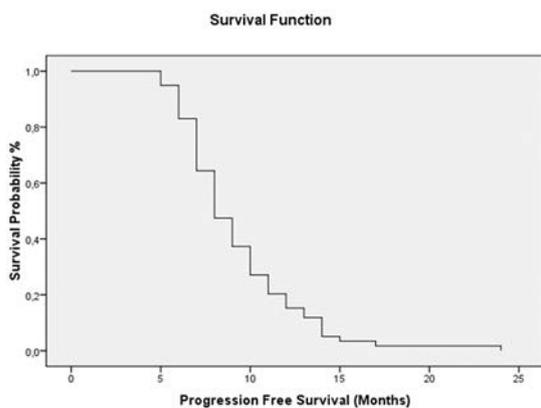
>139.8) and PFS (8 versus 8 months respectively and  $p=0.47$ ). There was no statistically significant relationship between lymphocytopenia and survival times (OS and PFS,  $p=0.29$  and  $p=0.44$  respectively). The relationship between systemic inflammatory response markers (NLR, PLR and lymphocytopenia) with survival analysis was shown in Table 2.

There was a statistically significant relationship between the presence of brain metastasis and NLR ( $p=0,01$ ). But the presence of cranial metastasis was not associated with PFS and OS ( $p=0,89$  and  $p=0,66$  respectively). Furthermore there was no correlation between disease features, response rates and these markers (NLR, PLR and lymphocytopenia) (Table-3)

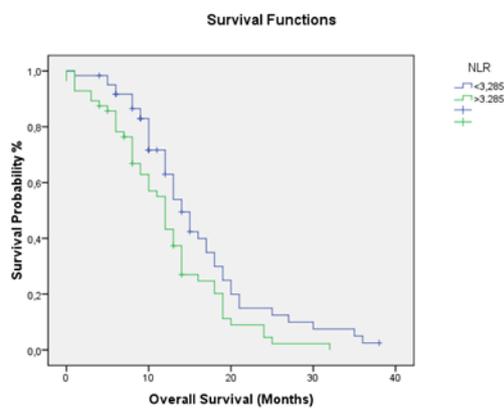
**Table-3:** Relationship between systemic inflammatory response markers with disease features and treatment outcomes

Variable	NLR			PLR			Lymphocytopenia		
	High	Low	P	High	Low	P	High	Low	P
Oligo metastatic disease									
Yes	42	44	0.72	52	34	0.24	22	64	0.70
No	14	17		15	16		9	22	
Cranium metastasis									
Yes	15	6	0.01 <sup>a</sup>	14	7	0.33	7	14	0.43
No	41	55		52	43		24	72	
Liver metastasis									
Yes	18	25	0.32	25	18	0.88	10	33	0.54
No	38	36		42	32		21	53	
Complete response									
Yes	29	36	0.43	39	36	0.50	16	49	0.71
No	27	25		28	24		15	37	

<sup>a</sup> Statistically significant



**Figure 2.** Kaplan–Meier estimates of progression-free survival (PFS) of whole patients in the study



**Figure-3:** Patients in the low NLR group had better overall survival than those with high NLR (14 versus 12 months respectively and  $p=0,013$ )

**DISCUSSION**

In this study we reviewed the prognostic significance of basal NLR, PLR and lymphocytopenia in ES SCLC patients. The important finding of this study is the basal NLRs effect on overall survival. Median OS was lower in patients who had high neutrophil lymphocyte ratio

(NLR). Our findings suggest that NLR was an independent prognostic marker for ES SCLC patients. But PLR and lymphocytopenia are not associated with survival.

The systemic inflammatory response was shown to be associated with a poor prognosis in various solid tumours. NLR is known as a biomarker with prognostic significance for many types of cancer<sup>8</sup>.

NLR, PLR and lymphocyte are easily measurable and repeatable parameters. However according to best our knowledge, cancer-induced inflammation can elevate the NLR, because both neutrophilia and relative lymphocytopenia occur in various tumors<sup>9</sup>. Several studies have suggested that increased cytokine levels may be responsible for changes in the NLR<sup>9-12</sup>.

There are negative and positive studies of NLR in different types of cancer in the literature. M H Kang et al investigated prognostic role of the NLR in SCLC patients and they showed that the prognostic significance of NLR for extensive stage patients<sup>13</sup>. Similarly, Liu et al demonstrated the prognostic significance of NLR and PLR with their retrospective studies with 139 patients. In this trial, 83 patients were extensive stage disease<sup>14</sup>. Käsman et al demonstrated that the prognostic significance of NLR in limited stage SCLC patients<sup>15</sup>. The studies for significance of NLR in NSCLC patients are more than SCLC patients in the literature. Liu H. et al showed that PLR maybe a potentially useful biomarker for predicting response to first-line treatment and prognosis in NSCLC<sup>16</sup>. In the literature, most of PLR studies have been conducted in NSCLC patients. The number of studies on systemic inflammation biomarkers related to SCLC is limited in the literature. Pretreatment lymphocytopenia has been showed to be a poor prognostic factor in patients with many type of cancer<sup>17, 18</sup>.

In our study, we also found that high NLR ratios in accordance with the literature were poor prognostic. However, unlike the literature, the prognostic value of PLR and lymphocytopenia could not be demonstrated in our study. Prognostic factors include ECOG performance status, gender, stage, number and location of metastases, SIADH and treatment response for ED SCLC and recent findings showed that basal NLR maybe one of them. Therefore, the present results, may serve beneficial in further stratification of SCLC patients into different prognostic groups just by using an easy to calculate, reproducible and economically cheap routine laboratory-test based scoring system in addition to other readily available prognostic factors. But before this judgment, additional studies investigating basal NLR role with other serum inflammation markers such as C- reactive protein, IL-6, TNF alfa or tissue inflammation signs such as tumor infiltrating lymphocytes should be performed.

There are several limitations of our study including retrospectively designed and including small size patients from limited centers.

In conclusion, high NLR were related poor prognosis on ED SCLC patients and we believe that the NLR maybe used to predict the mortality risks for newly diagnosed ED SCLC patients.

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