Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1259381

Anatolian Curr Med J. 2023;5(3):180-186

Lung immune prognostic index as a prognostic predictor in patients with advanced small cell lung cancer

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Cite this article as: Söyler Y, Akın Kabalak P, Kavurgacı S, Ayyürek M, Öztürk A, Yılmaz Ü. Lung immune prognostic index as a prognostic predictor in patients with advanced small cell lung cancer. *Anatolian Curr Med J.* 2023;5(3):180-186.

Received: 03.03.2023 • **Accepted**: 01.04.2023 • **Published**: 28.07.2023

ABSTRACT

Aims: Identifying prognostic markers in advanced small-cell lung cancer (A-SCLC) patients is important. Therefore, our study aimed to evaluate the prognostic value of pretreatment lung immune prognostic index (LIPI) in A-SCLC.

Methods: This was a retrospective and observational study of A-SCLC patients treated with platinum plus etoposide chemotherapy as first-line treatment. The association of LIPI with progression-free survival (PFS) and overall survival (OS) was analysed.

Results: One hundred eighteen patients were included in this study and divided into three groups LIPI 0 (n=27, 22.9%), LIPI 1 (n=57, 48.3%) and LIPI 2 (n=34, 28.8%). The median PFS of LIPI groups (0/1/2) was 8.9 (95% CI 3.83-13.96), 8 (95% CI 6.41-9.58), and 5.6 (95% CI 4.60-6.60) months, respectively (p=0.1) The median OS of LIPI groups (0/1/2) was 12 (95% CI 9.11-14.88), 10.1 (95% CI 9.16-11.03), and 7.7 (95% CI 6.55-8.84) months, respectively (p=0.02). Cox regression analysis revealed that LIPI 2 score was an independent risk factor for both PFS (HR 1.839, 95% CI: 1.075-3.144, p=0.02) and OS (HR 1.757, 95% CI: 1.006-3.071, p=0.04).

Conclusion: LIPI score can be used as a simple and easily accessible marker to predict prognosis for A-SCLC patients.

Keywords: Lung immune prognostic index (LIPI), prognostic marker, small-cell lung cancer (SCLC), systemic inflammatory indexes

INTRODUCTION

Small cell lung carcinoma (SCLC), a high-grade neuroendocrine carcinoma of the lungs, is characterised by poor histological differentiation, high aggressiveness and poor prognosis.[1-3] SCLC accounts for approximately 15% of all lung cancers and is one of the leading causes of cancer deaths worldwide, with a 5-year relative survival rate of 7% for all SEER stages combined.[4] There are promising developments in oncological procedures for the treatment of SCLC, but the prognosis remains very poor with a modest improvement in overall survival (OS), especially in patients with advanced-stage SCLC (A-SCLC).[3,5] Therefore, identifying prognostic factors to predict treatment response or survival is particularly important for selecting SCLC patients who are considered at risk for poor outcomes. Many factors may be associated with poor prognosis in SCLC patients, including performance status, age, smoking status and stage.[5,6] Moreover, systemic inflammatory indexes have received much attention recently, as the interplay between systemic inflammation and local immune response plays an important role in tumour development and progression.[7,8]

Several indexes such as neutrophil-to-lymphocyte ratio (NLR), derived neutrophil-to-lymphocyte ratio (dNLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI) and lung immune prognostic index (LIPI) has been studied and some of them have been associated with poor outcomes in various cancers. However, there are currently no validated biomarkers for SCLC patients.[5] Therefore, our study aimed to evaluate the prognostic value of systemic inflammatory indexes in A-SCLC.

METHODS

The study was carried out with the permission of Ankara Atatürk Sanatoryum Training and Research Hospital, Clinical Researches Ethics Committee (Date: 28.12.2022 Decision No:2012-KAEK-15/2617). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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Patients

In this retrospective and observational study, we enrolled 118 SCLC patients who were diagnosed from October 1, 2018, to October 31, 2020, and followed up at our hospital. The inclusion criteria were as follows: patients with pathologically diagnosed SCLC; with advanced (A-SCLC) based on the 8th edition TNM staging system proposed by the International Association for the Study of Lung Cancer (IASLC);[5,9] who treated with platinum plus etoposide chemotherapy as first-line treatment according to the guidelines;[10] with a complete record of pretreatment blood test results; who were over the age of 18 years. The exclusion criteria were as follows: patients with a history of other malignant tumours; who underwent surgery due to SCLC; with recent clinical evidence of acute infection or inflammation; whose clinical information could not be reached.

Data Collection

All clinical data were obtained from our hospital's electronic medical record system or patients' files. The demographic data (age, gender, smoking history, comorbidity), cancer data (date of diagnosis, IASLC stage, tumour size, lymph node involvement, metastasis status and location of metastasis, radiological findings, treatment history, whether cancer has progressed and if so, the date, whether the patient is alive or not, and if he died, the date) and laboratory parameters within 1 week of the initiation of anti-cancer treatment were recorded. The primary survival outcomes were determined as progression-free survival (PFS) and overall survival (OS). Progression-free survival (PFS) was considered as time (months) from the first treatment until disease progression or death due to any cause, whichever occurred first.[6] OS was considered as time (months) from the date of diagnosis of SCLC until the date of death from any cause or the last date of follow-up. Patients who were still alive and still did not show progression were censored at the final follow-up. The cut-off date for follow-up was November 1, 2022.

The systemic inflammatory indexes were calculated for each patient as follows: LIPI=the combination of baseline-derived neutrophil to lymphocyte ratio [dNLR=neutrophil count/(white blood cell count − neutrophil count)] and lactate dehydrogenase (LDH). Our hospital's upper limit of normal (ULN) LDH is 247 U/L. [Good (LIPI 0)=dNLR less than 3 and LDH lower than ULN, Intermediate (LIPI 1)=dNLR greater than 3 and LDH lower than ULN or dNLR less than 3 and LDH higher than ULN, Poor (LIPI 2)=dNLR greater than 3 and LDH higher than ULN], SII=platelet × neutrophil/lymphocyte and SIRI=neutrophil count X monocyte/lymphocyte count, PLR=platelet count/lymphocyte count.

Statistical Analysis

Categorical data were expressed as a number of cases (%) and compared using the Chi-square test or Fisher exact test. The normality of the distribution of continuous variables was evaluated by the Kolmogorov-Smirnov test. Continuous data were given as mean±standard deviation (SD) for normal distributions and were compared using Student's t-test for two independent groups and the ANOVA with TUKEY's correction for multiple independent groups. Continuous data were presented as medians and interquartile ranges (IQR) for skewed distributions and were compared using Mann-Whitney test for two independent groups, and the Kruskal-Wallis test with Bonferroni correction for multiple independent groups. The median follow-up duration was calculated by the reverse Kaplan-Meier method. OS and PFS were estimated using the Kaplan-Meier method and compared using the log-rank test. Cox proportional hazard regression model analysis was performed to identify risk factors independently associated with OS and PFS, and presented with the hazard ratios (HRs) and 95% confidence interval (95% CI). All significant variables which were identified by the univariate Cox regression analysis ($p<0.05$), were included in the multivariate Cox regression analysis. The optimal cut-off values for inflammatory indexes were determined by receiver operating characteristic (ROC) curves analysis using the highest Youden index, defined as sensitivity + specificity-1, to predict PFS and OS. A p-value of <0.05 was considered statistically significant. IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. was used for statistical analyses.

RESULTS

Patient Characteristics

One hundred eighteen [15 (12.7%) females, 103 (87.3%) males, mean age 64.3±7.9] A-SCLC patients were included in the study. Most of the patients (90.7%) had a history of smoking and 74 (62.7%) patients had at least one comorbidity. The most common T category was T4 (n=69, 58.5%). All of the patients were N (+) and 98 (83.1%) patients had multiple metastases (≥2 sides). The most metastasis side was bone (73.7%). The baseline characteristics and laboratory parameters of the study population were given in **Table 1**.

ROC analysis was used to assess the ability of the systemic inflammatory indexes (SIRI, SII, PLR, dNLR) to predict PFS and OS. None of them reached significant predictive value for PFS or OS (**Figure 1a** and **Figure 1b**, respectively).

Table 1. The baseline characteristics and laboratory parameters of the study population

	All Population n, (%)
Age (year±SD)	64.3±7.9
Age, n (%) < 65/≥65	62 (52.5)/56 (47.5)
Sex, n (%) Female/Male	15 (12.7)/103 (87.3)
Smoking (+), n (%)	107 (90.7)
Comorbidity (+), n (%)	74 (62.7)
T status, n (%) T1/T2/T3/T4	1 (0.8)/18 (15.3)/30 (25.4)/69 (58.5)
N status, n (%) N0/N1/N2/N3	-/ 4 (3.4)/27 (22.9)/87 (73.7)
M status, n (%) M0/M1a/M1b/M1c	-/9 (7.6)/12 (10.2)/97 (82.2)
Metastasis Count (< 2/ ≥2)	20 (16.9)/98 (83.1)
Bone Metastasis, n (%)	87 (73.7)
Liver Metastasis, n (%)	40 (33.9)
Adrenal Metastasis, n (%)	26 (22)
Cranial Metastasis, n (%)	18 (15.3)
Laboratory parameters	
White Blood Cell (mean±SD)	9729±2931
Neutrophils (mean±SD)	6852±2735
Lymphocytes (median, IQR)	1630 (1038)
Monocytes (mean±SD)	640±247
Platelets $\times 10^3$ (median, IQR)	282.5 (149)
Haemoglobin (mean±SD)	13.65±1.76
NLR (median, IQR)	3.90 (2.86)
dNLR (median, IQR)	2.54 (1.86)
PLR (median, IQR)	164 (150)
SII (median, IQR)	1053.5 (1169)
SIRI (median, IQR)	2426.5 (2388)
LDH (median, IQR)	301.5 (300)

Association of LIPI with Clinical Characteristics and OS/PFS

Patients were divided into three groups LIPI 0 (n=27, 22.9%), LIPI 1 (n=57, 48.3%), and LIPI 2 (n=34, 28.8%) (**Table 2**). The presence of bone metastasis was significantly lower in the LIPI 0 group. The LIPI 2 group had significantly higher levels of neutrophil-NLR-dNLR-PLR-SII-SIRI-LDH and lower levels of lymphocytes than those in the LIPI 0 and LIPI 1 groups. As none of the indexes reached a significant predictive value for PFS or OS, patients were not divided into groups with high or low levels according to the optimal cut-off values.

Overall, 113 (95.8%) patients had progressed and 106 (89.8%) patients had died during the median follow-up period of 34.9 (95% CI 30.91-38.88) months. The median PFS was 7.4 (95% CI 5.80 -8.99) months and the 1-year PFS was 21.2% in the entire population. The median PFS of LIPI groups (0/1/2) was 8.9 (95% CI 3.83-13.96), 8 (95% CI 6.41-9.58), and 5.6 (95% CI 4.60-6.60) months, respectively (p=0.1, **Figure 2a**) [(LIPI 0 vs LIPI 1, p=0.29), (LIPI 0 vs LIPI 2, p=0.07), (LIPI 1 vs LIPI 2, p=0.12)]. The 1-year PFS of LIPI groups (0/1/2) were 37%, 19.3% and 11.8%, respectively (p=0.05).

The median OS is 9.4 (95% CI 8.48-10.31) months and the 1-year OS was 33.9% in the entire population. The median OS of LIPI groups (0/1/2) was 12 (95% CI 9.11-14.88), 10.1 (95% CI 9.16-11.03), and 7.7 (95% CI 6.55-8.84) months, respectively (p=0.02, **Figure 2b**) [(LIPI 0 vs LIPI 1, p=0.41), (LIPI 0 vs LIPI 2, p=0.01), (LIPI 1 vs LIPI 2, p=0.02)]. The 1-year OS was 51.9%, 36.8% and 14.7%, respectively, and there was a significant difference in OS among LIPI groups (p=0.008).

Univariate and Multivariate Cox Regression Analysis for PFS and OS

A history of smoking, ≥2 metastases and LIPI 2 were associated with PFS on univariate cox regression analyses (p=0.04, 0.04 and 0.04, respectively). On multivariate analysis, a history of smoking (HR 2.417, 95% CI: 1.233-4.737, p=0.01), ≥2 metastases (HR 1.772, 95% CI: 1.042-3.014, p=0.03) and LIPI 2 (HR 1.839, 95% CI: 1.075-3.144, p=0.02) were independent prognostic factors for PFS (**Table 3**). On univariate cox regression analyses, ≥2 metastases, presence of bone metastasis, presence of liver metastasis and LIPI 2 were associated with OS (p=0.004, 0.03 and 0.01, respectively). Therefore, they were included in the multivariate analyses which revealed that ≥2 metastases (HR 2.365, 95% CI: 1.120-4.994, p=0.02) and LIPI 2 (HR 1.757, 95% CI: 1.006-3.071, p=0.04) were found to be the independent prognostic indicators of OS (**Table 4**).

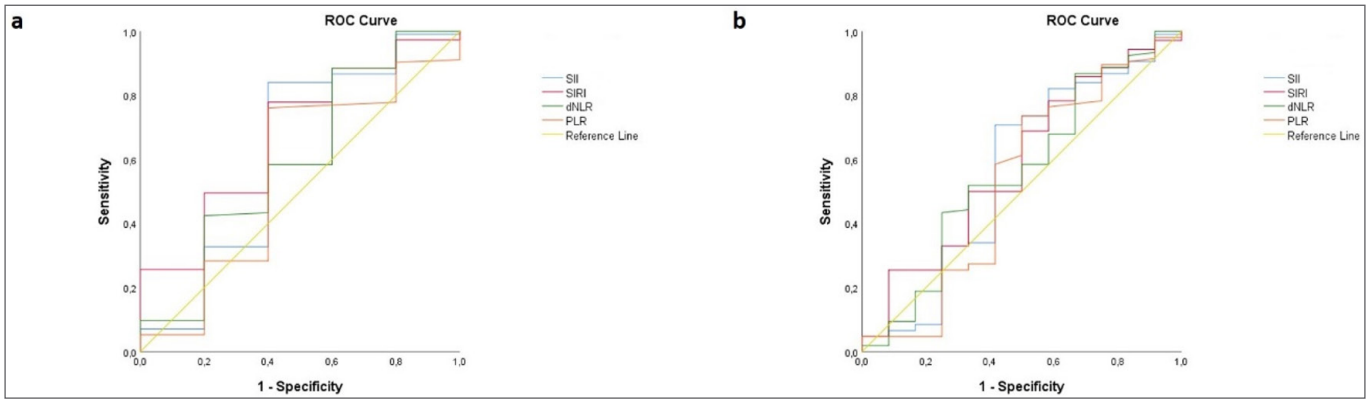

Figure 1. Receiver operating characteristic (ROC) curve of the systemic inflammatory indexes for progression-free survival (a) and overall survival (b)

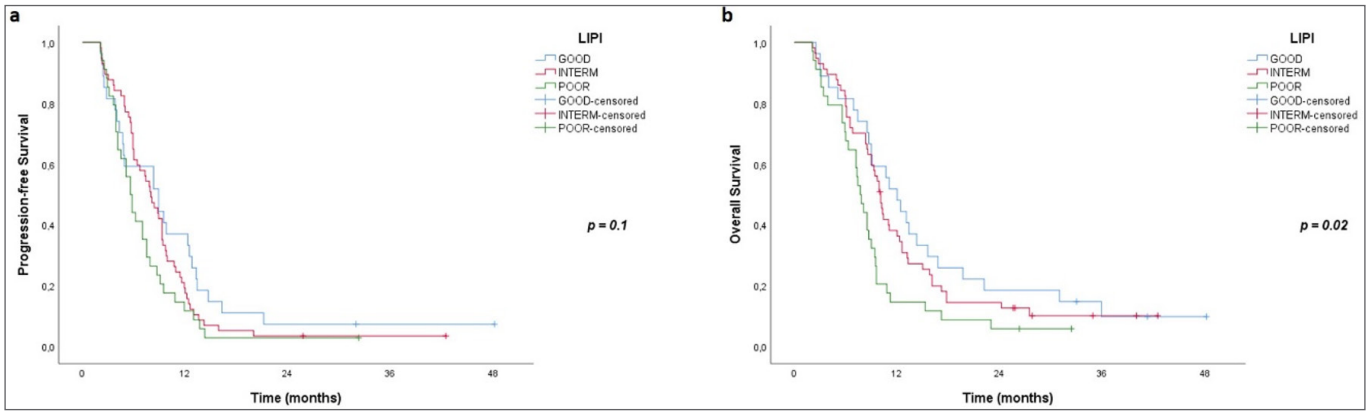

Figure 2. Kaplan-Meier plots of progression-free survival (a) and overall survival (b) according to the lung immune prognostic index (LIPI)

Table 2. The association of LIPI with clinical characteristics and laboratory parameters

	lıpı 0 group (n=27)	lıpı 1 group (n=57)	lıpı 2 group (n=34)	p value
Age (year±SD)	63.7±8.8	63.8±8.2	65.5±6.6	0.59
Age, n (%) <65/≥65	15 (55.6)/12 (44.4)	31 (54.4)/26 (45.6)	16 (47.1)/18 (52.9)	0.74
Sex, n (%) Female/Male	6 (22.2)/21 (77.8)	4 (7)/53 (93)	5 (14.7)/29 (85.3)	0.13
Smoking (+), n (%)	24 (88.9)	54 (94.7)	29 (85.3)	0.3
Comorbidity (+), n (%)	16 (59.3)	33 (57.9)	25 (73.5)	0.3
T status, n (%) T1/T2/T3/T4	- /6 (22.2)/8 (29.6)/13 (48.1)	1 (1.8)/7 (12.3) /13 (22.8)/36 (63.2)	-/5 (14.7) /9 (26.5)/20 (58.8)	0.76
N status, n (%) N0/N1/N2/N3	-/1 (3.7) / 8 (29.6)/18 (66.7)	-/2 (3.5) / 14 (24.6)/41 (71.9)	-/1 (2.9) / 5 (14.7)/28 (82.4)	0.7
M status, n (%) M1a/M1b/M1c	4 (14.8)/3 (11.1)/20 (74.1)	4 (7)/5 (8.8)/48 (84.2)	1 (2.9)/4 (11.8)/29 (85.3)	0.5
Metastasis Count (<2/≥2)	8 (29.6)/19 (70.4)	9 (15.8)/48 (84.2)	3 (8.8)/31 (91.2)	0.09
Bone Metastasis, n (%)	14 (51.9)	45 (78.9)	28 (82.4)	0.01
Liver Metastasis, n (%)	8 (29.6)	22 (38.6)	10 (29.4)	0.58
Adrenal Metastasis, n (%)	7 (25.9)	14 (24.6)	5 (14.7)	0.46
Cranial Metastasis, n (%)	5 (18.5)	7 (12.3)	6 (17.6)	0.68
Laboratory parameters				
WBC (mean±SD)	9256.7±2575.1	9426.7±2989.3	10613.2±2989.5	0.11
Neutrophils (mean±SD)	5734±2015	6254.9±2527	8741.5±2678.6	<0.001
Lymphocytes (median,IQR)	2150 (950)	1740 (1125)	1220 (705)	<0.001
Monocytes (mean±SD)	684±247	637±223	612±286	0.52
Platelets $\times 10^3$ (median,IQR)	320 (172)	271 (143.5)	282.5 (156.2)	0.58
Haemoglobin (mean±SD)	13.5±1.8	13.7±1.7	13.5±1.7	0.74
NLR (median, IQR)	2.65 (1.51)	3.27 (2.12)	6.84 (5.83)	<0.001
dNLR (median, IQR)	1.80 (0.97)	2.16 (1.07)	4.31 (2.82)	<0.001
PLR (median, IQR)	147 (84)	151 (107)	275 (180)	<0.001
SII (median, IQR)	827 (657)	839 (879)	2116 (1587)	<0.001
SIRI (median, IQR)	1721 (1609)	2020 (1923)	3927 (4036)	<0.001
LDH (median, IQR)	205 (42)	326 (244)	476 (689)	<0.001

Table 3. The univariate and multivariate analyses of factors associated with progression-free survival

Variables	Progression-free survival					
	Univariate analysis			Multivariate analysis		
	HR	95% Cl	p	HR	95% Cl	p
Age						
< 65 (Ref)	1					
≥65	1.195	0.824-1.732	0.34			
Gender						
Female (Ref)	1					
Male	0.91	0.530-1.573	0.74			
Smoking						
No (Ref)	1			1		
Yes	1.94	1.011-3.731	0.04	2.417	1.233-4.737	0.01
Comorbidities						
No (Ref)	1					
Yes	0.891	0.606-1.308	0.55			
Number of metastasis						
< 2 (Ref)	1			1		
≥2	1.700	1.012-2.857	0.04	1.772	1.042-3.014	0.03
Bone metastasis						
No (Ref)	1					
Yes	1.359	0.884-2.090	0.16			
Liver metastasis						
No (Ref)	1					
Yes	1.071	0.726-1.580	0.73			
Adrenal metastasis						
No (Ref)	1					
Yes	1.073	0.690-1.670	0.75			
Cranial metastasis						
No (Ref)	1					
Yes	1.149	0.683-1.933	0.6			
LIPI						
0 (Ref)	1			1		
1	1.260	0.781-2.033	0.34	1.123	0.694-1.818	0.63
2	1.731	1.022-2.933	0.04	1.839	1.075-3.144	0.02

Table 4. The univariate and multivariate analyses of factors associated with overall survival

Variables	Overall Survival					
	Univariate analysis			Multivariate analysis		
	HR	95% Cl	p	HR	95% Cl	p
Age						
< 65 (Ref)	1					
≥65	1.331	0.906-1.955	0.14			
Gender						
Female (Ref)	1					
Male	0.800	0.447-1.433	0.45			
Smoking						
No (Ref)	1					
Yes	1.807	0.877-3.722	0.1			
Comorbidities						
No (Ref)	1					
Yes	1.040	0.699-1.546	0.84			
Number of metastasis						
< 2 (Ref)	1			1		
≥2	2.289	1.296-4.041	0.004	2.365	1.120-4.994	0.02
Bone metastasis						
No (Ref)	1			1		
Yes	1.633	1.037-2.572	0.03	0.889	0.483-1.635	0.7
Liver metastasis						
No (Ref)	1					
Yes	1.211	0.811-1.810	0.34			
Adrenal metastasis						
No (Ref)	1					
Yes	0.841	0.529-1.338	0.46			
Cranial metastasis						
No (Ref)	1					
Yes	0.943	0.536-1.658	0.83			
LIPI						
0 (Ref)	1			1		
1	1.197	0.734-1.953	0.47	1.097	0.665-1.810	0.71
2	1.960	1.144-3.358	0.01	1.757	1.006-3.071	0.04

DISCUSSION

The present study investigated the association between pretreatment systemic inflammatory indexes and survival characteristics in patients with A-SCLC. Our results suggest that LIPI can serve as a reliable prognostic factor of PFS and OS, while the remaining systemic inflammatory indexes are not useful as prognostic factors associated with PFS and OS.

The development of biomarkers as an important component of oncology is ongoing. Recent studies have shown that systemic inflammation is one of the main mechanisms of cancer pathogenesis and plays a critical role in tumour development, growth and metastasis, as well as in response to treatment agents.[8,11,12] Therefore, systemic inflammatory indexes reflect the degree of systemic inflammation can be used as promising markers for predicting patient prognosis. Moreover, these indexes are attracting widespread interest because they are easy and cost-effective to obtain and reflect the level of inflammation in the host immune system.[12] However, few studies have been published on SCLC.

The LIPI score can be used to classify patients into poor (LIPI 0), intermediate (LIPI 1) and good (LIPI 2) prognostic groups based on the combination of dNLR and LDH levels.[13,14] High LDH levels and high dNLR levels are unfavourable prognostic factors in various tumours.[11,15] It can be assumed that the LIPI score proved to be a promising marker for predicting prognosis as it represents a combination of these values. In line with our study, Li et al.[16] and Qi et al.[17] reported that the LIPI score was an independent prognostic factor for OS in A-SCLC patients. Sun et al.[6] also demonstrated that LIPI stratification was a significant factor against OS or PFS of limited disease (LD)-SCLC patients. Sonehere et al.[13] showed that the LIPI score was an independent favourable prognostic factor for OS in patients with extensive disease (ED)-SCLC, but not in patients with LD-SCLC, and suggested that LD-SCLC had a lower systemic inflammatory response than ED-SCLC and was difficult to be reflected on NLR. On the other hand, the LIPI score had no prognostic relevance for LD-SCLC in Schnöller et al.'s[14] study and for ED-SCLC in Qi et al.'s[7] study. Even though there were some different results, our study supports the use of LIPI score as a prognostic marker in A-SCLC patients.

Although the underlying mechanisms are not yet fully elucidated, some theories can be put forward about the factors contributing to the prognostic value of the LIPI score. This score, based on LDH and circulating neutrophils and lymphocytes, indicates the interaction between the tumour microenvironment and the immune response.[18] Neutrophils play an important role in carcinogenesis, tumour cell proliferation, tumour progression and metastasis by releasing angiogenic factors such as growth factors, interleukins (IL-1, IL-6 and IL-8) and reactive oxygen species.[12,19] Lymphocytes significantly impact antitumour immunity by inducing cytotoxic cell death and inhibiting tumour cell proliferation and migration. Therefore, a reduced number of lymphocytes results in a poorer lymphocyte-mediated immune response to malignancy.[18,20] Furthermore, LDH, a key enzyme in tumour metabolism, regulates anaerobic glycolysis which is closely related to tumour cell proliferation. This enzyme can also promote tumour survival by inhibiting apoptosis and preventing necrosis in an anoxic environment.[11,17,21] Elevated levels of LDH reflect the tumour burden.[21] Taken together, a systemic inflammatory index dependent on increased neutrophils and LDH levels and decreased lymphocyte count may be a suitable predictive biomarker for assessing the survival status of A-SCLC patients.

Our study has some limitations. First, this was a retrospective study at a single centre with a small number of patients. Nevertheless, our results are promising and should be validated by prospective studies with a larger sample size. Second, all patients in the present study had an acceptably good performance status to receive cancer therapy, so the study population may not represent the entire SCLC population. However, our study was designed to provide a homogeneous group.

CONCLUSION

Our results show that the LIPI score can be used as a simple and easily accessible marker to predict prognosis for A-SCLC patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara Atatürk Sanatoryum Training and Research Hospital, Clinical Researches Ethics Committee (Date: 28.12.2022 Decision No:2012-KAEK-15/2617).

Informed Consent: Because the study was designed retrospectively, no written informed consent was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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