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Lung Immune Prognostic Index (LIPI): Prognostic predictor for patients with extensive-stage small-cell lung cancer

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ABSTRACT

Objective: Extensive-stage small-cell lung cancer (ES-SCLC) is an aggressive malignancy with a poor prognosis, for which prognostic factors are being investigated. In this study, we aimed to evaluate the prognostic significance of the Lung Immune Prognostic Index (LIPI) in ES-SCLC patients.

Patients and Methods: Our retrospective study evaluated 60 ES-SCLC patients who were followed-up and treated between 2014 and 2022 and whose data could be accessed. Demographic characteristics, treatments and laboratory parameters (lactate dehydrogenase, white blood cell, neutrophil, lymphocyte) were collected from patients' files and electronic system of our institution. Patients were divided into 3 groups (LIPI 0, LIPI 1 and LIPI 2).

Results: The worst survival outcome was in LIPI 2. Median progression-free survival (PFS) was 7.7 months for LIPI 0; 5.6 months for LIPI 1 and 5.4 months for LIPI 2 (p = 0.001). Median overall survival (OS) was 19.7 months, 10.2 months and 7.7 months for LIPI 0, LIPI 1 and LIPI 2, respectively (p = 0.001). In both univariate and multivariate analyses, LIPI was found to be an independent negative prognostic factor (p = 0.001).

Conclusion: Lung Immune Prognostic Index is a potentially valuable prognostic marker in ES-SCLC patients. It is thought to be helpful in individualized treatment decisions for ES-SCLC patients. However, further comprehensive multicenter studies are necessary to confirm our results.

Keywords: Small-cell lung cancer, Lung Immune Prognostic Index, Progression-free survival, Overall survival

1. INTRODUCTION

Extensive-stage small-cell lung cancer (ES-SCLC) accounts for approximately 15% of all lung cancers. With a 5-year relative survival rate of 7% across all stages, it is one of the leading causes of cancer death worldwide [1-2]. It has an aggressive course and a poor prognosis [3]. Patients are usually diagnosed at extensive stage. It is highly sensitive to chemotherapy and radiotherapy, but still has a short survival [4]. Survival is relatively improved with the addition of immunotherapy to platinum-based chemotherapy, but recurrence rates are still very high. This highlights the need for improved prognostic tools to better guide treatment strategies and predict outcomes.

Indexes of systemic inflammation have recently received much attention because the interplay between systemic inflammation and the local immune response plays an important role in tumor development and progression [5]. Previous studies have shown that a higher Lung Immune Prognostic Index (LIPI) score is associated with worse outcomes in several malignancies, but its prognostic role in SCLC is still unclear [6-11]. The LIPI consists of easily accessible markers, namely derived neutrophil-to-lymphocyte ratio (dNLR) and lactate dehydrogenase (LDH) levels.

Due to the high mortality rate associated with ES-SCLC, we aimed to investigate the prognostic role of LIPI as well as its association with clinicopathological characteristics in patients with ES-SCLC.

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2. PATIENTS and METHODS

In this retrospective study, 60 patients diagnosed with ES-SCLC who were followed-up and treated at our center between 2014 and 2022 were evaluated. To be included in the study, patients had to be over eighteen years of age with biopsy-proven SCLC. All ES-SCLC patients received first-line platinum-based chemotherapy.

Clinical and demographic data including age, gender, Eastern Cooperative Oncology Group performance status (ECOG-PS) [12] and number of metastatic sites, first-line treatment options, laboratory parameters such as complete blood count and LDH were analyzed.

Lung Immune Prognostic Index was assessed for each patient as follows: LIPI 0 (good) = dNLR less than 3 and LDH lower than ULN, LIPI 1 (intermediate) = dNLR more than 3 and LDH lower than ULN or dNLR less than 3 and LDH higher than ULN, LIPI 2 (poor) = dNLR more than 3 and LDH higher than ULN] [13].

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Approval was granted by the Ethics Committee of Gaziantep City Hospital (Approval Number 16.10.2024.75).

Statistical Analysis

All statistical analyses were performed using the SPSS statistics software version 23.0 (SPSS Inc., Chicago, IL). Continuous variables were expressed as a median (interquartile range) while categorical variables were expressed as a number (n) and percentage (%). Categorical measurements were analyzed using a Chi-square test.

Progression-free survival (PFS) was defined as the time from the date of diagnosis to first progression, death, or last disease-free visit. Overall survival (OS) was defined as the time from the date of diagnosis to death or last visit. The Kaplan-Meier method was used to estimate the median PFS and OS. Univariate and multivariate Cox proportional hazards models were used to identify predictors of OS. A value of $p < 0.05$ was accepted to indicate statistical significance.

3. RESULTS

The study included 60 patients with ES-SCLC who received platinum-based chemoterapy in the first-line setting. Median age was 61.6 years and 38.4% of the patients were over 65 years of age. Eighty-percent of the patients were male. ECOG performance status was 0 in only 30% of patients. Most common sites of metastases were the bone, liver and brain (55%, 28.4% and 52.7%, respectively), and 57% of patients had metastases in two or more sites (Table I).

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

	All patients	LIPI 0	LIPI 1	LIPI 2	P value
Age, n (%)					.69
<65	37 (61.6)	11 (58.9)	17 (68)	9 (22.3)	
≥ 65	23 (38.4)	8 (41.1)	8 (32)	7 (77.7)	
Gender, n (%)					.69
Female	12 (20)	5 (25.3)	4 (16)	3 (18.7)	
Male	48 (80)	14 (74.7)	21 (84)	13 (81.3)	
ECOG-PS, n (%)					.07
0	18 (30)	9 (47.3)	4 (16)	5 (31.2)	
1-2	42 (70)	10 (52.7)	21 (84)	11 (68.8)	
Metastasis Count, (%)					**.05**
< 2	26 (43.3)	11 (57.9)	12 (48)	3 (23)	
≥ 2	34 (56.7)	8 (42.1)	13 (52)	13 (77)	
Bone metastasis, n (%)					.28
No	27 (45)	8 (42.1)	14 (56)	5 (31.2)	
Yes	33 (55)	11 (57.9)	11 (44)	11 (68.8)	
Liver metastasis, n (%)					.56
No	43 (71.6)	15 (77.9)	18 (72)	10 (62.5)	
Yes	17 (28.4)	4 (22.1)	7 (28)	6 (37.5)	
Brain metastasis, n (%)					.53
No	29 (47.3)	10 (53.7)	10 (40)	9 (55.2)	
Yes	31 (52.7)	9 (46.3)	15 (60)	7 (44.8)	
First-line treatment, n (%)					.31
Cisplatin plus etoposide	47 (77.3)	17 (88.4)	19 (76)	11 (68.8)	
Carboplatin plus etoposide	13 (22.7)	2 (11.6)	6 (24)	5 (31.2)	
Platin; first line, n (%)					.10
<6 cycle	13 (21.6)	1 (5.2)	7 (28)	5 (31.2)	
6-8 cycle	47 (78.4)	18 (94.8)	18 (82)	11 (69.8)	

IQR: Interquartile range, ECOG-PS: Eastern Cooperative Oncology Group-Performance Status, LIPI: Lung Immune Prognostic Index

Tablo II. *Progression-free and overall survival times according to infammatory marker*

	Total (n)	Total (%)	PFS, months		OS, month	
			Median (95% CI)	p	Median (95% CI)	p
LIPI						
Group 0	19	31.6	7.7 (6.1-9.5)	**0.001**	19.7 (11.1-28.3)	**0.001**
Group 1	25	41.6	5.6 (3.7-7.4)		10.2 (7.1-13.3)	
Group 2	16	26.8	5.4 (3.9-6.9)		7.7 (0.9-14.5)	
Overall	60	100	6.1 (5.5-6.7)		10.4 (8.7-12.1)	

LIPI: Lung Immune Prognostic Index, PFS: Progression-free survival, OS: Overall survival

Median follow-up was 27 months. Distribution of LIPI was as follows: LIPI 0 (31.6%), LIPI 1 (41.6%), and LIPI 2 (26.8%). PFS was significantly different between groups; Median PFS was 7.7 months for LIPI 0; LIPI 1 of 5.6 months and 5.4 months for LIPI 2 (p = 0.001). OS difference was also significant: 19.7 months, 10.2 months, and 7.7 months for LIPI 0, LIPI 1, and LIPI 2, respectively (p = 0.001) (Table II).

In univariate analysis, number of metastatic sites and LIPI were significant predictors of survival. In multivariate analysis, LIPI 1 and LIPI 2 were associated with increased death risk compared with LIPI 0 (HR: 3.29, 95% CI: 1.54-7.03; HR: 6.57, 95% CI: 2.72-15.8, respectively; p = 0.001). Other parameters were not significant and had no effect on prognosis (age, gender, ECOG-PS, bone metastasis, liver metastasis, brain metastasis) (Table III).

Table III. *Univariate and multivariate analysis of potential prognostic factors for overall survival*

Parametres	Univariate		Multivariate	
	HR (95% CI)	p	HR	p
Age				
< 65 (Ref)	1	0.3	-	-
≥65	0.74 (0.42-1.32)			
Gender				
Female (Ref)	1	0.4	-	-
Male	1.32 (0.64-2.71)			
ECOG-PS				
0 (Ref)	1	0.6	-	-
1	1.15 (0.63-2.11)			
Number of metastasis				
< 2 (Ref)	1	**0.03**	1	0.13
≥ 2	1.88 (1.05-3.38)		1.57 (0.86-2.87)	
Bone metastasis				
No (Ref)	1	0.4	-	-
Yes	1.21 (0.69-2.11)			
Liver metastasis				
No (Ref)	1			
Yes	1.58 (0.87-2.87)	0.1	-	-
Brain metastasis				
No (Ref)	1	0.7	-	-
Yes	0.90 (0.52-1.55)			
LIPI				
0 (Ref)	1	**0.002**	1	**0.002**
1	3.29 (1.54-7.03)	**0.001**	3.29 (1.54-7.03)	**0.001**
2	6.57 (2.72-15.8)		6.57 (2.72-15.8)	

ECOG-PS: Eastern Cooperative Oncology Group performance status, LIPI: Lung Immune Prognostic Index, HR: Hazard ratio, CI: Confidence interval

4. DISCUSSION

As we mentioned before, despite new treatments, ES-SCLC is still the most common lethal cancer and has an aggressive course [14]. Therefore, studies are being conducted to find the factors that affect both the treatment and survival of this cancer. As in other cancers, the effect of easily accessible, low-cost laboratory parameters on prognosis in this cancer type is one of the current issues [7-8].

In our study, we aimed to emphasize the prognostic importance of the LIPI in ES-SCLC patients treated with first-line platinum-based chemotherapy. Our results showed that LIPI is an independent prognostic factor for survival and higher LIPI scores are associated with shorter survival. According to these findings, LIPI may be a reliable prognostic tool in ES-SCLC.

If we re-evaluate our findings, the median PFS of patients with LIPI 2 was 5.4 months, while it was 7.7 months for LIPI 0. Similarly, median OS was 7.7 months in patients with LIPI 2, while it was 19.7 months for LIPI 0. Both PFS and OS were statistically significant. These results were consistent with other previous malignancy studies showing that LIPI is associated with survival outcomes. LIPI is a parameter that is being investigated not only in cancer but also in other diseases [15]. The association between lower LIPI scores and longer survival may be attributed to underlying immune dysregulations reflected by a low dNLR and LDH.

Integrating LIPI into clinical practice could lead to more individualized treatment strategies and improved prognostic models for ES-SCLC. For example, patients with high LIPI may benefit from more frequent monitoring and possibly stronger therapeutic interventions.

The role of systemic inflammation in cancer progression and prognosis is still under study, although, the exact mechanism of action is unknown [16]. Elevated LDH and dNLR (a score based on circulating neutrophils and lymphocytes) play an important role in carcinogenesis, tumor cell proliferation, tumor progression and metastasis by enhancing the interaction between an immunosuppressive tumor microenvironment and the immune response [17]. LIPI is considered a marker of systemic inflammation. Thus, poor LIPI group (LIPI 2) is associated significantly with poor prognosis.

Although, many parameters were evaluated in the univariate analysis (such as age, sex, performance status and metastatic site), only LIPI confirmed to be an independent predictor of survival in both univariate and multivariate analyses. While the

number of metastases was significant in the univariate analysis, it failed to maintain statistical significance in the multivariate model.

Limitations and Future Directions

Although, our study has important findings, it also has some limitations. The most important limitation is the small number of patients and the retrospective nature of the study. Nevertheless, our findings are promising and should be supported by more comprehensive and prospective studies in the immunotherapy era. Another limitation is that only extensive stage disease was included in the study to ensure a homogeneous group and may not represent the entire SCLC population.

Future research efforts are needed to validate our discoveries in larger, prospective cohorts and investigate the underlying biological pathways linking systemic inflammation to the progression of ES-SCLC. By understanding these pathways, new therapeutic targets can be found and strategies can be developed to control the inflammatory response in patients with ES-SCLC cancer.

Conclusion

In conclusion, our study showed that LIPI is an independent prognostic factor in extensive stage SCLC receiving first-line platinum-based chemotherapy. A higher LIPI score was a worse prognostic marker for both PFS and OS. This simple and easily accessible laboratory parameter plays an important role in determining the treatment strategies of ES-SCLC patients. However, it should be supported by larger prospective studies integrating novel therapies such as immunotherapy.

Compliance with Ethical Standards

Ethical approval: This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Approval was granted by the Ethics Committee of Gaziantep City Hospital (Approval Number 16.10.2024.75).

Conflict of interest: The authors declare that there is no conflict of interest.

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Authors contributions: NM: Conceptualization, AKG and NM: Methodology, NM and MS: Software, NM and EK: Validation, BP and NM: Analysis, NM and AMT: Investigation, NM and IVB: Resources, NM, AKG and EK: Data curation, NM and MFK: Writing the draft, NM and PE: Writing the original manuscript, reviewing and editing, NM and YA: Visualization, NM: Supervision, project administration. They confirm that the manuscript has been read and approved by all named authors.

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