Original Article

Prognostic Significance of Fibrinogen-to-Albumin Ratio in Small Cell Lung Cancer

Küçük Hücreli Akciğer Kanserinde Fibrinojen-Albümin Oranının Prognostik Önemi

Hatice Yılmaz, Ali Aytaç, Büşra Niğdelioğlu, Özlem Yersal, Sabri Barutca

Department of Medical Oncology, Adnan Menderes University Faculty of Medicine, Aydın

ABSTRACT

Introduction: It has been found that fibrinogen-to-albumin ratio (FAR) is closely correlated with prognosis in some cancers. But prognostic importance of FAR in small cell lung cancer (SCLC) isn't known completely. We aimed to show the prognostic importance of FAR in SCLC in this study.

Materials and methods: 145 patients followed up with diagnosis of SCLC were included in the study retrospectively. According to the receiver operating characteristic (ROC) curve analysis, the optimal cut-off values were determined for the FAR, and the patients were divided into low (<0.138) and high (≥ 0.138) FAR groups. C-reactive protein (CRP)- albumin ratio (CAR), procalcitonin-CRP ratio (PCR), prognostic nutritional index (PNI) were grouped based on a cut-off point of 0.646, 6.1 and 33.9 respectively. Cox regression analyses were used for evaluating prognostic significances for progression-free survival (PFS) and overall survival (OS) of parameters.

Results: Both PFS (p<0.001, p:0.027, p:0.003, respectively) and OS (p<0.001, p:0.001, p<0.001, respectively) were found shorter in the group with higher FAR, CAR, PCR. Both PFS (p:0.020) and OS (p: 0.001) were found to be longer in the group with higher PNI compared to the group with low PNI. In multivariate analysis, FAR and PNI were found as an independent prognostic factor for both PFS and OS (p:0.039, p:0.021; p:0.034, p:0.016, respectively).

Conclusion: FAR and PNI are independent prognostic parameters predicting survival times in patients with SCLC.

Keywords: C-reactive protein, inflammation mediators, lung neoplasm, procalcitonin

ÖZET

Giriş: Fibrinojen-albümin oranının (FAR) bazı kanserlerde prognoz ile yakından ilişkili olduğu bulunmuştur. Ancak küçük hücreli akciğer kanserinde (KHAK) FAR' ın prognostik önemi tam olarak bilinmemektedir. Bu çalışmada FAR'ın KHAK' deki prognostik önemini göstermeyi amaçladık.

Gereç ve yöntemler: KHAK tanısı ile takip edilen 145 hasta geriye dönük olarak çalışmaya dahil edildi. Alıcı çalışma karakteristiği (ROC) eğrisi analizine göre FAR için optimal cut-off değerleri belirlendi ve hastalar düşük (<0.138) ve yüksek (≥ 0.138) FAR gruplarına ayrıldı. C-reaktif protein (CRP)-albümin oranı (CAR), prokalsitonin-CRP oranı (PCR), prognostik nütrisyonel indeks (PNI) sırasıyla 0.646, 6.1 ve 33.9'luk bir kesme noktasına göre gruplandırıldı. Parametrelerin progresyonsuz sağkalım (PFS) ve genel sağkalım (OS) için prognostik önemlerini değerlendirmek için Cox regresyon analizleri kullanıldı.

Bulgular Hem PFS (sırasıyla p<0,001, p: 0,027, p: 0,003) hem de OS (sırasıyla p<0,001, p: 0,001, p<0,001) FAR, CAR, PCR yüksek olan grupta daha kısa bulundu. Hem PFS (p: 0.020) hem de OS (p: 0.001), PNI'si yüksek olan grupta, PNI'si düşük olan gruba göre daha uzun bulundu. Çok değişkenli analizde FAR ve PNI, hem PFS hem de OS için bağımsız bir prognostik faktör olarak bulundu (sırasıyla p: 0.039, p: 0.021; p: 0.034, p: 0.016).

Tartışma ve Sonuç: FAR ve PNI, KHAK' li hastalarda sağkalım sürelerini öngören bağımsız prognostik parametrelerdir.

Anahtar kelimeler: C-reaktif protein, inflamasyon mediatörleri, akciğer neoplazmı, prokalsitonin

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Introduction

Small cell lung cancer (SCLC) is a histological subtype with the most aggressive clinical course within lung cancers (LC), which frequently appears with metastatic disease at regional lymph nodes or distant organs at the time of diagnosis [1]. Although SCLC is quite sensitive to chemotherapy, patients may respond differently to similar therapies [2]. Therefore, predicting prognosis in SCLC in the clinical setting is important. Although various prognostic factors such as performance score, age, gender and serum lactate dehydrogenase level, have been investigated in order to predict prognosis, no standardized prognostic marker is currently available [3]. Therefore, new prognostic markers are required.

It is known that there is a close relationship between carcinogenesis and systemic inflammation [4]. Proinflammatory mediators tumor necrosis factor-α (TNF-α), interleukin (IL)-1, IL-6, interferon-γ (IFN-γ) increase during carcinogenesis [4]. These cytokines, which are elevated during inflammation cause a decrease in albumin level, which is known as a negative acute phase reactant and produced in liver [5]. Fibrinogen is also a protein, synthesized in hepatocytes, and similarly, it is produced as a response to proinflammatory cytokines [6]. Increased proinflammatory cytokines, especially IL-6, cause an increase in C-reactive protein (CRP) simultaneously [7]. Similar to CRP, procal-citonin (PCT) concentration is also recognized as a marker for systemic inflam-mation [8]. Homeostasis is disturbed along with changing levels of inflammatory markers and antioxidant/anti-inflammatory activity and apoptosis decrease [5]. As a result, these elevated cytokines trigger inflammation and contribute in tumor progression and metastasis [9].

CRP/albumin ratio (CAR) is one of the inflammatory markers, found to be prognostic and predictive in many cancers, including esophagus cancer (EC), pancreas cancer (PC) and non-small cell lung cancer (NSCLC) [10-12]. It has been demonstrated that PCT and CRP are prognostic in many cancers, such as colon cancer and NSCLC [13-14]. Prognostic nutritional index (PNI), one of systemic immune-inflammatory indicators, which is calculated by using albumin value, has been found to be associated with prognosis in many solid organ malignancies such as urinary system cancer and LC [15,16]. Raised fibrinogen-to-albumin ratio (FAR) that was started to be used as a new marker recently has been found to be associated with poorer survival and higher recurrence risk in many malignancies, such as hepatocellular cancer (HCC), gastric cancer (GC), NSCLC [17-19]. Despite increasing evidence about effects of inflammation-based scores on prognosis of SCLC patients, there is limited knowledge about the prognostic significance of FAR in SCLC. Therefore in this study, we aimed to exhibit prognostic significance of FAR and other parameters in SCLC.

Materials and Method

In this study, 195 patients, followed-up with pathologically confirmed histological diagnosis of SCLC, were analyzed retrospectively in Medical Oncology Clinic between September 2013 and January 2021. The inclusion criteria of this study were: 1) cytological or histological diagnosis of SCLC, 2) age of at least 18 years, 3) presence of at least one measurable lesion, 4) presence of pretreatment blood test and sufficient laboratory data. The exclusion criteria were: 1) receipt of non-platinum chemotherapy or checkpoint inhibitors as first-line therapy; 2) presence second primary solid organ malignancy, 3) presence of benign or malign

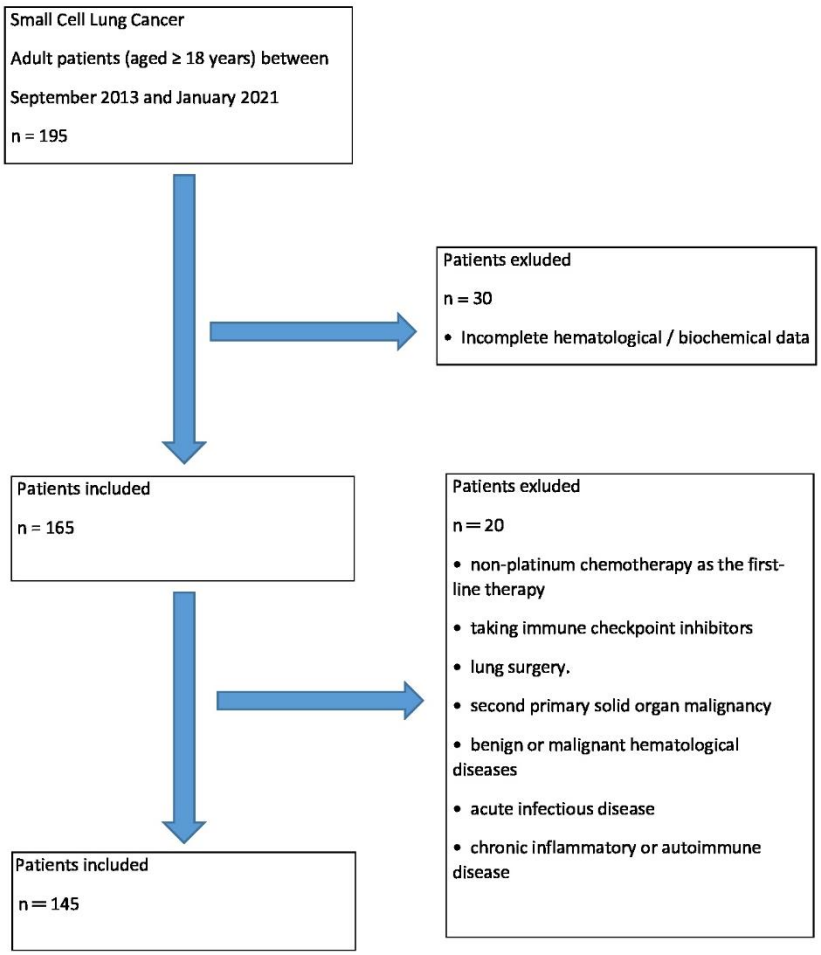

Figure 1. Study inclusion and exclusion criteria.

hematological diseases, acute infectious diseases, chronic inflammatory or auto-immune diseases, 4) history of pulmonary surgery. A total of 50 patients were excluded from study due to these reasons, and 145 patients with SCLC diagnosis were included in the study (Figure 1). Tumor staging was assessed according to the American Joint Committee on Cancer (AJCC) guidelines, 8th edition [20].

Clinical variables, such as, gender, age, Eastern Cooperative Oncology Group (ECOG) performance status and tumor characteristics, were obtained from the patient file records. Laboratory findings, such as, fibrinogen, albumin and CRP at the time of diagnosis were obtained from the hospital data system. CAR was obtained by dividing CRP to albumin. PCR was obtained from ratio of PCT to CRP. PNI values were calculated using the formula of [(10 × albumin (g / L)) + (0.005 × lymphocyte count)]. FAR was obtained by dividing fibrinogen to albumin.

Ethical Approval

All procedures performed in this study were compliant with the ethical standards of the institutional research committee and with 1964 Helsinki Declaration, as amended or comparable ethical standards. Approval was obtained from the local ethics committee of our hospital (2020/235).

Follow-Up

During the treatment period, starting from the date of diagnosis, physical examination and serum chemistry tests of the patients were

performed on a monthly basis and thoracic-abdominal computed tomography (CT) test was performed when necessary. Follow-up visits were provided bimonthly for the first year, quarterly in the 2nd and 3rd years, semi-annually in the 4th and 5th years, and then annually. Thoracic-abdominal CT was performed at each visit, and cerebral magnetic resonance imaging (MRI) or CT was performed every three months in the first year and every six months for two years after the first year.

Study Endpoints

Progression-free survival (PFS) was defined as the time from diagnosis to disease progression or death. OS was defined as the period from the time of diagnosis until death or the last follow-up period for living patients.

Statistics

The receiver operating characteristic (ROC) curve analysis was performed to determine the best cut-off value for variables and the areas under the curve (AUCs) were calculated. CAR, PCR, PNI and FAR were evaluated as dichotomized variables by obtaining the best cut-off value. Shapiro–Wilk test was used to determine if variables were normally distributed. The Chi-square (χ^2) test or Fisher's exact test was used to analyze the relationship between the group of low and high CAR, PCR, PNI and FAR with clinic-pathological parameters. Associations between parameters and survival were analyzed using Kaplan–Meier curves and were compared by the log-rank test. Hazard ratios (HRs), estimated from the Cox analysis, were reported as relative risks with corresponding 95% confidence intervals (CIs). All variables with a p-value <0.05 in the univariate analysis were included in multivariate Cox regression analysis with backward selection. $p < 0.05$ was considered statistically significant in multivariate Cox regression analysis. All analyses were performed using the SPSS statistical software package (SPSS Version, 21, Armonk; NY: IBM Corp).

Results

Determining Optimal Cut-off Values of FAR and Other Parameters

According to ROC curve analysis, best cut-off point for FAR was 0.138, providing 72% sensitivity and 64% specificity. Cut-off values for highest sensitivity and specificity for CAR, PCR and PNI were 0.646, 6.1 and 33.9, respectively. FAR had the highest AUC (0.73) among prognostic factors. AUC values for CAR (0.63), PCR (0.60) and PNI (0.68) were found to be as indicated. The cut-off value determined by the local laboratory was used for serum LDH level (243).

Relationship between FAR with Clinical and Pathological Variables

Median age of 145 patients included in the study was 65±9.5 years. 43 of patients (29.7%) were 60 years and of age and younger and 102 (70.3%) were above 60 years. The clinical and demographic characteristics of the patients are shown in Table 1. Higher FAR was significantly related to; poor ECOG performance status, extensive stage, number of extrapulmonary lesions, higher CAR and higher PCR (p:0.001, p:0.008, p:0.0025, p:0.031, p:0.003 respectively).

Relationship between Survival Results with FAR and Other Parameters

At the end of a median follow up of 15± 15.3 months; while 66 (45.5%) patients showed progression, 40 (27.6%) patients have lost their lives.

According to Kaplan Meier analysis, in the group with FAR≥0.138, both PFS (11.7 months vs. 42.1 months, p<0.001) and OS (16.6 months vs. 64.3 months, p<0.001) were found to be short. Both PFS and OS were found to be shorter in patients with high ECOG

Table 1. Clinical and demographic characteristics of patients

		n (%)
Age groups (years)		
	≤ 60	43 (29.7)
	> 60	102 (70.3)
Gender		
	Male	133(91.7)
	Female	12 (8.3)
ECOG		
	0	49 (33.8)
	1	61 (42.1)
	2	35 (24.1)
Smoking		
	Yes	71 (49)
	No	74 (51)
Comorbidity		
	Yes	92 (63.4)
	No	53 (36.6)
Stage		
	Limited	65 (44.8)
	Extensive	80 (55.2)
PCI		
	Yes	18 (12.4)
	No	127(87.6)
Thoracic RT		
	Yes	29 (20)
	No	116 (80)
Palliative RT		
	Yes	11 (7.6)
	No	134 (92.4)
Extrapulmonary lesion		
	0	65 (44.8)
	1	40 (27.6)
	2	40 (27.6)
LDH		
	< 243	41 (28.3)
	≥ 243	104 (71.7)
PNI		
	< 33.9	60 (41.4)
	≥ 33.9	85 (58.6)
CAR		
	< 0.646	79 (54.5)
	≥ 0.646	66 (45.5)
FAR		
	< 0.138	72 (49.7)
	≥ 0.138	73 (50.3)
PCR		
	< 6.1	107 (73.8)
	≥ 6.1	38 (26.2)

ECOG Eastern Cooperative Oncology Group performance status, TNM tumor, node, metastasis, PCI prophylactic cranial irradiation, Thoracic RT: Thoracic Radiotherapy, Palliative RT: Palliative Radiotherapy, LDH: lactate dehydrogenase, CAR C-reactive protein/ albumin ratio, PCR procalcitonin/ C-reactive protein ratio, PNI prognostic nutritional index, FAR fibrinojen-to-albumin ratio,

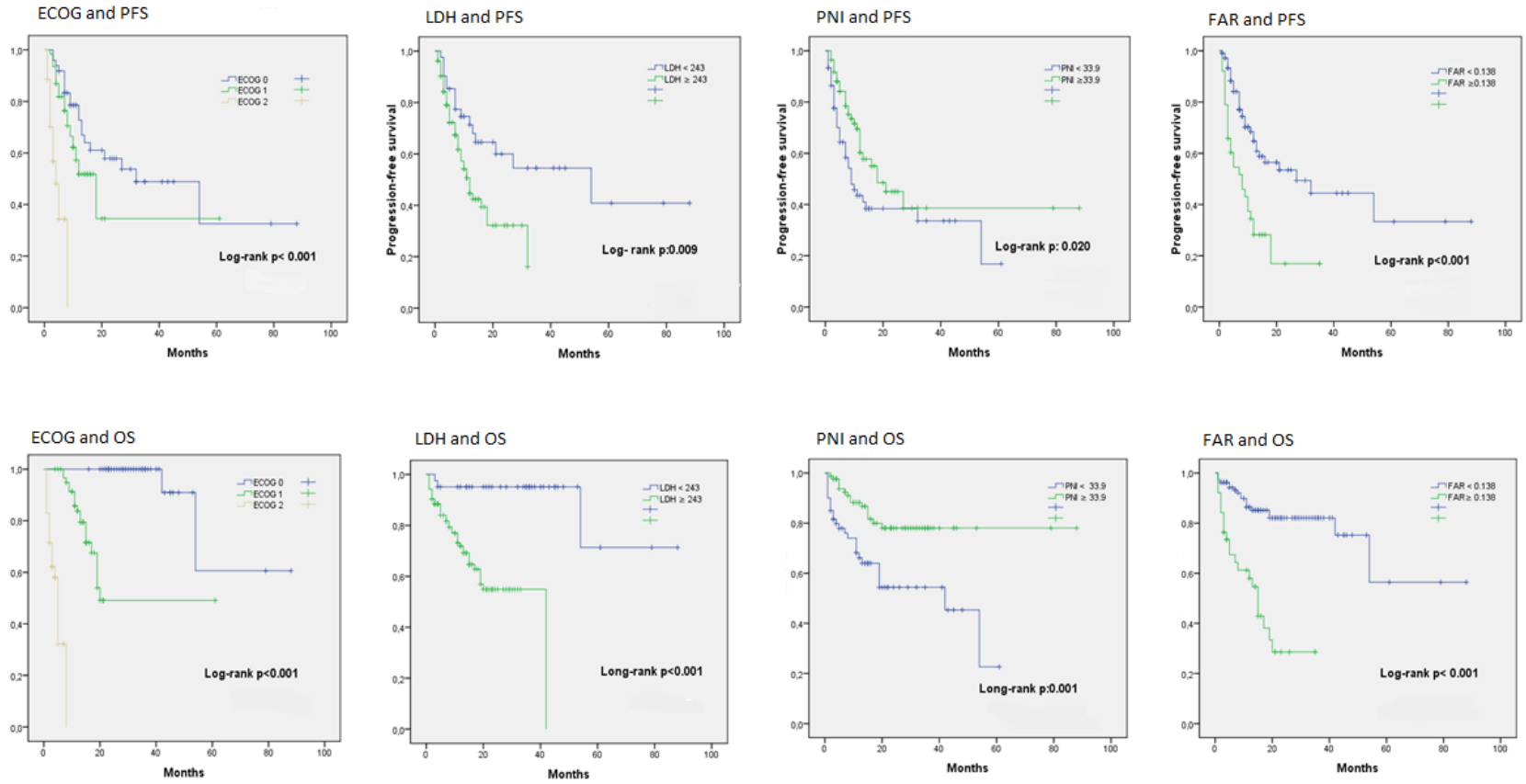

Figure 2. Kaplan-Meier curves for PFS/ OS according to ECOG and markers.

Table 2. Univariate and multivariate cox regression analyses for factors predicting progression-free survival

	Univariate HR (95% CI)	p	Multivariate HR (95% CI)	p
Age groups (years)				
> 60 (ref=≤ 60)	0.817 (0.486-1.373)	0.445		
Gender				
Female (ref=male)	0.818 (0.373-1.794)	0.616		
ECOG				
1 (ref=0)	0.110 (0.051-0.236)	**<0.001**	0.204(0.083-0.501)	**0.001**
2	0.183 (0.093-0.361)	**<0.001**	0.195(0.095-0.400)	**<0.001**
Smoking				
Yes (ref=no)	1.149 (0.698-1.891)	0.586		
Comorbidity				
Yes (ref=no)	0.792 (0.485-1.295)	0.353		
TNM Stage				
Extensive (ref=limited)	1.898 (1.142-3.156)	**0.013**	1.154 (0.569-2.342)	0.691
PCI				
No (ref=yes)	0.380 (0.163-0.890)	**0.026**	0.563(0.175-1.812)	0.335
Thoracic RT				
No (ref=yes)	0.510 (0.266-0.978)	**0.043**	1.018(0.400-2.590)	0.971
Palliative RT				
No (ref=yes)	1.840 (0.876-3.864)	0.107		
Extrapulmonary lesion				
1 (ref=0)	0.525 (0.287-0.962)	**0.037**	1.223(0.642-2.329)	0.540
2	0.995(0.530-1.867)	0.988		
LDH				
≥ 243 (ref= < 243)	2.135 (1.180-3.864)	**0.012**	1.988(1.009-3.916)	**0.047**
CAR				
≥ 0.646 (ref= <0.646)	1.705 (1.045-2.779)	**0.032**	0.527(0.208-1.334)	0.176
PCR				
≥6.1(ref= <6.1)	2.005(1.241-3.385)	**0.005**	2.006(0.778-5.172)	0.150
PNI				
< 33.9 (ref= ≥ 33.9)	0.574(0.353-0.932)	**0.025**	0.531(0.302-0.934)	**0.028**
FAR				
≥0.138 (ref=<0.138)	2.685(1.641-4.393)	**<0.001**	2.096 (1.172-3.747)	**0.013**

ECOG Eastern Cooperative Oncology Group performance status, TNM tumor, node, metastasis, PCI prophylactic cranial irradiation, Thoracic RT: Thoracic Radiotherapy, Palliative RT: Palliative Radiotherapy, LDH: lactate dehydrogenase, CAR C-reactive protein/ albumin ratio, PCR procalcitonin/ C-reactive protein ratio, PNI prognostic nutritional index, FAR fibrinojen-to-albumin ratio, Statistically significant (P < 0.05) values are in bold

performance status. Both PFS and OS were shorter in the group with LDH≥243. Both PFS and OS were longer and the difference was significant in the group with PNI ≥ 33.9 compared to low PNI (Figure 2). Only OS was significantly shorter in smoking group (20 months, 61 months, p:0.033). With increasing number of extrapulmonary lesions, both PFS (14 months, 17 months, 41 months, p:0.037) and OS (30 months, 33 months, 62 months, p:0.025) were found to be significantly shorter. Both PFS (16 months, 41 months, p:0.010) and OS (34 months, 62 months, p:0.007) were found as shorter in the group

Table 3. Univariate and multivariate cox regression analyses for factors predicting overall survival

	Univariate HR (95% CI)	p	Multivariate HR (95% CI)	p
Age groups (years)				
> 60 (ref=≤ 60)	1.676 (0.772-3.639)	0.192		
Gender				
Female (ref=male)	1.155 (0.355-3.758)	0.811		
ECOG				
1 (ref=0)	0.001 (0.000-0.009)	**<0.001**	0.001(0.000-0.013)	**<0.001**
2	0.024 (0.006-0.094)	**<0.001**	0.019(0.004-0.098)	**<0.001**
Smoking				
Yes (ref= no)	2.006 (1.037-3.884)	**0.039**	0.694(0.299-1.608)	0.394
Comorbidity				
Yes (ref=no)	1.339 (0.680-2.636)	0.398		
TNM Stage				
Extensive (ref= limited)	2.467 (1.239-4.913)	**0.010**	1.255(0.487-3.233)	0.638
PCI				
No (ref=yes)	0.211 (0.050-0.894)	**0.035**	0.249(0.021-2.916)	0.268
Thoracic RT				
No (ref= yes)	0.293 (0.103-0.836)	**0.022**	0.567(0.109-2.960)	0.501
Palliative RT				
No (ref=yes)	1.599 (0.625-4.091)	0.327		
Extrapulmonary lesion				
1 (ref=0)	0.378(0.173-0.825)	**0.015**	1.132(0.482-2.656)	0.776
>1	0.871(0.409-1.854)	0.721		
LDH				
≥ 243 (ref=< 243)	13.421 (3.021-59.613)	**0.001**	8.105(1.374-47.797)	**0.021**
CAR				
≥ 0.646 (ref= < 0.646)	2.786 (1.431-5.427)	**0.003**	0.607(0.214-1.725)	0.349
PCR				
≥6.1(ref=<6.1)	4.036(1.914-8.512)	**<0.001**	2.851(0.872-9.319)	0.083
PNI				
< 33.9 (ref= ≥ 33.9)	0.355(0.187-0.676)	**0.002**	0.331(0.143-0.765)	**0.010**
FAR				
≥0.138 (ref=<0.138)	5.389(2.814-10.320)	**<0.001**	2.875 (1.356-6.099)	**0.006**

ECOG Eastern Cooperative Oncology Group performance status, TNM tumor, node, metastasis, PCI prophylactic cranial irradiation, Thoracic RT: Thoracic Radiotherapy, Palliative RT: Palliative Radiotherapy, LDH: lactate dehydrogenase, CAR C-reactive protein/ albumin ratio, PCR procalcitonin/ C-reactive protein ratio, PNI prognostic nutritional index, FAR fibrinojen-to-albumin ratio, Statistically significant (P < 0.05) values are in bold

with extensive stage compared to the group with limited stage. Both PFS (48 months, 30 months, p:0.018) and OS (70 months, 48 months, p:0.020) were found to be longer in those receiving prophylactic cranial RT compared to those, who did not. Both PFS (21 months, 12 months, p:0.035) and OS (53.4 months, 31.2 months, p:0.014) were found to be longer in those receiving thoracic RT compared to those, who did not. There was no difference for PFS (37.5 months, 12.7 months, p:0.094) and OS (56 months, 33 months, p:0.318) in patients receiving palliative RT. Both PFS (19.5 months vs. 39.8 months, p:0.027) and OS (29.6 months vs. 62.6 months, p:0.001) were shorter in the group with CAR ≥ 0.646. Both PFS (18.5 months vs 42.3 months, p:0.003) and OS (29.1 months vs 65.2 months, p<0.001) were found to be shorter in the group with PCR ≥ 6.1.

As seen in Table 2 and 3, in multivariate analysis, ECOG performance status, PNI and

FAR were found to be independent prognostic factors for both PFS and OS.

Discussion

SCLC, known for its aggressive biological behavior, has a poor prognosis and despite novel treatment modalities, satisfactory survival times can not be obtained. ECOG performance status, PNI and FAR were found as independent prognostic factors both for PFS and OS in SCLC for the first time in this study. According to our best knowledge, this study is the first of its kind, showing prognostic importance of FAR in SCLC patients.

It is known that CAR, one of systemic inflammatory indicators, has a predictive and prognostic importance in many cancers, such as, nasopharyngeal carcinoma and pancreatic cancer, GC [21-23]. There is only one study, involving 367 patients with diagnosis of SCLC, and OS was found to be short and independently prognostic in the group with high CAR (cut-off: 0.441) [24]. In our study, while both PFS and OS were shorter and the difference was significant for patients with high CAR, it could not be deemed as independently prognostic. We think that differences between studies might have been originated from limit values used and differences of analysis times.

Another inflammatory indicator is PCR obtained from the ratio of PCT to CRP. PCT level is an important prognostic factor for survival in malignancies such as HCC, colorectal cancer (CRC), GC and also it was found to be associated with postoperative infections [25-27]. In a study on 147 patients with LC, a high PCT level was found as independently prognostic [28]. In a meta-analysis of 3165 patients with early stage NSCLC, high baseline CRP level had been found to be in significantly correlation with poor prognosis [29]. PCR has been examined only in one study on solid tumors, and it has been demonstrated that it had increased specificity for sepsis and localized infection and that it could have been a safe method to exclude infection, but its correlation with prognosis and mortality has not been examined [30]. Our study is important in the sense that it is the first study, showing the correlation of PCR with prognosis in a solid organ malignancy. In our study, PFS and OS were found to be shorter in the group with high PCR (≥ 6.1), and the difference was significant.

PNI, which is an immune-nutritional indicator, is calculated with serum albumin level and lymphocyte count, and it has been found as independently prognostic in many malignancies such as gynecologic cancers, PC, CRC [31-33]. In a study on limited stage SCLC patients, PNI (≥ 53) had been found as independently prognostic both for PFS and OS [34]. In a study on 97 patients with extensive SCLC, it has been found that while there had been no difference in terms of PFS between groups with high PNI (≥ 44.3) and low PNI, PNI had been found as independently prognostic for OS [35]. In line with other studies, we also found both PFS and OS to be longer in the group with high PNI (≥ 33.9). Also, we found PNI to be an independent prognostic factor both for PFS and OS.

FAR is another parameter reflecting systemic inflammatory balance, and prognostic importance of FAR has been demonstrated in various malignancies such as GC, breast cancer and gallbladder cancer [36-38]. Fibrinogen is an acute phase protein produced by liver, and its level increases in case of malignancy or systemic inflammation, leading to prothrombotic effects [39]. Also, fibrinogen plays an important role in tumor metastasis and angiogenesis [39]. Thrombocyte-fibrin clusters, formed by conversion of fibrinogen into fibrin, surround tumor cells and may help the concealment of

tumor cells from immune system [40]. Moreover, it contribute in the invasive and metastasize ability of tumor cell by causing binding and distribution of tumor cells into vascular wall with an angiogenetic effect [41]. Albumin is a negative acute phase protein, level of which decreases along with release of inflammatory cytokines, such as, TNF-α and IL-6, thereby showing immuno-inflammatory status [42]. It is thought that FAR alone may demonstrate immuno-inflammatory status more extensively compared to plasma fibrinogen or albumin. In a study on 194 patients with lung adenocarcinoma diagnosis, it has been found to be independently prognostic only for PFS, although both PFS and OS were shorter in the group with high FAR [43]. In a study on 270 patients with advanced NSCLC, albumin fibrinogen ratio (AFR) had been examined, and high AFR had been correlated with longer PFS and OS and it had been found to be independently prognostic for both [44]. In a study on 529 patients with NSCLC, who had undergone a resection, pre-operative high AFR measured had been found to be correlated with longer OS and DFS and it had been found as independently prognostic [45]. Our study is the first showing prognostic importance of FAR in SCLC patients, and FAR was found to be independently prognostic both for PFS and OS.

Limiting point of our study is that it was retrospective and included relatively small number of patients. Therefore, studies with prospective and multicenter cohorts including more variables are needed.

Conclusion

FAR can be accepted as a new parameter predicting survival times for patients with SCLC. Due to its useability in daily practice and its low cost, it is an advantageous biomarker.

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Corresponding author e-mail: drhaticeyilmaz19@gmail.com

Orcid ID:
Hatice Yılmaz 0000-0001-5341-5646
Ali Aytaç 0000-0001-9753-8517
Büşra Niğdelioğlu 0000-0003-2868-972X
Özlem Yersal 0000-0001-8220-4223
Sabri Barutca 0000-0002-1941-0531

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