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WHICH HEMATOLOGIC PARAMETERS PREDICT SURVIVAL IN PATIENTS WITH SMALL CELL LUNG CANCER?

KÜÇÜK HÜCRELİ AKCİĞER KANSERİ HASTALARINDA HANGİ HEMATOLOJİK PARAMETRELER YAŞAM SÜRESİNİN BELİRTEÇLERİDİR?

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Anahtar Sözcükler: Küçük hücreli akciğer kanseri, inflamasyon skorları, hematolojik parametreler, yaygın evrede prognoz.

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SUMMARY

Introduction : *Small cell lung cancer(SCLC) is the most aggressive form of lung cancer. Recent studies showed that inflammation plays an important role in carcinogenesis. In this study, we investigated the survival impact of pre-treatment multiple inflammatory and hematological blood parameters and their relation between each other in SCLC.*

Material and Method: *This retrospective study enrolled 110 SCLC patients. The patients underwent platinum-based combination chemotherapy as a first-line treatment between 2012-2015. Untreated patients' hematological tests were taken into evaluation at initial diagnosis. Neutrophil, lymphocyte, platelet, hemoglobin (HGB), mean corpuscular volume (MCV), and mean platelet volume (MPV) values were collected. neutrophil-lymphocyte ratio (NLR)and the platelet-lymphocyte ratio (PLR), immune-inflammation index (SII) were calculated. Overall survival of patients (OS) was calculated until to January 2017. All analyses were conducted by SPSS v23.0 statistical software.*

Results: *Favorable prognostic factors were found to be age <65 years, limited stage, presence of curative radyotherapy and good performans status. In univariate analysis showed that neutrophil-lymphocyte ratio (NLR)<5, and mean corpuscular volume (MCV)>85 fl predicted better survival outcomes in extensive-stage SCLC patients. In our study; patients at extensive-stage with platelet-lymphocyte ratio(PLR)<250 or systemic immune-inflammation index (SII)<1,600x109/L had longer overall survival (OS) but statistical significance could not be achieved. COX regression analyses showed that age (≥65 years), NLR≥5, and MCV≤85 fl were independent unfavorable prognostic factors for OS in extensive-stage. However mean platelet volume(MPV), MPV/platelet ratio and hemoglobin have no effect on survival in all stage SCLC patients.*

Conclusion: *Our study demonstrates that NLR and MCV could help to predict poor prognosis in extensive-stage, treatment naive SCLC patients. Nevertheless prospective studies are needed to confirm these results.*

ÖZ

Giriş: *Küçük hücreli akciğer kanseri(KHAK) akciğer kanserleri arasında en agresif türdür. İnflamasyonun bir çok kanser türünün gelişmesi ve progresyonunda kritik rol aldığı gösterilmiştir. Bu çalışmada KHAK'i hastalarında tedavi öncesi inflamasyon ile ilgili skorların ve hematolojik parametrelerin sağkalım için prognostik değeri incelenmiştir.*

Gereç ve Yöntem*: KHAK'i tanılı 110 olgunun tedavi öncesi klinik ve hematolojik verileri retrospektif olarak incelendi. 2012-2015 yılları arasında birinci basamak tedavide platin bazlı kombinasyon kemoterapisi uygulanan hastaların tanı anında tedavi öncesi hematolojik testleri değerlendirildi. Nötrofil, lenfosit, trombosit, hemoglobin (HGB), ortalama korpusküler hacim (MCV) ve ortalama trombosit hacmi (MPV) değerleri toplandı. Nötrofil lenfosit oranı (NLR) ve trombosit-lenfosit oranı (PLR), immün inflamasyon indeksi (SII) hesaplandı. Hastaların genel sağkalımı Ocak 2017'ye kadar hesaplandı. Tüm analizler SPSS v23.0 istatistik yazılımı ile yapıldı.*

Bulgular*: Tüm hastalardaki yaşam süresi analizinde iyi prognostik kriter; <65 yaş, sınırlı evre, küratif radyoterapi varlığı ve iyi performans durumu olarak tesbit edildi. Tek değişkenli analizde yaygın evre KHAK hastalarında, nötrofil lenfosit oranı (NLR) <5 ve ortalama korpuskülar volüm (MCV)> 85 fl ise sağkalım sonuçlarının daha iyi olduğu gösterilmiştir. Çalışmamızda; trombosit-lenfosit oranı (PLR) <250 olan veya sistemik immün inflamasyon indeksi (SII) <1,600x109 / L olan yaygın evredeki hastalarda genel sağkalım(OS) daha uzundu ancak istatistiksel olarak anlamlı değildi. COX regresyon analizinde, yaş(≥65 yaş), NLR≥5 ve MCV≤85 fl'nin yaygın evre hastalıkta, OS için negatif prognostik faktörler olduğu görüldü. Ancak tüm evredeki KHAK hastalarında ortalama trombosit hacmi (MPV), MPV / trombosit oranı ve hemoglobinin sağkalım üzerinde hiçbir etkisi yoktu.*

Sonuç: *Çalışmamızda tedavi almamış yaygın evredeki KHAK hastalarında NLR ve MCV'nin kötü prognozu belirlemede istatistiksel olarak anlamlı düzeyde etkili olduğu tesbit edilmiştir. Bu bulguları doğrulamak için büyük prospektif çalışmalar gerekmektedir.*

INTRODUCTION

Small cell lung cancer (SCLC) is the most aggressive form and accounted for nearly 14% of all lung cancers. SCLC tumors are classified as neuroendocrine tumors and originate from small, rapidly dividing lung cells. The aggressive tumors in SCLC are known to grow fastly and lead to the early development of metastases (1). Unfortunately, chemotherapy and radiotherapy have limited effects on this type of lung cancer. Therefore, SCLC has very poor prognosis in extensive-stage cancers even with the treatment. The median survival time is no more than 13 months (2).

Recent studies showed that inflammation plays an important role in carcinogenesis. The production of inflammatory mediators, including cytokines and chemokines, causes the development and progression of various cancers by promoting cancer cell proliferation, survival, angiogenesis and metastasis.Tumor-induced hypoxia, tissue damage, and tumor necrosis further enhance inflammation. Thus, the systemic inflammatory response has been associated with a poorer prognosis among patients with various cancers including lung cancer (3).

Inflammation may cause neutrophilia, thrombocytosis, lymphopenia and low MPV due to cytokines and chemokines. Tumor-associated neutrophils are stimulated by tumor growth factor-beta (TGFbeta) and, thus, increase tumor angiogenesis. Circulating neutrophils may cause metastases due to the tumor cells that escape from the neutrophil extracellular traps (4). In addition, lymphocytes, T helper cells, NK cells and CD8+T cells are anti-cancer cells affecting growth and metastasis in different cancers. The increase in the number of neutrophils contributes to the tumor growth by affecting the cytolytic activity of lymphocytes or NK cells (5). Lymphopenia increases tumor cell proliferation and migration and decreases cytotoxic cell death (3,6). Additionally, platelets are pro-inflammatory cells and the activation of thrombosis in bone marrow is one of the causes of thrombocytosis in cancer patients (7). Thrombosis can be activated due to the effects of cytokines, such as tumor necrosis factor-alpha, interleukin IL-1, and IL-6. Thrombocytosis can promote tumor growth with increasing angiogenesis through VEGF release and also interact with neutrophils and contribute to the escape of neutrophil extracellular traps (8,9). Large platelets become more sensitive to stimulation, which causes selective consumption of large platelets in circulation and the reduction of MPV (10). Low MCV (Mean Corpuscular Volume) means microcytosis, which is caused by

high expression of thymidylate synthase (TS) in erythroid precursor cells. TS is critical for DNA replication/repair and cancer cell proliferation and it is a target of some antitumor drugs, which are TS inhibitors (11,12). When TS expression is high in tumor tissues, studies showed that DNA replication and cell proliferation are increased (13). The data indicates that high expression of TS in tumor tissues might be associated with a significantly decreased OS in gastrointestinal cancers (14-17). Several studies reported that low TS expression was associated with good prognosis of NSCLC, but others showed that the high expression is beneficial. (18).

Based on all these blood parameters, several inflammation-based scores were created. Inflammation-based scores, which are easy to obtain and measure, are quick biomarkers of systemic inflammation, which can predict prognostic outcomes of patients.

Prognostic factors of SCLC were investigated within several studies (19). Most of the studies demonstrated that poor performance status (PS), extensive-stage of the disease, male gender, old age, and the elevated lactate dehydrogenase (LDH)levels are poor prognostic indicators for patients with SCLC (19-22). Current studies show that blood parameters are also prognostic factors before treatment for lung cancers as well as the other cancer types. The most studied paramaters are the neutrophil-lymphocyte ratio (NLR), the platelet-lymphocyte ratio (PLR), immune-inflammation index (SII), and the mean platelet volume (MPV)-platelet ratio (8,23-27). However, not much knowledge had studied about the various inflammatory and hematological paramaters in the prognosis of SCLC.

In this study, we investigated the effect of pre-treatment multiple inflammatory and hematological blood parameters on survival and their relation between each other in SCLC.

MATERIALS AND METHODS

Patient Selection

This retrospective (descriptive case series study) study enrolled 110 patients with histologically confirmed primary SCLC. The patients underwent platinum-based combination chemotherapy as a first-line treatment between 2012-2015. Overall survival of patients (OS) was calculated until to January 2017. Clinical information on each patient was obtained from the database of hospital medical records. The study was approved by the medical ethics committee of Adnan Menderes University. Since the study was retrospective, no approval form was obtained from the patients.

The following clinicopathological characteristics were collected: sex (male vs. female), age (< 65 years vs. ≥ 65 years), smoking status (non-smokers vs. smokers), performans status (PS: 0,1,2), disease stage (limited vs. extensive), date of diagnosis, date of death, and the presence or absence of curative radiotherapy (RT). Patients who did not want to take systemic chemotherapy (CT) or radiotherapy (RT) were excluded from the study. Patients with poor PS (PS:3,4) due to the terminal stage of cancer or additional diseases were excluded from the study. Patients who could not receive a standard dose of CT or RT were removed from the study. Since there were only 2 non-smokers, statistical analysis was not performed for smokers or non-smokers seperately. Patients were staged according to the Veterans Administration Lung Study Group (VALG) classification and their performans scores were determined by the Eastern Cooperative Oncology Group (ECOG) scores.

Untreated patients' hematological tests were taken into evaluation at initial diagnosis. Neutrophil, lymphocyte, platelet, hemoglobin (HGB), mean corpuscular volume (MCV), and mean platelet volume (MPV) values were collected. An elevated platelet count was accepted if higher than 300×10^9/L. Low HGB was defined as <12.0 g/L. MCV levels > 85 fl were considered as high, and low MPV was defined as < 85 fl. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. NLR and PLR were calculated by dividing the absolute neutrophil count by the absolute lymphocyte count and multiplying the platelet count by the absolute lymphocyte count, respectively. NLR ≥ 5 and PLR ≥ 250 were accepted as high levels, according to Proctor et als' study (28). The SII was defined as the platelet count multiplied by the neutrophil count and divided by the lymphocyte count (23), and an SII ≥ 1,600 ×

10^9/L was considered as the cut-off value. The cut-off value for the low MPV/PC ratio was defined as <0,408730 (25).

Statistical Analysis

All analyses were conducted by SPSS v23.0 statistical software. Continuous variables were presented by means and standard deviation values and categorical variables were expressed by frequencies and percentages. Relationship between categorical variables was analyze with Chi-square Test.Univariate survival analysis was performed using the Kaplan-Meier method with the log-rank test. A COX regression analysis was run to understand multivariate interaction of prognostic factors. A p-value less than 0.05 was considered as statistically significant.

RESULTS

Patient Characteristics and Treatment Properties

In total, 102 (92.7%) male and 8 (7.3%) female patients were included. The characteristics of the 110 patients are summarized in Table 1. Favorable prognostic factors were found to be age < 65 years, limited stage, presence of curative radiotherapy and good PS (Table 1). Male gender was associated with a poor prognostic outcome (11.3 months for males vs 16.2 months for females). However, it was not statistically significant (p=0.180). Patients with limited-stage SCLC had longer OS than those with extensive-stage SCLC (p<0.001). Patients who received curative radiotherapy (RT) had longer survival time.

Survival Analysis of Hematological and inflammatory Parameters

Univariate analyses of blood parameters of untreated patients' results are listed in Table 2. No significant correlations were observed between inflammation-based scores and other blood parameters. Kaplan–Meier analysis of all patients showed that there was no significant association between survival and inflammation-based scores and other blood parameters in SCLC. Kaplan-Meier survival analysis was done in both limited-stage and extensive-stage SCLC. Inflammation-based scores and other blood parameters at diagnosis were not associated with OS in limited-stage. However, two parameters were found to be associated with OS in extensive stage (Table 3). NLR<5 (11.8 vs. 5,3 months, P=0.020) and MCV >85 fl (9.5 vs. 11.3 months, P=0.016) values resulted in significantly better survival outcomes(Figure 1 and 2, respectively). Although it is not significant statistically, the OS was longer in patients with SII<1,600x109/L (11.8 vs 5.3 months, P=0.106) and PLR<250 (11.3 vs 6.1 months, P=0.062) in extensive-stage SCLC. COX Regression analyses showed that age (≥ 65 years), NLR ≥ 5, and MCV ≤ 85 fl were independent unfavorable prognostic factors for OS in extensive-stage (Table 4).

Table 1. Patient distribution and characteristics associated with OS.

	Number of Patients	%	OS (months) (95% CI)		P
Age*(n, %)*					
< 65 years	40	64	13.2	(11.3-15.0)	p< 0.001
≥ 65 years	70	36	9.4	(6.4-12.3)	
Sex*(n, %)*					
Male	102	92.7	11.3	(9.5-13.0)	p:0.180
Female	8	7.3	16.2	(0.0-39.1)	
Curative RT *(n, %)*					
Absent	80	73	10.7	(9.6-11.7)	p< 0.001
Present	30	27	18.5	(11.3-25.6)	
Stage *(n, %)*					
Limited-stage SCLC	35	32	12.1	(5.8-18.3)	P<0.001
Extensive-stage SCLC	75	68	10.9	(8.8-12.9)	
PS					
0	13	12	14.6	(9.7-19.5)	P<0.033
1	56	51	11.7	(9.6-13.8)	
2	41	37	10.7	(9.6-11.7)	

n:number of patients,SCLC:Small Cell Lung Cancer,PS: performance status, OS:Overall Survival, RT:radiotherapy

Table 2. Overall survival analysis of multiple inflammatory and hematological markersin all SCLC patients.

	Number of Patients %	OS (months)	
SII			
<1,600x10^9/L	76(%69)	12.1 (10.5-13.6)	
≥1,600x10^9/L	34(%31)	10.3(8.5-12.1)	P=0.298
PLR			
< 250	77(%70)	11.9 (10.5-13.2)	
≥ 250	33 (%30)	10.3 (6.6- 14.0)	P=0.120
NLR			
< 5	81(%74)	12.6 (11.1- 14.1)	
≥ 5	29 (%26)	9.2(5.4- 13.0)	P=0.076
MPV/PLT			
<0,408730	87 (%79)	11.8 (9.9- 13.7)	
≥0,408730	23 (%21)	10.9 (7.5- 14.3)	P=0.906
MPV			
≤ 8.5 fl	42 (%38)	10.7 (8.6-12.7)	
>8.5 fl	68 (%62)	11.7(9.6-13.9)	P=0.698
MCV			
≤ 85 fl	43(%39)	11.3(9.4- 13.1)	
>85 fl	67(%61)	13.0(10.2- 15.9)	P=0.061
HGB			
<12	40(36%)	11.9 (9.5- 14.3)	
≥12	70(64%)	10.9 (9.4- 12.3)	P=0.747

SCLC:Small Cell Lung Cancer, OS: Overall Survival, SII:systemic immune-inflammation index, PLR:platelet-lymphocyte ratio,NLR:neutrophil-lymphocyte ratio,MPV:mean platelet volume, MCV:mean corpuscular volume,MPV/PLT:mean platelet volume/platelet ratio, HGB: Hemoglobin.

Table 3. Overall survival analysis of multiple inflammatory and hematological markers in extensive-stage SCLC patients.

	Number of Patients %	OS (months)	
SII			
<1,600x10^9/L	51(%68)	11.8 (9.6-13.9)	
≥1,600x10^9/L	24 (%32)	5.3 (1.6-9.1)	P=0.106
PLR			
< 250	51(%68)	11.3 (9.8-12.7)	
≥ 250	24 (%32)	6.1 (0.2- 12.0)	P=0.062
NLR			
< 5	54(%72)	11.8 (9.7- 13.9)	
≥ 5	21 (%28)	5.3 (1.2- 9.5)	P=0.020
MPV/PLT			
<0,408730	60 (%80)	11.3 (8.9- 13.7)	
≥0,408730	15 (%20)	9.0 (4.6- 13.4)	P=0.168
MPV			
≤ 8.5 fl	25 (%33)	10.7 (6.6-14.8)	
>8.5 fl	50 (%67)	10.9 (8.9-12.9)	P=0.931
MCV			
≤ 85 fl	32(%43)	9.5 (7.2- 11.8)	
>85 fl	43(%57)	11.3 (8.5- 14.1)	P=0.016
HGB			
<12	28(37%)	11.9 (9.5- 15.3)	
≥12	47(63%)	10.2 (8.2- 12.1)	P=0.283

SCLC:Small Cell Lung Cancer, OS: Overall Survival, SII:systemic immune-inflammation index, PLR:platelet-lymphocyte ratio,NLR:neutrophil-lymphocyte ratio,MPV:mean platelet volume, MCV:mean corpuscular volume,MPV/PLT:mean platelet volume/platelet ratio, HGB: Hemoglobin.

Table4. COX Regression –Survival Analyses in Extensive-Stage SCLC patients.

	OVERALL SURVIVAL			
	p	HR	95.0% CI	
			Lower	Upper
Age	0.04	1.027	1.001	1.053
Sex	0.518	1.47	0.459	4.700
Smoking	0.279	0.450	0.000	12.319
PLT	0.285	0.999	0.997	1.001
HGB	0.463	1.057	0.911	1.226
MCV	0.009	0.960	0.930	0.990
MPV	0.244	0.944	0.857	1.040
NLR	0.023	0.549	0.328	0.919
PLR	0.064	6.21	0.375	1.029
SII	0.109	0.666	0.406	1.094
MPV/PLT	0.171	1.493	0.841	2.651

HR:hazard ratio,SII:systemic immune-inflammation index, PLR: platelet-lymphocyte ratio,NLR: neutrophil-lymphocyte ratio,MPV: mean platelet volume, MCV: mean corpuscular volume, MPV/PLT: mean platelet volume/ platelet ratio, HGB: Hemoglobin, PLT: platelet

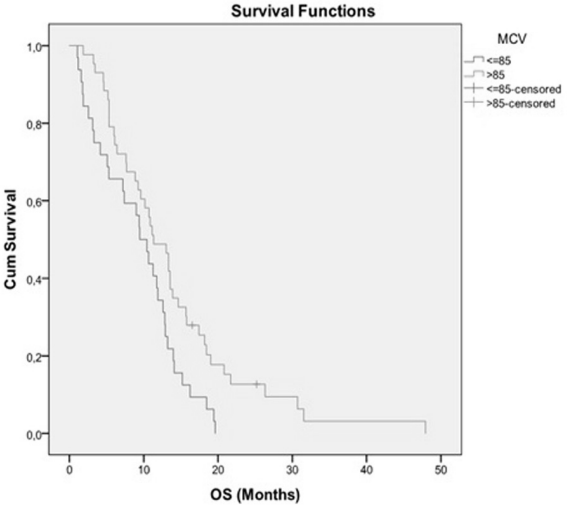


Figure 1. Kaplan-Meier survival curves stratified by neutrophil to lymphocyte ratio (NLR) in extensive-stage small cell lung cancer patients (p= 0.02). Cum: cumulative, neu/lenf: neutrophil /lymphocyte,OS: Overall Survival.

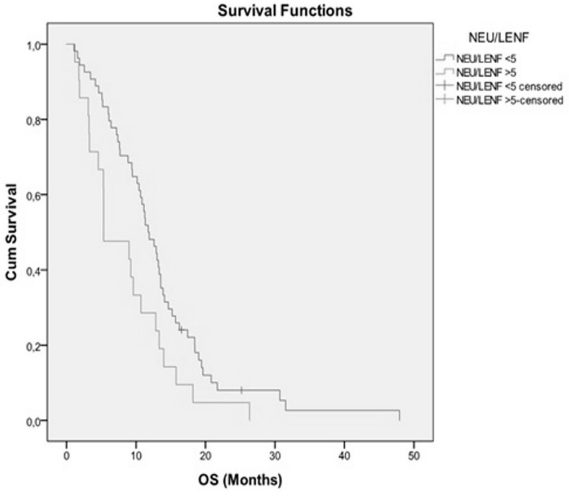


Figure 2. Kaplan-Meier survival curves stratified bymean corpuscular volume (MCV) in extensive-stage small cell lung cancer patients (p= 0.01). Cum: cumulative,MCV: mean corpuscular volume,OS: Overall Survival.

DISCUSSION

When compared with non–small cell lung cancers (NSCLC), SCLC is characterized by the rapid doubling time of its tumor cells and the early, widespread metastases. Usually, most patients are at the extensive stage when they are diagnosed. New targeted agents and cytotoxic drugs for NSCLC have been identified. On the other hand, new agents that can prolong the OS are not yet defined for SCLC patients (2). Good PS, young age, female sex, limited stage, non-smoking status, white ethnicity, single metastatic lesion, high LDH and low blood sodium levels are favorable prognostic features for patients with SCLC (19-22). Cisplatin plus etoposide (EP) therapy is the most common regimen for SCLC patients, who did not receive therapy before. EP plus curative RT prolong the median survival in limited stage cancers (1). Consistent with the previous findings, our study also identified young age (< 65 years), limited stage, presence of curative RT and good PS as favorable prognostic factors.

Previous studies including chemotherapy and radiotherapy-naive patients have shown that elevated NLR and PLR values were associated with worse OS and disease-free interval. Kang et al. showed that increased NLR could predict worse OS and PFS whereas PLR was not associated with OS or PFS (5). In another study, 938 patients with SCLC (555 extensive stage SCLC and 383 limited stage SCLC) were analyzed. NLR ($p< 0.0001$) and PLR ($p< 0.0001$) were found to be prognostic risk factors in extensive and limited stages, respectively (29). Hong et al. found SCLC patients' univariate analysis of NLR and PLR were significantly associated with overall survival but they were not significant in multivariate analysis(30).

Dirican et al. analyzed the data of 136 SCLC patients and showed that NLR was significantly associated with OS in all analysis. However, they showed that PLR, hemoglobin, MCV and MPV were not associated with OS (31).

The purpose of our work was to emphasize the impact of multiple inflammation-based scores for OS in treatment-naive SCLC patients. Univariate analysis exhibited that no significant correlation was observed between inflammation-based scores and other blood parameters in SCLC patients at all stages.Whereas NLR and MCV were significantly associated with OS in extensive-stage. In our study, patients at extensive-stage with PLR< 250 had 5.2 months longer OS (11.3 vs 6.1 months, P=0.062). However, this difference did not reach statistical significance. The low number of the patients might have led to the statistical insignificance. Nevertheless, 5-month difference in the OS in extensive-stage SCLC is very important. In multivariate analysis, age (≥ 65 years), NLR ≥ 5, and MCV ≤ 85 fl were found to be independent unfavorable prognostic factors for OS in extensive-stage SCLC patients. We think that the reason fort his is the SCLC is a very rapidly-dividing type of tumor and the TS protein expression is mich higher in these tumors. Our study is the first that showed the relationship between SCLC and MCV.

The SII, a combination of circulating platelet count and neutrophil-lymphocyte ratio, is defined as a representative index of systemic inflammatuary responses. SII was initially used to indicate the host inflammatory and immune status in resected HCC patients and high SII scores were related with poor prognosis and high circulating tumor cell levels (23). In another study, SII was found to be a poor prognostic factor in SCLC patients (32). In the present study, patients with SII>1,600x109/L had worse OS than patients with SII<1,600x109/L (11.8 vs 5.3 months, P=0.106) in extensive-stage SCLC. There were 6.5 months of OS difference between the groups. However, it was not significant in statistical analysis.

Many studies have demonstrated that the MPV and MPV / platelet ratio can affect overall survival in patients with various disorders, including ischemic cardiovascular disease and malignancies(2). In NSCLC patients, OS was significantly decreased due to the low MPV and MPV/PC ratio (25,33,34). However, another study showed that high MPV level was associated with poor prognosis and also that MPV/PC ratio was not different between patients with lung cancer and healthy controls (26). In the literature, there is no data about MPV/platelet ratio in SCLC patients. However, in our study MPV, MPV/platelet ratio and hemoglobin had no

statistically significant effects on survival in all stages of SCLC patients.

There are some limitations in our study. Firstly, patients with poor PS (PS:3,4) were removed from the study. Since these patients had not received chemotherapy or standart chemotherapy because of their PS or additional diseases, standardization was performed. Secondly, there was no analysis of PFS because of the data collection methods. Further, prospective studies on larger patient groups are needed to determine the effects of inflammation-based scores on PFS.

In conclusion, the present study demonstrates that NLR and MCV could help to predict a poor prognosis in ECOG 0,1 and 2, extensive-stage, treatment-naive SCLC patients. Due to the retrospective nature and the small size of the present study, statistical significance could not be achieved. However, SII and PLR results clearly demonstrated that patients with PLR< 250 or SII>1,600x109/L had better OS in extensive-stage SCLC patients. Inflammation-based scores are blood tests that are easily available and may serve as a useful prognostic biomarker in extensive-stage SCLC, which do not require any additional resources for routine use. The results of the present study could assist clinicians to accurately predict individualized survival probability in SCLC. Nevertheless, prospective studies are needed to confirm these results.

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