Original Article

Prognostic Role of Pan Immune Inflammation Value and Systemic Inflammation Response Index in Small Cell Lung Cancer

Küçük Hücreli Akciğer Kanserinde Pan İmmün Enflamasyon Değeri ve Sistemik Enflamasyon Yanıt İndeksinin Prognostik Rolü

Mehmet Uzun[1], Eda Çalışkan Yıldırım[1], Savaş Gökcek[1], Bilgin Demir[2], Aziz Karoğlu[1]

[1]Department of Medical Oncology, Dokuz Eylül University, Izmir, Turkiye
[2]Department of Medical Oncology, Adnan Menderes University, Aydın, Turkiye

ABSTRACT

Introduction: Small cell lung cancer (SCLC) is a highly lethal form of lung cancer with very poor prognosis. Systemic inflammation is an important risk factor for cancer development. Circulating immune cells play an important role in fighting against cancer. This study was designed to investigate the prognostic value of different peripheral blood leukocyte biomarkers as components of circulating immune cells in small cell lung cancer.

Materials and methods: A total of 81 SCLC patients followed up at Dokuz Eylül University Hospital Department of Medical Oncology between 2012 and 2021 were included in this study. Demographic characteristics and clinic-pathological features of each patient were recorded. Peripheral blood tests of patients were recorded at the time of diagnosis. Systemic immune-inflammation index (SIRI) was defined as (neutrophil count×monocytes count)/lymphocyte count. Pan-immune inflammation value (PIV) was calculated as follows: (neutrophil count × platelet count × monocyte count)/lymphocyte count. The optimal cut-off values were determined according to the receiver operating characteristic (ROC) curve. These values were 2.8 and 585 in limited stage SCLC, and 1.33 and 497 in all-stage SCLC for SIRI and PIV, respectively. Overall survival (OS) was calculated by Kaplan-Meier method and compared by log rank test. Multivariate analysis was calculated using the Cox regression model.

Results: Among 81 SCLC patients,28 (34.6%) patients had LS-SCLC while 53 (65.4%) patients had extensive stage disease. In whole group, median SIRI was 2.37 (IQR, 0.34–18.59), while median PIV was 634.80 (IQR, 61.57–8320). Although there was a numerical difference between survival in analysis performed in the patient group including all stages, statistical significance could not be achieved for both markers (p=0.20 for SIRI; p=0.058 for PIV). While statistical significance was found for OS and ECOG; SIRI, and PIV status in univariate analysis ofpatients with limited stage SCLC, no significant difference was found between the variables with multivariate analysis..

Discussion: Our findings show that SIRI and PIV may be promising predictors for prognosis in SCLC.

Keywords: Small cell lung cancer; inflammation index; inflammation value

ÖZET

Giriş: Küçük hücreli akciğer kanseri (KHAK), çok kötü prognozlu, oldukça ölümcül bir akciğer kanseri türüdür. Sistemik inflamasyon, kanser gelişimi için önemli bir risk faktörüdür. Dolaşan bağışıklık hücreleri, kansere karşı mücadelede önemli bir rol oynar. Bu çalışma, küçük hücreli akciğer kanserinde dolaşımdaki bağışıklık hücrelerinin bileşenleri olarak farklı periferik kan lökosit biyobelirteçlerinin prognostik değerini araştırmak için tasarlanmıştır.

Gereç ve yöntemler: Bu çalışmaya 2012-2021 yılları arasında Dokuz Eylül Üniversitesi Hastanesi Tıbbi Onkoloji Anabilim Dalı'nda izlenen toplam 81 KHAK hastası dahil edildi. Her hastanın demografik özellikleri ve klinikopatolojik özellikleri kaydedildi. Hastaların tanı anında periferik kan testleri kaydedildi. Sistemik immün-inflamasyon indeksi (SIRI) (nötrofilsayısı×monosit sayısı)/lenfosit sayısı olarak tanımlandı. Pan-immüninflamasyon değeri (PIV) şu şekilde hesaplandı: (nötrofil

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sayısıxtrombosit sayısıxmonosit sayısı)/lenfosit sayısı. Optimal cut-off değerleri, ROC eğrisine göre belirlendi. Bu değerler SIRI ve PIV için sınırlı evreli KHAK'de sırasıyla 2,8 ve 585 ve yaygın evre KHAK'de 1,33 ve 497 idi. Genel sağkalım (GS), Kaplan-Meier yöntemiyle hesaplandı ve log rank testiyle karşılaştırıldı. Cox regresyon modeli kullanılarak çok değişkenli analiz tahmin edildi.
Bulgular: 81 KHAK'li hastanın 28'inde (%34,6) sınırlı evre KHAK, 53'ünde (%65,4) yaygın evre hastalık vardı. Tüm grupta medyan SIRI 2,37 (IQR, 0,34–18,59), medyan PIV ise 634,80'di (IQR, 61,57–8320). Tüm evreleri içeren hasta grubunda yapılan analizde sağkalım arasında nümerik fark olmasına rağmen her iki belirteç için istatistiksel anlamlılık elde edilememiştir (SIRI için p=0,20; PIV için p=0,058). Sınırlı evre KHAK'li hastaların GS, ECOG, SIRI ve PIV durumu için istatistiksel anlamlılık bulunurken, çok değişkenli analizde değişkenler arasında anlamlı bir fark bulunmadı.
Tartışma: Bulgularımız, SIRI ve PIV'in KHAK'de prognoz için umut verici belirleyiciler olabileceğini göstermektedir.

Anahtar kelimeler: Küçük hücreli akciğer kanseri; inflamasyon indeksi; inflamasyon değer

Introduction

Lung cancer is a subset of tumours with poor prognosis among various solid tumours due to its high morbidity and mortality rate and is divided into two main groups: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC)[1]. SCLC represents the most aggressive form of lung cancer. Although it is characterized by a rapid response to chemotherapy and sensitivity to radiotherapy (RT), the 5-year survival rate is less than 10%[2]. The incidence of SCLC has decreased in the last decade, with a prevalence of 1-5/10,000 people in the European population, and is therefore considered an orphan disease[3,4]. According to a lung study group, SCLC is classified in two stages: limited stage SCLC (LS-SCLC) and extensive stage SCLC (ES-SCLC)[5]. Despite the advances in diagnosis and treatment, the prognosis remains poor and overall survival is short as the doubling tumor time is rapid, the growth fraction is high and development of metastasis is early [6].

The essential component of treatment for SCLC is systemic therapy.The primary treatment is chemo-radiotherapy for limited stage disease, whereas palliative chemo-therapy remains at the forefront for extensive stage disease[7]. Although SCLC is highly sensitive to chemotherapy, most patients relapse within 6 months. The response rate to second-line therapy depends on the treatment-free time following first-line therapy and response to first-line platinum-based induction therapy. The response rate to second-line therapy is usually around 20% to 30% in platinum-sensitive patients and 15% in platinum-resistant patients [8].

In terms of prognosis, the relationship between systemic immunity and cancer-related inflammation is important. Several blood and biochemical parameters, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), cytokines and lactate dehydrogenase (LDH), have been studied as potential biomarkers associated with inflammation to predict drug efficacy and prognosis [9,10]. High lymphocyte and low neutrophil counts were associated with better prognosis in various tumor models[11]. Recently two immune biomarker models were developed: the systemic inflammation response index (SIRI) and the pan-immune-inflammation-value (PIV). SIRI, which integrates different inflammatory parameters (neutrophils, monocytes and lymphocytes), has proved to be a promising prognostic marker in different cancers[12,13], while PIVis derived from neutrophil, platelet, monocyte and lymphocyte counts. PIV, which has the potential to comprehensively reveal the state of systemic immune and cancer-related inflammation, has been recognised as a reliable marker for clinical outcomes in patients with advanced cancer[14]. In SCLC, some prognostic parameters such as poor performance score, extensive stage, higher lactate dehydrogenase (LDH), and weight loss

were recognized as major poor prognostic factors in retrospective studies.

This study was designed to investigate the prognostic value of different peripheral blood leukocyte biomarkers, as components of circulating immune cells, in small cell lung cancer. We analyzed the prognostic role of SIRI and PIV in patients with SCLC.

Materıals and Method

Study Population:

The study population included 81 SCLC patients (n=120), who applied to Medical Oncology Outpatient Clinic of Dokuz Eylül University Hospital between 2012 and 2021 for diagnosis and treatment. Medical information was retrieved retrospectively from patient files. Gender, age, comorbidities, albumin, hemoglobin, lymphocyte, monocyte, neutrophil and platelet levels at the time ofdiagnosis, disease stage, site of metastasis, treatments received and responses of patients were recorded. Tumor staging was evaluated according to the eighth edition of the American Joint Committee on Cancer (AJCC) guidelines[15]. SCLC was defined in two stages: (a) limited stage: patients with Stage I-III disease that can be reliably treated with precise radiation doses (T any, N any, M0), and (b) extensive stage: patients with Stage IV disease (T any, N any, M 1a/b/c) or T3-4 tumor due to multiple lung nodules that are too extensive or have higher tumor/nodal volume. It includes tumors that are too large to be encompassed in a tolerable radiation plan. The end point of our study was overall survival (OS), whichwas defined as the time from diagnosis to date of death or last check-up visit.

The inclusion criteria were as follows: (1) pathologically diagnosed small cell lung adenocarcinoma; (2) suffering relapsed or metastasized disease; (3) suffering limited stage patients; (4) complete record of blood test results and follow-up data prior to initiation of therapy. The exclusion criteria were as follows: (1) history of other malignant tumors; (3) clinical evidence of recent acute infection or inflammation.

This study was approved byDokuz Eylül University Clinical Research Ethics Committee (dated: 28/09/2022, with decision number: 2022/31-05).

SIRI and PIV:

Systemic immune-inflammation index (SIRI) was defined as (neutrophil count×monocytes count)/lymphocyte count. Pan-immune inflammation value (PIV) was calculated as follows: (neutrophil count×platelet count×monocyte count)/lymphocyte count. The optimal cut-off value was determined according to the receiver operating characteristic curve (ROC) and these values were 2.8 and 585 for SIRI and PIV in limited stage SCLC (LS-SCLC), while values were 1.33 and 497 for SIRI and PIV in all-stage SCLC, respectively.

Statistical Analysis:

Descriptive statistical analyses were performed for demographic, clinic-pathological and treatment modalities of patients. Analysis of study data was performed using IBM SPSS software version 24.0. Descriptive statistics of participants were shown as percentages and (n) for categorical variables, and as mean±SD for continuous variables. Before performing the hypothesis tests, the Kolmogorov Smirnov test was used to determine whether the data were normally distributed. The sensitivity and specificity of SIRI and PIV for prognosis prediction were evaluated using a time-dependent receiver operating characteristic (ROC) curve in R software. Multivariate Cox hazard regression analysis was performed on the factors that were found to be significant in the univariate analysis. Overall Survival was defined as the time from randomization to death. OS was estimated using the Kaplan-Meier method, and the results were compared using the log-rank test.The results were evaluated at a confidence interval of 95% and a significance level of $p<0.05$.

Table 1. Clinicopathological characteristics and inflammatory markers of patients

Variable	No of patients(%)/median(range)
Age(years)	
≤60	29(35.8)
>60	52(64.2)
Sex	
Male	67(82.7)
Female	14(17.3)
TNM stage	
LS-SCLC	28(34.6)
ES-SCLC	53(65.4)
ECOG performance score	
0	25(30.9)
1	28(34.6)
2	23(28.4)
3	5(6.2)
Death	
No	10(12.3)
Yes	71(87.7)
Neutrophils, $\times 10^9$/L	6.5(1-23.9)
Monocytes, $\times 10^9$/L	0.7(0.2-1.5)
Lymphocytes, $\times 10^9$/L	1.85(0.2-15)
Platelets, $\times 10^9$/L	274(105-687)
SIRI	2.37(0.34-18.59)
PIV	634.8(61.57-8320)
SIRI in LS-SCLC	
≤2.80	16(57.1)
>2.80	12(42.9)
PIV in LS-SCLC	
≤585	13(46.4)
>585	15(53.6)

Results

Patient Characteristics:

The characteristics of 81 patients included in this retrospective analysis aresummarized in Table 1. Among these 81 patients, 67(82.7%) were male, and 14 (17.3%) were female. The mean age was 63.38±8.7 years. Twenty eight (34.56%) patients had limited stage disease while53 (65.43%) patients had extensive stage disease.

Systemic Treatment:

In all patients, 32.1% received cisplatin+ etoposide and 38.3% received carboplatin+ etoposide chemotherapy regimens. For first-line treatment, platinum-based chemotherapy could be applied to 95.9% of all patients. Prophylactic cranial radiotherapy was applied to 3.8% of the patients and definitive radiotherapy was applied to 23.1%. In the LS-SCLC group, 9% of patients received concurrent radiotherapy with chemotherapy. After first-line chemotherapy, radiological complete response was obtained in 10 (15.3%) patients, partial response in 23 (28.4%) patients,

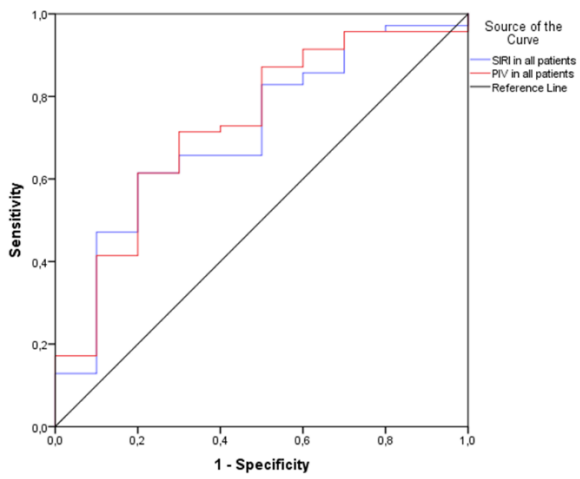


Figure 1. Receiver operating characteristic curve analysis of the optimal cut-off value for systemic inflammation response index (SIRI) and pan-immune-inflammation value(PIV) in 81patients with small cell lung cancer. Areas under the curve for overall survival were 0.711and 0.730 for SIRI and PIV, respectively (P<0.05). P>0.05 for all other indicators.

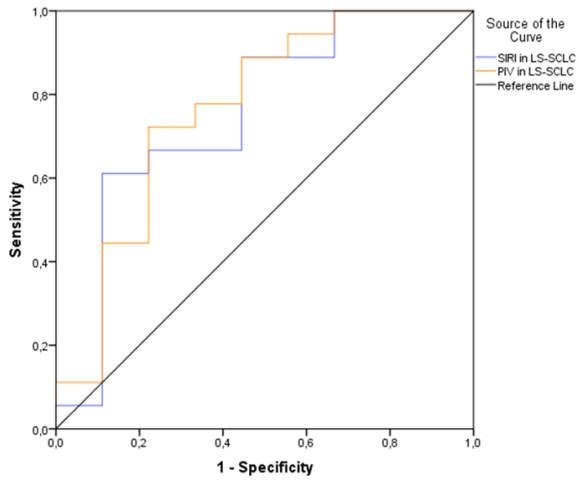


Figure 2. Receiver operating characteristic curve analysis of the optimal cut-off value forsystemic inflammation response index (SIRI) and pan-immune-inflammation value(PIV) in 28 patients with limited stage small cell lung cancer. Areas under the curve for overall survival were 0.753and 0.765 for SIRI and PIV, respectively (P<0.05). P>0.05 for all other indicators.

progression in 20 (24.7%) patients, and stable response in the remaining patients.

Analysis of SIRI and PIV:

The median PIV of patients was 634.80 (IQR, 61.57–8320), while median SIRI was 2.37 (IQR, 0.34–18.59). For all stages, cut-off values were determined as ≥497 and ≥1.33 to establish the prediction of PIV and SIRI biomarkers and estimate prognosis for OS using the time-dependent ROC curves, respectively. In the limited stage group comprising 28 patients, the SIRI and PIV cut-off values were ≥2.80 and ≥585, respectively. Median follow-up was 29.73 (3-131) months. AUC for SIRI and PIV were 0.711(95%CI: 0.541-0.881, P=0.031) and 0.730 (95%CI:0.562-0.898, P=0.019), respectively, for all stages (Figure 1).

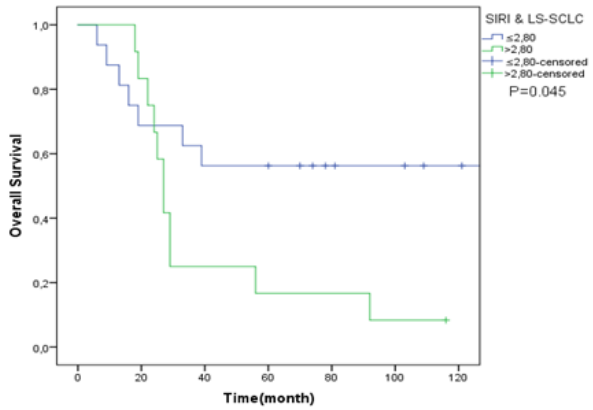
Survival Analyses:

At the end of follow-up, 87.7% of patients had died, and 12.3%were alive. For survival analysis, patients were stratified according to their optimal threshold values for SIRI and PIV. No statistically significant difference was found forsurvival between genders (p=0.67). Survival graphs for patients stratified for SIRI and PIV according to different cut-off values are shown in Figure 2. While the mOS for all patients were 17 months, the mOS were 31 months in the LS-SCLC group and 11 months in the ES-SCLC group.

Survival Analyses according to SIRI and PIV:

The mOS was 45.05 months for patients with SIRI value below 1.33, the cut-off value determined for all patients including both limited stage and extended stage diseases, while it was 27.76 months for those with a value above 1.33. The mOS was 48.85 months for patients with a PIV value below 497, the cut-off value determined for all patients including both limited stage and extended stage diseases, while it was 25.44 months for patients with PIV value above 497. The mOSwas 65 months in the patient group with

A



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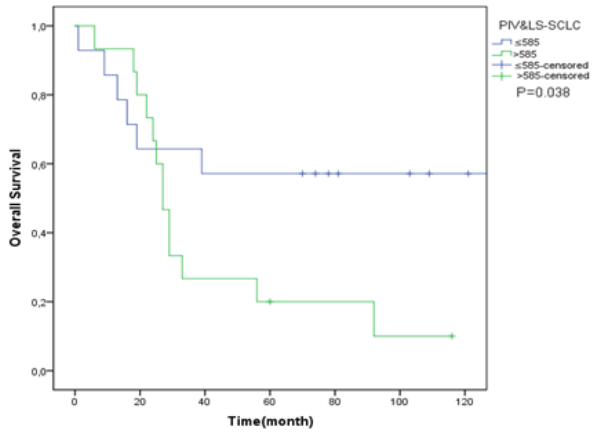

Figure 3. Kaplan-Meier curves for overall survival (OS) according tosystemic inflammation response index (SIRI) and pan-immune-inflammation value(PIV)in 28 patients with limited stage small cell lung cancer. (A) and (B).

a SIRI value below 2.80, the cut-off value determined for limited stage patients, while it was 31 for the patient group with SIRIvalue above 2.80 (p=0.045, Figure 3). Similarly, themOSwas 74 months in the patient group with a PIV value below 585, the cut-off value determined for limited stage patients, while it was 27 months for the patient group with a PIV value above 585 (p=0.038, Figure 3).

In this analysis, although there was a numerical difference between the survival rates for the patient group including all stages, statistical significance could not be obtained for both biomarkers (p=0.20 for SIRI; p=0.058 for PIV). However, when SIRI and PIV were evaluated individually in the limited and extensive stage patient groups, survival analysis showed no statistical significance in the patient group with extensive stage, whereas both biomarkers had statistically significant prediction power for prognosis in patients with limited stage disease. Univariate analysis showed statistically significant differences between OS and ECOG, SIRI and PIV status in patients with limited stage SCLC, while multivariate analysis showed no difference between the variables (Table 2).

Discussion

The markers with prognostic value in predicting the survival of the patients are lacking. Therefore, it is important to find reliable tumor markers of prognosis and facilitate treatment adjusting and patient stratification. In the present study, we evaluated prognostic effect of blood-based immune-inflammation indices, including SIRI and PIV, in small cell lung cancer. We think that SIRI and PIV may play a prognostic role especially in patients with limited stage SCLC. There is no study has examined the prognostic impact of the SIRI and PIV in SCLC patients. Consistent with these previously published data for other types of cancers, we found that a high SIRI and PIV was independently associated with worse patient OS.

Through recent advances in molecular biology, remarkable improvement has been achievedfor non-small-cell lung cancer with the use of targeted therapy and immuno-therapy. However, survival still remains short in SCLC due to the lack of effective new therapies and prognostic markers. The mean survival is 2 to 4 months in untreated patients, while it is prolonged with the use of platinum/etoposide or platinum/ irinotecan regimens to 10 months in extensive stage disease and up to 3 years in limited stage disease[16,17]. There is a lack of prognostic markers to predict survival of patients. As it is important to identify tumor markers to predict prognosis and facilitate treatment planning and patient classification, we investigated the prognostic power of two immune inflam-mation indices, SIRI and PIV, based on

Table 2.Univariate and multivariate Cox regression analyses for overall survival in LS-SCLC

Variables		Univariate analysis		Multivariate analysis	
	N(%)	HR (95% CI)	P value	HR (95% CI)	P value
Sex					
Male	26(92.9)	0.52(0.07-3.9)	0.53		
Female	2(7.1)				
Age					
≤60	11(39.3)	1.59(0.59-4.24)	0.35		
>60	17(60.7)				
ECOG PS					
0-1	19(67.9)	4.45(1.63-12.1)	**0.003**	0.22(0.04-1.02)	0.05
2-3	9(32.1)				
Hemoglobin					
≤12	8(28.6)	1.87(0.60-5.75)	0.27		
>12	20(71.4)				
SIRI					
≤2.80	16(57.1)	2.5(0.9-6.6)	**0.045**	1.90(028-12.5)	0.50
>2.80	12(42.9)				
PIV					
≤585	13(46.4)	2.8(1-8.1)	**0.04**	0.44(0.83-2.33)	0.33
>585	15(53.6)				

SIRI: systemic inflammation response index; HR: hazard ratio; CIL confidence interval; PIV: Pan-immune-inflammation value; ECOG PS: ECOG performance status scale

peripheral blood samples for SCLC. SIRI and PIV were found to be prognostic factors for OS in patients with limited stage SCLC. Inflammation is a hallmark of cancer[18]. Recent studies have shownthat prognosis is associated with patient-related factors such as inflammation, immune deficiency and nutrition in several types of cancer and the correlation between nutritional status and prognosis of cancer is particularly striking. Local and systemic inflammation is a significant promoter of tumorigenesis, tumor cell proliferation, invasion and metastasis, and it also plays a role in the response to therapeutic agents[19]. Based on this working principle of the immune system, a model consisting of peripheral blood inflammatory cells has been established. Grivennikov et al.suggest that tumor-induced inflammation results in peripheral hematological changes, including in neutrophils, lymphocytes, monocytes and platelets via release of various cytokines[20]. Therefore, blood cell count is an easy to obtain and cost-effective index to represent the host immune inflammation status. Li et al reported that SIRI is an independent prognostic factor in lung cancer patients after thoracoscopic surgery. However, the prognostic role of SIRI in advanced stage lung cancer patient remains unclear[21]. In our study, we found that SIRI can be a prognostic marker in limited-stage small cell lung cancer, both easily and cost-effectively. PIV is a biomarker that was recently developed based on neutrophils, monocytes, platelets and lymphocytes, and its relationship with OS has been well established[14]. High PIV was a strong predictor of poor PFS and OS in colorectal cancer, breast cancer, renal cancer, melanoma and NSCLC treated with immunotherapy [14,22,23]. Ligorio et al. reported that the PIV was a useful predictor of OS in HER2+ advanced breast cancer patients treated with first-line trastuzumab-pertuzumab containing biochemotherapy[24]. Our results demonstrate that there is a significant relation-ship between inflammatory markers and cancer. Our findings with SIRI and PIV reflecting the systemic immunological status

demonstrated that it is possible to predict prognosis. In the present study, we found a statistically insignificant difference in OS across all patient groups when patients with low SIRI and low PIV were compared to those with high SIRI and PIV. However, for limited stage SCLC patients, our results showed that patients in the low SIRI and PIV group (SIRI≤2.80; PIV≤585) had longer OS compared to those in the high SIRI and PIV group (p=0.045; p=0.038). We of course acknowledge that future studies are needed to confirm our findings, and also to examine other potential mechanism(s) by which SIRI and PIV affects clinical outcome in cancer patients. Besides SIRI and PIV, ECOG performance score (PS) and disease stage have also been shown to be independent prognostic factors. In our patients with extensive stage disease and poor ECOG PS, higher SIRI and PIV levels may reflect impairment in the overall status of systemic inflammation. While there was a statistical significance between OS and ECOG, SIRI and PIV status in univariate analysis, no significance was found between the variables with multivariate analysis. This may be associated with our restricted number of patients. Although our study included patients with all stages of SCLC, we suggest that SIRI and PIV may play prognostic roles, particularly in patients with limited stage SCLC.Considering that prognostic markers such as SIRI and PIV have been studied relatively lessin SCLC compared to other cancers in previous studies, we believe that our study will contribute to increasing knowledge in this field.

Although our study, together with previous researches, demonstrated that SIRI and PIV are promising tools for predicting prognosis in SCLCpatients, the results of our research should be interpreted with caution due to the obvious limitation of the research.The mainlimitations include its retrospective design and restricted patient population. To the best of our knowledge, the number of studies ofpatients with SCLC is low in this field.

Conclusion

In conclusion, SIRI and PIV may be suitable, cost-effective and reliable markers of immune inflammation, especially for predicting prognosis in patients with limited-stage SCLC. They may help therapeutic planning and patient classification. However, well-designed prospective studies are required.

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Corresponding author e-mail: memed.uzun3846@gmail.com

Orcid ID:
Mehmet Uzun 0000-0002-8596-4233
Eda Çalışkan Yıldırım 0000-0003-0785-0238
Savas Gökcek 0000-0001-5928-0447
Bilgin Demir 0000-0003-4380-9419
Aziz Karoğlu 0000-0001-5500-156X

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