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Prognostic significance of pretreatment inflammatory response, immune, and nutritional status in small cell lung cancer

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Abstract:

BACKGROUND AND AIM: Various markers are used to determine the prognosis of many types of cancer. We investigated the relationship of nutritional status, immunity, and inflammation markers with progression-free survival (PFS) and overall survival (OS) to predict the prognosis of patients diagnosed with small cell lung cancer (SCLC) at the time of the diagnosis.

METHODS: We retrospectively reviewed 149 patients who were diagnosed with SCLC, treated, and followed up by our clinic between 2010 and 2012. We examined the relationship between the complete blood count of patients, lactate dehydrogenase (LDH), c-reactive protein (CRP), albumin, and protein parameters, as well as neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio, lymphocyte–monocyte ratio, modified Glasgow prognostic score (mGPS), prognostic nutritional index (PNI), and systemic immune-inflammation index (SII) values, before treatment with PFS and OS.

RESULTS: We found a strong prognostic relationship between PFS and serum albumin, protein, CRP, leukocyte, neutrophil, NLR, PNI, SII, mGPS, and PNI score. Also, there was a prognostic relationship between OS and albumin, protein, LDH, CRP, neutrophil, NLR, PNI, SII, mGPS, and PNI score.

CONCLUSIONS: We determined that simple and easily accessible parameters representing nutritional status, inflammation, and immunity are good prognostic markers in SCLC. Predicting prognosis with these tests can guide clinicians in treatment modalities.

Keywords:

Inflammation, immunity, nutrition, small cell lung cancer

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Introduction

Small cell lung cancer (SCLC) is aggressive neuroendocrine lung cancer with a poor prognosis, constituting 15% of all lung cancers.[1] Life expectancy is low because of the high growth rate and early development of metastases and short doubling time.[2] The average survival time is 15–20 months in limited stage disease, 9–12 months in extensive-stage disease.[3,4]

Unlike complex and often difficult-to-access examinations used so far, simple and easily accessible biomarkers based on systemic inflammation and nutritional status have been developed recently to predict prognosis in various cancer types.[5]

The modified Glasgow prognostic score (mGPS), consisting of serum c-reactive protein (CRP), and albumin concentrations, is considered the prognostic factor in most cancers,[6,7] while the prognostic nutritional index (PNI), which is calculated based on the number of albumin and total lymphocytes, is very useful in predicting overall survival (OS).[8]

The immune and inflammatory response is characteristic of tumor development.[9,10] Platelets play roles in numerous physiological and pathological pathways, containing homeostasis and inflammation. In many studies, it has been reported that increased platelet count is associated with poor prognosis for various solid cancers, including lung cancer.[11] Many systemic inflammatory markers, such as neutrophil–lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR), have a prognostic role in various malignancies.[12,13]

In addition, NLR, PLR, and lactate dehydrogenase (LDH) are effective and easily accessible markers in the evaluation of inflammation and immune status.[12] Albumin, protein, CRP, leukocyte, neutrophil, PNI, systemic immune-inflammation index (SII), and mGPS, which are systemic inflammatory and immune status parameters, have been examined in many studies.[5,8]

Many recent publications showed that SII, consisting of platelets, lymphocytes, and neutrophils, is an important prognostic marker in malignancies.[14,15]

In our study, we aimed to investigate the effects of immune, inflammatory, and general nutritional status markers on prognosis in patients monitored in our center with SCLC.

Materials and Methods

We retrospectively analyzed the patients who were followed up in our clinic between 2010 and 2012 with histopathologically diagnosed SCLC. The study was approved by the ethics committee of our hospital (date: May 9, 2018–3530 issues) and conducted in accordance with the Helsinki declaration.

Patients' age, gender, smoking history, diagnosis date, stage, Eastern Cooperative Oncology Group (ECOG) performance status,[16] treatments, progression, and mortality dates were recorded. Smokers were evaluated as active smokers until 6 months before the diagnosis. The patients were staged according to the Veterans Administration Lung Study Group classification.[17] Progression-free survival (PFS) was calculated based on those who remained responsive from the initiation of treatment to the day of detection of progression or until December 2018. OS was calculated based on the date of death from the date of diagnosis or December 2018 for survivors.

Patients with other organ malignancies were excluded from the study. Patients with liver and kidney failure, those with severe cardiac disease, patients with autoimmune disease, and patients with the serious cerebral disease were also excluded from the study.

The patients had not received chemotherapy (CT) and/or radiotherapy (RT) before the study. The blood samples of the patients belonged to a maximum of 15 days before the treatment and included complete blood count, LDH, CRP, albumin, and protein parameters.

Etoposide+cisplatin/carboplatin CT regimen was given to the patients. In limited-stage patients, after four cycles of CT, radical RT to the thorax and prophylactic cranial irradiation (PCI) were applied. Afterward, the treatment was completed with two more cycles of CT. Patients in the extensive stage received six cycles of CT. The patients whose stage was regressed in the controls were followed up with radical RT and PCI.

Systemic inflammation index was calculated by the formula of platelet count×neutrophil count/lymphocyte count. PNI value was calculated with the formula of 10×serum albumin value+0.5×lymphocyte count. PNI score was evaluated as 0 if the PNI value was ≥45 and it was evaluated as 1 if PNI <45. mGPS was recorded as 0 if

CRP ≤10 mg/L, 1 if CRP >10 mg/L and albumin ≥35 g/L, 2 if CRP >10 mg/L and albumin <35 g/L.

Statistical analysis

Continuous variables were summarized as mean ± standard deviation (SD) and medians with minimum–maximum values. Frequencies and percentages were used to summarize categorical variables. Median survival times with 95% confidence interval (CI) for OS and PFS were calculated with the Kaplan–Meier method. Cox proportional hazard model was used to investigate the relationship between prognostic factors and PFS or OS. Prognostic factors with p<0.1 in the univariate analysis were included in the multivariate models. The forward stepwise method was used in the selection strategy of the multivariate Cox regression model. Considering the correlation between prognostic factors, three different multivariate models were constructed for OS and PFS to prevent multicollinearity. The results of Cox models were presented with hazard ratios and 95% CI. A p-value less than 0.05 was considered statistically significant, and all statistical analyses were performed with IBM SPSS Statistics software (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY, USA) in this study.

Results

The data of the 149 patients who were diagnosed with SCLC between 2010 and 2012 were retrospectively analyzed. Of the patients, 90.6% were males, and the mean age was 61.42±9.66 years. Of the total patients, 60.4% were active smokers, and only 4.7% of them never smoked cigarettes. Among the patients, 48.3% were at the limited stage of the disease. Considering the ECOG performance status, we found that 91.3% of the patients were ECOG 0–2. In the treatment process, we found that 36.2% of the patients had radical thoracic RT and 26.2% had received PCI. Only 3 patients had no CT. In December 2018, when we recorded the last data, 10 patients were still alive and the progression was not observed after the first series of treatments in 7 patients. Qualitative and quantitative characteristics of the patients are shown in Tables 1 and 2.

We calculated median PFS as 7 months (95% CI [6.30–7.70]) and median OS as 8.7 months (95% CI [7.23–10.50]). At the end of the first year, the OS rate was 37.2% and the PFS rate was 18.6%. At the end of the second year, the OS rate was 11.5% and the PFS rate was 8.9%. At the end of the third year, the OS rate was 7.4% and the PFS rate was 8%. At the end of the fifth year, we observed the OS rate as 7.4% and the PFS rate as 7.3% (Table 3).

Table 1: Qualitative characteristics of the patients

Variable	Frequency (n)	%
Gender		
Male	135	90.6
Female	14	9.4
Smoking history		
Active smoker	90	60.4
Ex/never smoker	59	39.6
PFS		
Not bad	7	4.7
Bad	142	95.3
Survival		
Survived	10	6.7
Died	139	93.3
ECOG		
0	76	51.0
1	43	28.9
2	17	11.4
3	8	5.4
4	5	3.4
Comorbidity		
Yes	73	49.0
No	76	51.0
Stage of the disease		
Limited	72	48.3
Extended	77	51.7
Thoracal RT		
Yes	54	36.2
No	95	63.8
PCI		
Yes	39	26.2
No	110	73.8
mGPS		
0	117	78.5
1	20	13.4
2	12	8.1
PNI score		
0	104	69.8
1	45	30.2

PFS: Progression-free survival, ECOG: Eastern Cooperative Oncology Group, RT: Radiation therapy, PCI: Prophylactic cranial irradiation, mGPS: Modified Glasgow prognostic score, PNI: Prognostic nutritional index

Univariate analyses

When we examined the general characteristics of the patients, age, gender, and smoking history were not effective on PFS (p=0.682, p=0.401, and p=0.946, respectively) and OS (p=0.904, p=0.274, and p=0.831 respectively). However, if the stage of the disease was limited, ECOG performance status was low (0–2) and the patient had RT and PCI. We found that these parameters had a positive effect on both PFS and OS in univariate analysis (p=0.001) (Table 4).

Table 2: Quantitative characteristics of the patients

Variable	Mean±SD	Median	Min	Max
Age (years)	61.42±9.66	62.00	39	82
Albumin	3.74±0.51	390	2.20	5.10
Protein	7.05±0.76	7.10	4.20	8.70
LDH	324.21±374.38	226.00	112	4093
CRP	5.51±8.38	1.50	0.02	50.90
Leucocyte	9.44±3.65	8.90	1.10	22.10
Neutrophil	6.22±3.11	5.60	0.73	16.90
Lymphocyte	2.26±0.95	2.04	0.33	6.03
Platelet	337.54±154.67	331.00	83	1116
Eosinophil	0.26±1.13	0.15	0.01	14.00
Hemoglobin	12.86±1.51	13.20	8.60	16.10
Monocyte	0.66±0.41	0.57	0.04	2.33
PNI	48.77±7.33	48.85	27.65	67.75
LMR	5.66±9.33	3.71	0.85	97.80
SII	1095.7±970.16	777.88	105.94	4873.95
NLR	3.16±2.18	2.76	0.37	13.09
PLR	171.30±99.58	148.03	20.90	578.79

LDH: Lactate dehydrogenase, CRP: C-reactive protein, PNI: Prognostic nutritional index, LMR: Lymphocyte monocyte ratio, SII: Systemic inflammation index, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio

Table 3: OS and PFS rates according to the years

Time	OS (%)	PFS (%)
First year	37.2	18.6
Second year	11.5	8.9
Third year	7.4	8.1
Fifth year	7.4	7.3

OS: Overall survival, PFS: Progression-free survival

When we studied the relationship of PFS and OS with systemic immune, inflammation, and nutritional parameters, we found that albumin, protein, LDH, CRP, leukocyte, neutrophil, PNI, PNI score, SII, mGPS, and NLR values were all significantly effective on OS (p=0.001, p=0.001, p=0.012, p=0.001, p=0.023, p=0.002, p=0.001, p=0.001, p=0.007, p=0.001, and p=0.0.001, respectively), and all of them affected PFS significantly except LDH (p=0.001, p=0.001, p=0.060, p=0.001, p=0.024, p=0.003, p=0.001, p=0.001, p=0.019, p=0.004, and p=0.001, respectively). We observed that increasing albumin, protein, and PNI levels extended PFS and OS, while increasing CRP, neutrophils, PNI scores, mGPS, and NLR had negative effects on both parameters (Table 4). The effect of PNI score and mGPS on PFS and OS is shown in Figures 1–4.

Multivariate analyses

In multivariate analyses, OS was significantly associated with ECOG 2 and above (model 1: ECOG 2: p=0.005, ECOG 3: p=0.001, and ECOG 4: p=0.001), absence of RT (model 1: p=0.003), eosinophil (model 1: p=0.021), and CRP (model 1: p=0.002) in all three models. Leucocyte (model 1: p=0.035) was found to be significant only in the model with albumin, in which albumin (p=0.001) itself was significant. In addition, PNI score (model 2: p=0.002; model 3: p=0.004) was associated with OS in both models (Table 5).

All three models constructed for PFS revealed that PFS was affected by ECOG 3 and above (model 1: ECOG 3: p=0.001 and ECOG 4: p=0.001), absence of RT (model 1: p=0.003), and eosinophil (model 2: p=0.047). Similar to OS results, albumin (p=0.005) and PNI score (p=0.040) were found to be statistically significant (except in model 2 for PNI score) (Table 6).

On the other hand, lymphocyte, platelet, hemoglobin, monocyte, lymphocyte–monocyte ratio, and PLR were not effective on PFS (p=0.370, p=0.323, p=0.227, p=0.740, p=0.938, and p=0.067, respectively) and OS (p=0.364, p=0.471, p=0.211, p=0.729, p=0.713, and p=0.055, respectively) (Table 4).

Discussion

SCLC is a common aggressive tumor and is an important health problem worldwide. Because the tests used to predict the course of the disease are expensive and difficult to access, there is a need for new prognostic markers that are effective and simple in SCLC. However, studies on this issue are very limited.

Recently, many articles have emphasized that systemic inflammation and immune status of the patient play an important role in cancer progression.[12,18] Immunosuppression and systemic inflammation at the onset of the disease are associated with poor prognosis.[19,20] One of the factors responsible for cancer cachexia is impaired immunity.[21] To summarize, systemic inflammation, immune, and nutritional status are interrelated, and they play an active role in the cancer formation and the progression of existing cancer.

In our study, the data of the patients with SCLC were analyzed retrospectively to examine the effects of immune, inflammatory, and general nutritional status markers on their prognosis.

We found that age, gender, smoking history, and additional disease status, including the general characteristics of the patients, were not effective on OS and PFS. Minami

Table 4: Univariate analysis of potential association between patient characteristics and survival outcomes

Variable	OS			PFS		
	Hazard ratio	95% CI	p	Hazard ratio	95% CI	p
Albumin	0.336	0.239–0.472	**0.001**	0.389	0.279–0.541	**0.001**
Protein	0.629	0.503–0.786	**0.001**	0.673	0.541–0.836	**0.001**
LDH	1.00	1.000–1.001	**0.012**	1.000	1.000–1.001	0.060
CRP	1.045	1.028–1.062	**0.001**	1.036	1.018–1.054	**0.001**
Leucocyte	1.059	1.008–1.112	**0.023**	1.058	1.008–1.111	**0.024**
Neutrophil	1.091	1.032–1.154	**0.002**	1.088	1.088–1.029	**0.003**
Lymphocyte	0.911	0.745–1.114	0.364	0.914	0.751–1.113	0.370
Platelet	1.00	0.999–1.002	0.471	1.001	0.999–1.002	0.323
Eosinophil	1.139	0.985–1.318	0.079	1.131	0.978–1.307	0.096
Hemoglobin	0.938	0.829–1.042	0.211	0.931	0.829–1.046	0.227
Monocyte	0.932	0.624–1.389	0.729	1.068	0.723–1.068	0.740
PNI	0.923	0.895–0.952	**0.001**	0.934	0.907–0.962	**0.001**
SII	1.00	1.000–1.000	**0.007**	1.00	1.000–1.000	**0.019**
LMR	1.003	0.987–1.020	0.713	0.999	0.982–1.017	0.938
NLR	1.137	1.060–1.220	**0.001**	1.132	1.052–1.218	**0.001**
PLR	1.002	1.000–1.004	0.055	1.002	1.000–1.003	0.067
Age	0.999	0.980–1.018	0.904	1.004	0.985–1.023	0.682
mGPS						
0	1.00			1.00		
1	3.074	1.858–5.087	**0.001**	2.098	1.258–3.496	**0.004**
2	3.377	1.822–6.259	**0.001**	2.479	1.353–4.543	**0.003**
PNI score						
0	1.00			1.00		
1	3.088	2.108–4.523	**0.001**	2.479	1.698–3.620	**0.001**
Gender						
Male	1.00			1.00		
Female	1.364	0.782–2.380	0.274	1.269	0.727–2.216	0.401
Smoking						
Active smoker	1.00			1.00		
Ex/never smoker	1.038	0.769–1.569	0.831	0.988	0.719–1.463	0.946
ECOG						
0	1.00			1.00		
1	1.337	0.960–1.973	0.144	1.241	0.842–1.831	0.275
2	2.772	1.602–4.797	**0.001**	2.015	1.158–3.508	**0.013**
3	19.636	8.281–46.561	**0.001**	19.416	8.009–47.074	**0.001**
4	18.606	6.890–50.225	**0.001**	27.961	9.256–84.471	**0.001**
Comorbidity						
Yes	1.00			1.00		
No	1.287	0.920–1.801	0.141	1.375	0.986–1.919	0.061
Stage						
Limited	1.00			1.00		
Extended	2.203	1.560–3.111	**0.001**	2.423	1.695–3.464	**0.001**
RT						
Yes	1.00			1.00		
No	3.018	2.079–4.381	**0.001**	3.114	2.135–4.542	**0.001**
PCI						
Yes	1.00			1.00		
No	2.389	1.609–3.547	**0.001**	2.485	1.670–3.679	**0.001**

SII OS: HR 1.00028; 95% CI [1.000063–1.000393] and PFS: HR 1.000194; 95% CI [1.000032–1.000356]. OS: Overall survival, PFS: Progression-free survival, CI: Confidence interval, LDH: Lactate dehydrogenase, CRP: C-reactive protein, PNI: Prognostic nutritional index, SII: Systemic inflammation index, LMR: Lymphocyte–monocyte ratio, NLR: Neutrophil–lymphocyte ratio, PLR: Platelet–lymphocyte ratio, mGPS: Modified Glasgow prognostic score, PNI: Prognostic nutritional index, ECOG: Eastern Cooperative Oncology Group, RT: Radiation therapy, PCI: Prophylactic cranial irradiation

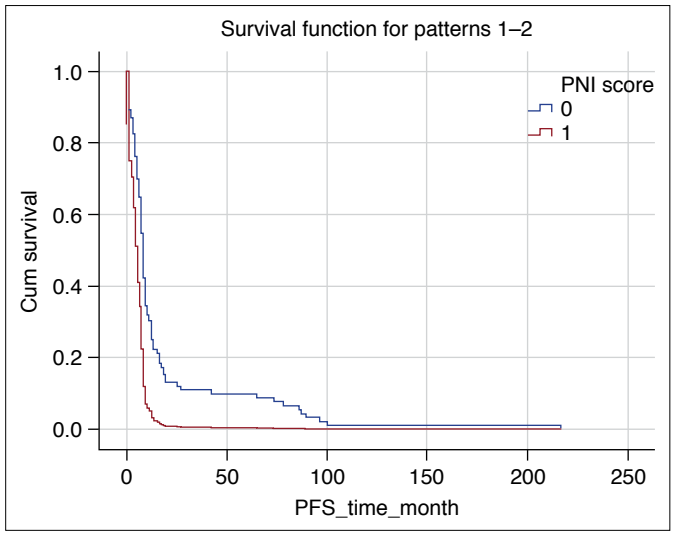

Figure 1: Effect of PNI score on PFS

PNI score: Prognostic nutritional index score, PFS: Progression-free survival

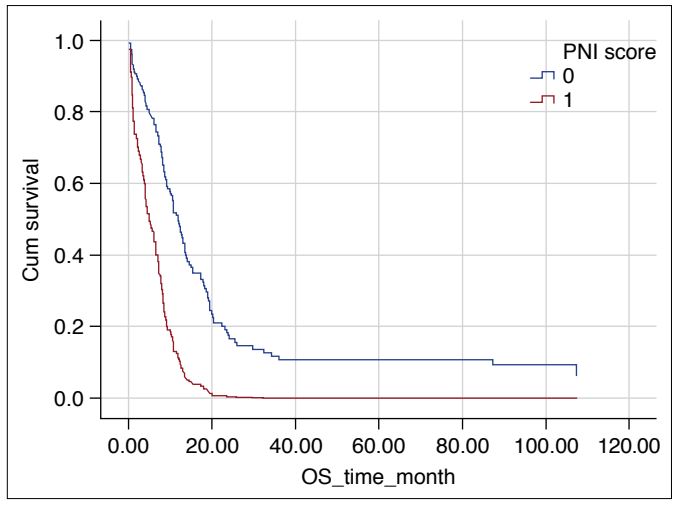

Figure 3: Effect of PNI score on OS

PNI Score: Prognostic nutritional index score, OS: Overall survival

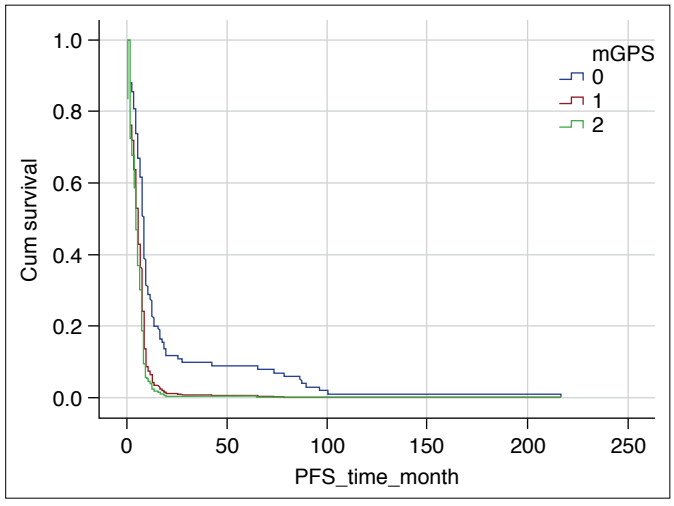

Figure 2: Effect of mGPS on PFS

mGPS: Modified Glasgow prognostic score, PFS: Progression-free survival

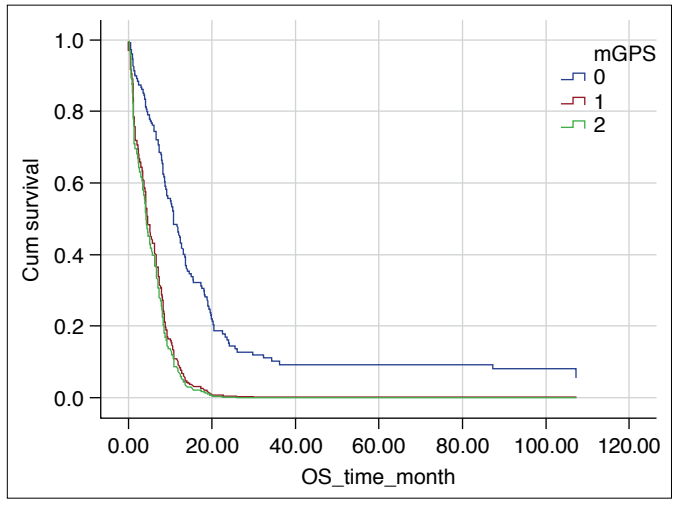

Figure 4: Effect of mGPS on OS

mGPS: Modified Glasgow prognostic score, OS: Overall survival

et al.[5] found that age, gender, and smoking history were not effective on OS and PFS, similar to our study. Similarly, Suzuki et al.[22] did not find any relationship between smoking history and OS, but unlike our study, they found a relationship between age and gender and OS.

The prognosis of advanced lung cancer is poor, and in our study, we found that the stage of the disease affects both OS and PFS as expected. In their studies, Zhou et al. and Hong et al. also found that there was a relationship between the stage and OS similar to our study.[8,14]

ECOG performance status is one of the most important factors affecting the treatment decision and prognosis of patients. In our study, we found that OS and PFS were negatively affected in patients with ECOG 2 and above. In patients with ECOG 2, OS was 2.7 times and PFS was 2 times shorter than those with ECOG 0, OS and PFS were 19 times in ECOG 3, and in ECOG 4 OS was 18.6 times shorter and PFS was 27.9 times shorter. In their study, Deng et al. found ECOG had a similar effect on OS and PFS, and Suzuki et al. also found that ECOG was similarly effective on OS.[12,22]

SCLC is an aggressive tumor needs a multidisciplinary treatment. RT is a form of treatment that plays a role in all stages of SCLC. In our study, we found that radical RT and PCI acquisitions were effective on both OS and

Table 5: Models for OS

Model 1				Model 2				Model 3			
Variable	**HR**	**95% CI**	**p**	**Variable**	**HR**	**95% CI**	**p**	**Variable**	**HR**	**95% CI**	**p**
ECOG 1	1.134	0.748–1.721	0.553	ECOG 1	1.044	0.686–1.588	0.841	ECOG 1	1.080	0.707–1.650	0.721
ECOG 2	2.466	1.318–4.613	**0.005**	ECOG 2	2.103	1.136–3.895	**0.018**	ECOG 2	2.213	1.189–4.117	**0.012**
ECOG 3	9.033	3.415–23.891	**0.001**	ECOG 3	8.735	3.333–22.893	**0.001**	ECOG 3	9.644	3.604–25.809	**0.001**
ECOG 4	7.017	2.281–21.586	**0.001**	ECOG 4	6.284	2.052–19.249	**0.001**	ECOG 4	6.460	2.148–19.427	**0.001**
Stage	0.897	0.553–1.456	0.660	Stage	0.909	0.562–1.470	0.696	Stage	0.870	0.535–1.416	0.576
RT	2.417	1.338–4.367	**0.003**	RT	2.309	1.280–4.163	**0.005**	RT	2.342	1.303–4.210	**0.004**
PCI	1.213	0.670–2.196	0.523	PCI	1.268	0.696–2.312	0.438	PCI	1.275	0.702–2.315	0.425
Protein	1.097	0.779–1.545	0.595	Protein	0.849	0.626–1.152	0.294	Protein	0.849	0.626–1.151	0.292
LDH	1.000	0.999–1.000	0.583	LDH	1.000	1.000–1.001	0.655	LDH	1.000	1.000–1.001	0.580
Leucocyte	0.932	0.873–0.995	**0.035**	Leucocyte	0.971	0.908–1.038	0.381	Leucocyte	0.870	0.717–1.056	0.160
Eosinophil	1.201	1.028–1.403	**0.021**	Eosinophil	1.210	1.036–1.413	**0.016**	Eosinophil	1.213	1.039–1.417	**0.015**
CRP	1.031	1.011–1.051	**0.002**	CRP	1.026	1.006–1.047	**0.011**	CRP	1.025	1.005–1.046	**0.014**
Albumin	0.361	0.214–0.608	**0.001**	NLR	1.049	0.936–1.177	0.411	PNI score	2.057	1.254–3.372	**0.004**
NLR	1.107	0.997–1.229	0.057	PNI score	2.171	1.322–3.567	**0.002**	Neutrophil	1.168	0.930–1.466	0.182

OS: Overall survival, HR: Hazard ratio, CI: Confidence interval, ECOG: Eastern Cooperative Oncology Group, RT: Radiation therapy, PCI: Prophylactic cranial irradiation, LDH: Lactate dehydrogenase, CRP: C-reactive protein, PNI: Prognostic nutritional index, NLR: Neutrophil-lymphocyte ratio

Table 6: Models for PFS

Model 1				Model 2				Model 3			
Variable	**HR**	**95% CI**	**p**	**Variable**	**HR**	**95% CI**	**p**	**Variable**	**HR**	**95% CI**	**p**
ECOG 1	1.041	0.695–1.557	0.846	ECOG 1	0.981	0.651–1.476	0.926	ECOG 1	1.009	0.667–1.525	0.966
ECOG 2	1.779	0.954–3.315	0.070	ECOG 2	1.511	0.819–2.786	0.186	ECOG 2	1.602	0.863–2.973	0.135
ECOG 3	9.249	3.453–24.771	**0.001**	ECOG 3	8.792	3.305–23.390	**0.001**	ECOG 3	9.631	3.540–26.203	**0.001**
ECOG 4	9.639	2.877–32.292	**0.001**	ECOG 4	9.749	2.947–32.250	**0.001**	ECOG 4	9.967	3.027–32.815	**0.001**
Comorbidity	1.243	0.858–1.799	0.250	Comorbidity	1.345	0.936–1.933	0.109	Comorbidity	1.388	0.961–2.005	0.080
Stage	0.922	0.564–1.508	0.747	Stage	0.965	0.591–1.575	0.885	Stage	0.915	0.555–1.509	0.728
RT	2.530	1.364–4.690	**0.003**	RT	2.445	1.310–4.563	**0.005**	RT	2.469	1.328–4.593	**0.004**
PCI	1.234	0.661–2.307	0.509	PCI	1.246	0.663–2.341	0.494	PCI	1.250	0.667–2.343	0.485
Protein	1.098	0.769–1.569	0.607	Protein	0.885	0.651–1.204	0.437	Protein	0.881	0.648–1.197	0.417
LDH	1.000	0.999–1.000	0.957	LDH	1.000	1.000–1.001	0.477	LDH	1.000	1.000–1.001	0.424
Leucocyte	0.960	0.903–1.021	0.197	Leucocyte	0.986	0.925–1.050	0.660	Leucocyte	0.898	0.749–1.078	0.249
Eosinophil	1.166	0.999–1.361	0.051	Eosinophil	1.168	1.002–1.361	0.047	Eosinophil	1.170	1.004–1.363	0.045
NLR	1.084	0.977–1.203	0.130	NLR	1.046	0.933–1.173	0.444	CRP	1.012	0.990–1.034	0.288
Albumin	0.464	0.272–0.793	**0.005**	CRP	1.014	0.992–1.036	0.225	PNI score	1.622	0.997–2.640	0.052
CRP	1.017	0.996–1.039	0.112	PNI score	1.687	1.025–2.777	0.40	Neutrophil	1.144	0.921–1.421	0.225

PFS: Progression-free survival, HR: Hazard ratio, CI: Confidence interval, ECOG: Eastern Cooperative Oncology Group, RT: Radiation therapy, PCI: Prophylactic cranial irradiation, LDH: Lactate dehydrogenase, NLR: Neutrophil–lymphocyte ratio, PNI: Prognostic nutritional index, CRP: C-reactive protein

PFS, and the risk of mortality of patients who could not receive RT increased by 3 times, and that of patients who did not receive PCI mortality was increased by 2.38 times. However we think that the main factor affecting the survival is the stage of the disease rather than the treatment modality. Similarly Deng et al.[12] showed that RT was effective on both OS and PFS, while PCI was only effective on OS. The study of Suzuki et al.[22] also found that RT was related to OS. Zhou et al. found RT was effective on OS, whereas Bernhardt et al. found PCI was related to OS.[8,18]

Chronic inflammation often acts as a tumor promoter, causing the tumor to progress aggressively, thereby negatively affecting survival. Considering the nutritional status and inflammatory response, which is the most important factor determining the immune status and immune status at the time of diagnosis, we observed that albumin, protein, LDH, CRP, leukocyte, and neutrophil values were effective on OS. Other parameters other than LDH also had a significant role in PFS. It is assumed that interleukin 1 and 6, known as proinflammatory cytokines, cause CRP increase and albumin decrease. These

cytokines are also known to be associated with neoangiogenesis. This situation is effective both in the formation of the tumor and in the progression of the existing tumor. At the same time, we think that the inflammatory response and nutritional status are also effective in the clinical performance of the patient and may affect the course of the disease in this way and be effective on OS. Zhou et al.[8] observed that albumin, LDH, CRP, and neutrophil values were also effective on OS, similar to our study.

Neutrophil–lymphocyte ratio and PLR are known markers that affect prognosis in many types of cancer, but their role in the prognosis of SCLC is controversial. In our study, we found that NLR had effect on both OS and PFS, but we found that PLR had no effect on both. Similar to our study, Deng et al.[12] showed that NLR was effective in OS and PFS, but unlike our study, they observed that PLR was effective in PFS. Similar to our study, Suzuki et al.[22] found no correlation between PLR and OS. Qi et al.[23] also defined NLR as an ineffective prognostic factor but found PLR as an independent prognostic factor in their study, which included 53 patients with SCLC, in the opposite direction of our study. In a study conducted in Italy, the effect of NLR on both PFS and OS was also demonstrated.[24]

Also, SII is a parameter that shows a systemic inflammatory response. We determined the effectiveness of SII on both OS and PFS in our study. Hong et al.[14] also found that SII negatively affected OS superiorly to NLR, PLR, and PNI, similar to our study.

mGPS is a score measured based on serum albumin level and CRP, and it is an important indicator in predicting prognosis in SCLC. When we studied the effect of mGPS on OS and PFS, with those of mGPS 1, we found that OS was shortened by 3 times and PFS was shorter by 2 times. If mGPS was 2, OS was shortened by 3.3 times and PFS was shortened by 2.4 times. Minami et al.[5] found that mGPS negatively affected OS, similar to our study.

PNI is a marker that shows the patient's nutritional status. It is also an important tool for determining prognosis in solid tumors, but the data are insufficient in SCLC. We found a statistically significant relationship between PNI and SCLC. We observed that PNI score 1 negatively affected OS and PFS. Compared with OS, Minami et al., Zhou et al., and Hong et al. observed that PNI is effective on OS, similar to our study.[5,8,14]

Conclusion

We found that the systemic inflammatory response, immune, and nutritional status of the patients played an active role in the prognosis of SCLC. We have seen that albumin, protein, LDH, CRP, leukocyte, neutrophil, PNI, PNI score, SII, mGPS, and NLR value are easily accessible, inexpensive, and effective parameters in forecasting OS and PFS. We think that the physician's ability to predict the prognosis after the diagnosis is important in terms of both treatment planning and informing the patients and their relatives about the course.

Conflicts of interest

There are no conflicts of interest.

Ethics Committee Approval

The study was approved by the University of Health Sciences Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital Ethics Committee (No: 3530, Date: 09/05/2018).

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Peer-review

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Authorship Contributions

Concept – N.K., P.Ç.; Design – N.K., T.Ş., P.Ç.; Supervision – P.Ç., F.F.T.; Funding – N.K., T.Ş., S.A.; Materials – None; Data collection &/or processing – N.K., T.Ş., S.A.; Analysis and/or interpretation – N.K., F.F.T.; Literature search – N.K., S.A., F.F.T.; Writing – N.K., P.Ç.; Critical review – N.K., P.Ç.

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