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Prognostic Significance of the Advanced Lung Cancer Inflammation Index in Metastatic Small Cell Lung Cancer: A Retrospective Analysis of 96 Patients

Authors' Contribution:

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Data Collection B

Statistical Analysis C

Data Interpretation D

Manuscript Preparation E

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Background: The advanced lung cancer inflammation index (ALI) is regarded as a potential indicator of systemic inflammation. This retrospective study aimed to evaluate the prognostic role of the ALI in 96 patients with advanced small cell lung cancer (SCLC).

Material/Methods: This retrospective study included 96 patients who were diagnosed with extensive stage SCLC in a single institution between 2016 and 2022. The formula for ALI is body mass index (kg/m^2) $\times$ serum albumin (g/dL)/neutrophil to lymphocyte ratio. Patients were divided into low inflammation ($\text{ALI} \geq 32.5$) and high inflammation ($\text{ALI} < 32.5$) groups. Kaplan-Meier analysis and Cox proportional analysis were conducted to assess the association between the ALI and patient prognosis.

Results: Median age was 61 (range: 41-82) years. Median follow-up was 9 months, and median overall survival (OS) was 10 months (95% CI: 7.75-12.45). A lower ALI score ($\text{ALI} < 32.5$) was correlated with a poorer OS than was a higher ALI score (median OS 7 months for $\text{ALI} < 32.5$ 95% CI: 4.6-9.3 vs 15 months for $\text{ALI} \geq 32.5$, 95% CI: 10.6-19.3, $P < 0.001$). In the multivariate analysis, ALI score, Eastern Cooperative Oncology Group performance status, brain metastasis, and bone metastasis were identified as independent prognostic factors.

Conclusions: ALI score is a substantial predictor of survival in SCLC as in other types of cancer types. Patients with a low ALI score have poorer survival. Assessment of ALI can identify lung cancer patients at high risk of poor prognosis and can be a useful prognostic marker in clinical practice.

Keywords: Lung • Small Cell Lung Carcinoma • Neutrophils • Lymphocytes • Inflammation

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Introduction

In 2020, approximately 1.8 million deaths worldwide were attributed to lung cancer [1]. Despite advancements in treatments, lung cancer still accounts for more deaths than the combined total of breast, prostate, colorectal, and brain cancers [2]. Small cell lung cancer (SCLC) comprises less than 20% of all lung cancer cases. Without intervention, survival for individuals with SCLC rarely extends beyond a few months. Nevertheless, SCLC exhibits a high responsiveness to dual chemotherapeutic regimens based on platinum compounds. Platinum-based chemotherapeutic regimens were standard therapy in first-line treatment because they extend survival, compared with the most effective palliative care [3]. For an extended period, the primary recommended treatment for individuals with extensive-stage SCLC was platinum plus etoposide. However, the currently favored treatment protocols incorporate immune checkpoint inhibitors that target the programmed death ligand 1, such as atezolizumab or durvalumab [4]. Currently, the established primary treatment for patients with extensive-stage SCLC involves a combination of platinum-based chemotherapy and immunotherapy utilizing durvalumab or atezolizumab, followed by maintenance immunotherapy, based on the results obtained from key studies such as CASPIAN [5,6] and IMPOWER [7,8]. This benefit of treatment can be seen even in patients with advanced disease, poor performance status, and severe organ dysfunction [9,10].

Upon diagnosis, around 30% of patients with SCLC will present with tumors confined to the hemithorax of origin, mediastinum, and supraclavicular lymph nodes. These patients are categorized as having limited-stage disease [11]. Despite being sensitive to initial chemotherapy, most patients with SCLC relapse within a year and have a limited response to second-line therapy [12]. Median overall survival (OS) is 15 to 20 months for patients with limited-stage disease and 8 to 13 months for patients with extensive-stage disease [13].

The occurrence and development of cancer are significantly influenced by systemic inflammation [14]. Lung cancer frequently presents with systemic inflammation and compromised nutritional status [15,16]. Various signaling molecules and cytokines secreted by cancer cells trigger cachexia and cause progression. These signaling molecules lead to a decrease in muscle mass by suppressing muscle protein synthesis and increasing muscle proteolysis. Furthermore, oxidative stress, inflammation, energy imbalance, and hormonal changes significantly contribute to the development of cancer cachexia [17].

Cancer cells are characterized by inducing systemic inflammation in the host, which triggers the activation of oncogenic signaling pathways, ultimately resulting in the dissemination, growth, and metastasis of cancer [18]. Systemic inflammation

is widely recognized as a detrimental prognostic factor, commonly linked with malnutrition, hypoalbuminemia, weight loss, and other manifestations of cancer cachexia [19]. Several relevant parameters, including C-reactive protein level, lactate dehydrogenase level, white blood cell count, absolute neutrophil count, and the neutrophil to lymphocyte ratio (NLR), have been explored as potential biomarkers of systemic inflammation in patients with cancer [19,20].

The advanced lung cancer inflammation index (ALI) was introduced in 2013 as a valuable prognostic indicator for metastatic non-small cell lung cancer (NSCLC) [21]. The assessment of the ALI, which incorporates indicators of the host's nutritional and inflammatory status, holds promise as a potential reflection of cancer-induced systemic inflammation and cachexia. Therefore, it stands as an appealing candidate biomarker for assessing treatment efficacy in patients with cancer. While a low ALI score has been demonstrated as an independent poor prognostic factor in patients with advanced NSCLC [21,22], its predictive value remains unknown for patients with SCLC.

The identification of an effective prognostic and predictive index for survival in patients with cancer can help clinicians in their choice of treatment. Therefore, this retrospective study aimed to evaluate the prognostic role of the ALI in 96 patients with advanced SCLC.

Material and Methods

Study Design and Ethical Issues

This retrospective study included patients who were followed and treated in the oncology clinic of Dursun Odabaşı Medical Center, Faculty of Medicine, Van Yüzüncü Yıl University between 2016 and 2022. This study was conducted in accordance with the Declaration of Helsinki, and approval was granted by the Ethics Committee of Van Yüzüncü Yıl University (ethics no: 2022/10-18). Patient consent was waived due to the retrospective observational design of the study.

Participants and Data Collection

Patients aged 18 years and above with a diagnosis of SCLC, extensive-stage disease at diagnosis, and no previous treatment were included. Patients below the age of 18, with more than one primary malignancy, limited-stage disease, or missing data were excluded. During the study period, in accordance with Turkish insurance regulations, immunotherapy was not eligible for reimbursement in our country. First-line chemotherapy was initiated for patients. While few patients underwent chemoimmunotherapy, they had to be excluded from the study. Height, weight, absolute lymphocyte count, absolute neutrophil count, platelet count,

and serum albumin levels were retrieved from medical records from the date of diagnosis or the date closest to the date of diagnosis. Data records were eligible for inclusion if they were obtained within a maximum of 10 days before the date of diagnosis. The overall survival was calculated as the time from the date of diagnosis to either the date of death or the latest follow-up.

Statistical Analysis

Descriptive statistics were presented as numbers and percentages for categorical variables and as median and ranges for continuous variables. The variables were investigated using visual (histogram, probability plots) and analytic methods (Kolmogorov-Smirnov, Shapiro-Wilk tests) to determine whether or not they were normally distributed. Due to the lack of normal distribution in the quantitative variables, a comparison between 2 independent groups was performed using the Mann-Whitney U test. The chi-square test and Fisher exact test were used, where appropriate, to compare the proportions in different groups. Survival curves were performed with the Kaplan-Meier method, and survivals were compared with the log-rank test. Prognostic factors for OS were investigated with Cox regression analysis. Statistically significant factors in univariate analysis were included in the backward stepwise regression model. ALI score is calculated as follows: $ALI = \text{body mass index (BMI)} \times \text{albumin (g/dL)} / \text{NLR}$. $BMI = \text{weight (kg)} / [\text{height (m)}]^2$. $NLR = \text{absolute neutrophil count} / \text{absolute lymphocyte count}$. The receiver operating characteristic curve was used to identify the optimal cut-off point for the ALI, comparing it with other clinical indicators for predicting survival. The optimal cut-off point for the ALI score was 32.5, with a sensitivity of 65.2% and a specificity of 72.6%. A *P* value of less than 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 26 (IBM Corp, Armonk, NY, USA).

Results

Patient Demographics and Characteristics

The study included 96 patients. **Table 1** summarizes the characteristics and results of the patients. The median age was 61 years (range: 41-82). Among them, 84 (87.5%) were male. All patients had a favorable Eastern Cooperative Oncology Group performance status (ECOG PS 0-2). Twenty percent of the patients had lymph node involvement, and 79.2% presented with at least 1 distant metastasis. The median follow-up duration was 9 months, and the median OS was 10 months (95% CI: 7.75-12.45).

ALI Score and Overall Survival

A lower ALI score (<32.5) was associated with a poorer OS than was a higher ALI score (median OS: 7 months for ALI

<32.5 [95% CI: 4.6-9.3] vs 15 months for ALI ≥ 32.5 [95% CI: 10.6-19.3], $P < 0.001$), as shown in **Figure 1**.

Univariate and Multivariate Analysis of Prognostic Factors

In the univariate analysis, ALI score less than 32.5, worse ECOG PS, lower weight, lower BMI, higher neutrophil count, higher NLR, higher platelet to lymphocyte ratio (PLR), and presence of brain, bone, and surreal metastasis were found to be worse prognostic factors of OS, as shown in **Table 2**. In the multivariate analysis, ALI score, ECOG PS, brain metastasis, and bone metastasis were identified as independent prognostic factors, as shown in Table 2.

Discussion

In the present study, we demonstrated that the ALI score, a straightforward combination of anthropological and laboratory markers regularly evaluated in clinical settings, can predict the clinical benefit from chemotherapy in extensive-stage SCLC treated with platinum plus etoposide in the first-line treatment. Patients with an ALI score ≥ 32.5 had statistically significantly longer survival than those with an ALI score < 32 (15 months vs 7 months, respectively).

Accumulating evidence has demonstrated that inflammatory and nutritional-based markers predict OS reliably in patients with cancer; however, it remains uncertain which specific marker is more suitable for which type of cancer. The variation of tumor-associated changes in inflammatory cells depends on the extent of the inflammatory response elicited by the tumor, and typically, a more intense inflammatory response correlates with a poorer prognosis. During the initial phases of tumor development, diverse inflammatory cells and proinflammatory cytokines become activated. These factors facilitate the formation of new blood vessels and lymphatic channels, creating a favorable tumor microenvironment that promotes tumor cell growth and differentiation [23]. In advanced stages, inflammation induced by cancer inhibits the activity of immune cells, consequently facilitating the spread of tumor cells [24,25]. Consequently, it is expected that inflammatory markers will serve as valuable prognostic biomarkers in cancer.

A study on patients with NSCLC identified a low lymphocyte count as an independent and unfavorable prognostic factor for disease-free survival [26]. The NLR has also been recognized as an indicator predicting survival outcomes in patients with NSCLC. However, it did not show any association with survival in individuals with SCLC [27]. In a study of patients with stage IV NSCLC, a high NLR, high PLR, and low lymphocyte to monocyte ratio were correlated with diminished survival [28]. Lochowski et al [29] demonstrated that elevated PLR was an independent

Table 1. Baseline characteristics and comparison by advanced lung cancer inflammation index (ALI) score.

Characteristic	Total (n=96)	ALI <32.5 (n=61)	ALI ≥32.5 (n=35)	P
Age	61 (41-82)	62 (41-82)	60 (42-77)	0.766
Sex				
Male	84 (87.5)	56 (91.8)	28 (80)	0.115
Female	12 (12.5)	5 (8.2)	7 (20)	
ECOG PS				
0	23 (24)	9 (14.8)	14 (40)	0.004
1	43 (44.8)	27 (44.3)	16 (45.7)	
2	30 (31.3)	25 (41)	5 (14.3)	
Height, cm	170 (145-196)	170 (146-185)	170 (145-196)	0.688
Weight, kg	69 (45-130)	64 (45-90)	74 (60-130)	<0.001
BMI, kg/m ²	24.2 (16.9-42.5)	22.8 (16.9-30.9)	26.4 (21.1-42.5)	<0.001
Albumin, g/dL	3.8 (2.7-4.9)	3.7 (2.7-4.7)	4.3 (2.7-4.9)	<0.001
Neutrophil, cell/mm ³ ×10 ³	5.9 (1.4-14.4)	6.7 (2.5-14.4)	4.7 (1.4-8.9)	<0.001
Lymphocyte, cell/mm ³ ×10 ³	1.7 (0.3-4.1)	1.5 (0.3-2.7)	2.2 (0.9-4.1)	<0.001
Monocyte, cell/mm ³ ×10 ³	0.7 (0.1-2.3)	0.7 (0.1-2.3)	0.7 (0.2-1.3)	0.302
Platelet, cell/mm ³ ×10 ³	281.5	278 (135-581)	286 (100-656)	0.752
NLR	3.4 (0.5-21.9)	5 (2.3-21.9)	2.1 (0.5-3.3)	<0.001
LMR	2.3 (0.8-18.6)	1.9 (0.8-18.6)	3.9 (1.9-12.4)	<0.001
PLR	172 (50.3-868)	236.5 (53.8-868)	131.8 (50.3-253.9)	<0.001
Lymph node involvement	20 (20.8)	14 (23)	6 (17.1)	0.500
Distant metastasis	76 (79.2)	48 (78.7)	28 (80)	0.662
Brain	30 (31.3)	21 (34.4)	9 (25.7)	0.375
Liver	31 (32.3)	19 (31.1)	12 (34.3)	0.752
Bone	56 (58.3)	34 (55.7)	22 (62.9)	0.496
Surrenal	50 (52.1)	30 (49.2)	20 (57.1)	0.452

Results were presented as n (%) or median (range). ALI – advanced lung cancer inflammation index; ECOG PS – Eastern Cooperative Oncology Group performance status; BMI – body mass index; NLR – neutrophil to lymphocyte ratio; LMR – lymphocyte to monocyte ratio; PLR – platelet to lymphocyte ratio.

prognostic factor for survival in patients with NSCLC who underwent surgery. A high neutrophil count and low lymphocyte count are indicative of a robust inflammatory response and a weakened immune response. A meta-analysis showed that NLR was a strong prognostic marker [30]. In another meta-analysis, a high PLR was associated with poor OS [31]. In our study, univariate analysis showed that among inflammatory markers, a high neutrophil count, high NLP, and high PLR were poor prognostic factors for survival, which was consistent with previous studies.

Several studies have confirmed that BMI and serum albumin levels are prognostic markers in patients with cancer [32,33]. Persistent systemic inflammation is associated with low body weight and hypoproteinemia [34,35]. In a research study involving individuals with inoperable NSCLC, weight loss and low serum albumin levels were associated with poor survival and were considered to be linked to persistent systemic inflammation [36]. A study found that low BMI and weight loss were associated with poor OS in patients with advanced lung

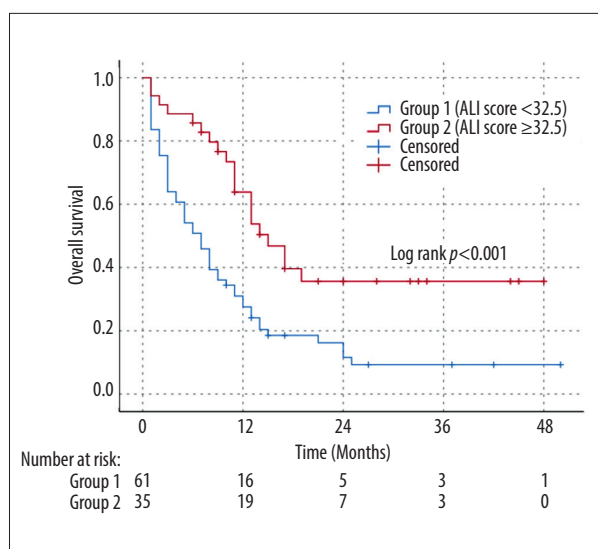


Figure 1. Kaplan-Meier survival curve for overall survival between patients with advanced lung cancer inflammation index of <32.5 and ≥32.5.

cancer [37]. Our study findings revealed that low weight and low BMI were correlated with diminished survival outcomes in the univariate analysis, consistent with previous literature.

In a meta-analysis, the ALI score showed a prognostic value on the survival outcomes of patients with cancer, and a lower ALI

score was associated with a less favorable prognosis ($P<0.001$). This association was also observed individually in cancer subgroups, including lung, colorectal, kidney, and lymphoma cancers [22]. Two studies have assessed the ALI score in SCLC. In one study, Seo et al examined the prognostic value of the ALI in patients with limited-stage SCLC receiving definitive chemo-radiotherapy. They discovered that a high pretreatment ALI (ALI ≥44.3) was significantly associated with improved OS in these patients [38]. In another study, He et al investigated the correlation between ALI and the prognosis of SCLC. They found that patients with a high ALI (ALI ≥19.5) experienced longer OS than did those with a low ALI (ALI <19.5). This association between ALI and OS was also observed in patients with extensive-stage disease (15.93 vs 8.51 months, respectively, $P=0.001$), but not in those with limited-stage disease ($P=0.387$) [39]. The results of the 2 studies in patients with limited-stage SCLC are discordant. On the other hand, the results of our study are compatible with the results in patients with extensive-stage SCLC. A high pretreatment ALI was associated with improved OS. However, the cut-off value is still unclear. The ALI score was 32.5, with a sensitivity of 65.2% and a specificity of 72.6%, in our study. An ALI score below 32.5 was an independent factor for survival in univariate and multivariate analyses. OS was 7 months in patients with a low ALI score, whereas it reached 15 months in those with a high ALI score. ALI stands out as the sole indicator that incorporates anthropometric, nutritional, and inflammatory factors

Table 2. Prognostic factors for overall survival.

Characteristic	Univariate analysis			Multivariate analysis		
	P	OR	95% CI	P	OR	95% CI
ALI score (ref: <32.5)	0.001	0.42	0.25-0.71	0.008	0.48	0.28-0.82
ECOG PS	<0.001			0.005		
0	Ref			Ref		
1	0.044	1.94	1.02-3.69	0.123	1.67	0.87-3.22
2	<0.001	4.11	2.08-8.12	0.002	3.13	1.53-6.40
Weight	0.008	0.97	0.95-0.99			
BMI	0.020	0.93	0.87-0.99			
Albumin	0.007	0.56	0.37-0.86			
Neutrophil cell/mm ³ ×10 ³	0.011	1.13	1.03-1.24			
NLR	0.008	1.09	1.02-1.15			
PLR	0.035	1.002	1.001-1.003			
Brain metastasis	0.003	2.08	1.28-3.38	0.002	2.17	1.32-3.56
Bone metastasis	0.005	2.05	1.24-3.38	0.002	2.27	1.36-3.80
Surrenal metastasis	0.021	1.75	1.09-2.82			

OR – odds ratio; CI – confidence interval; ALI – advanced lung cancer inflammation index; ECOG PS – Eastern Cooperative Oncology Group performance status; BMI – body mass index; NLR – neutrophil to lymphocyte ratio; PLR – platelet to lymphocyte ratio.

associated with the prognosis of lung cancer. This distinction could account for its superior performance in predicting survival, compared with other markers. In the multivariate analysis, patients' ECOG PS and the existence of brain and bone metastases were also correlated with survival.

Our study has several limitations. First, the retrospective design can introduce selection bias and limit the ability to establish causality. Second, the study was conducted at a single center, which can limit the generalizability of the findings to other populations and settings. Additionally, the sample size of 96 patients was relatively small.

Conclusions

ALI score is a significant predictor of survival in SCLC, as in other types of cancer types. Survival is worse in patients with a low

ALI score. Assessment of ALI can identify lung cancer patients at high risk of poor prognosis and can be a useful prognostic marker in clinical practice. In the future, large, prospective, and well-designed studies are needed to confirm the prognostic properties of ALI and the relationship between the threshold value of ALI and tumor stage in this patient population.

Department and Institution Where Work Was Done

The work was done in the Division of Medical Oncology, Department of Internal Medicine, Van Yüzüncü Yıl University, Van, Türkiye.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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