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# A noteworthy prognostic marker in extensive small cell lung cancer: lymphocyte/C-reactive protein ratio

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## ABSTRACT

**Aims**: We aimed to investigate the pre-treatment prognostic significance of lymphocyte/C-Reactive protein ratio (LCR), one of the inflammatory factors, in patients with extensive-stage small cell lung cancer (SCLC).

**Methods**: Medical records of 514 patients who were diagnosed with extensive-stage SCLC between 2010 and 2020 were examined retrospectively. LCR was calculated using the blood test results prior to chemotherapy.

**Results**: The mean survival time for extensive-stage SCLC is 6 months (5.3-6.7). A statistically significant difference exists between limited and extensive stages in terms of median overall survival (OS) ($p<0.001$). The baseline LCR value of the patients was determined as 0.5 (0-311). LCR exerts a statistically significant effect on overall survival (0.025). Every 1 unit increase in LCR reduces death by 1.004 times.

**Conclusion**: Pre-treatment LCR value can be used as an independent prognostic parameter associated with mean survival in extensive SCLC.

**Keywords**: Small cell lung cancer, lymphocyte/CRP ratio, prognostic factor, survival

## INTRODUCTION

Small cell lung cancer (SCLC) constitutes approximately 15% of all lung cancers with the worst histological course.[1] 60-70% of these carcinomas are extensive-stage, and the median overall survival (OS) is averagely 6 to 8 months.[2] There is still no standardized prognostic marker that can determine survival,[3] therefore there is a need for new markers. Studies show a strong link between systemic inflammation and cancer. Inflammation paves the way for cancer development and effects all stages of tumor formation.[4] Several cytokines and mediators produced secondary to inflammation may increase cell proliferation, invasion, and metastasis development.[5] Systemic immune-inflammation index (SII), prognostic nutrition index (PNI) and neutrophil/lymphocyte ratio (NLR), which are thought to reflect systemic inflammation, have been associated with prognosis in many solid organ malignancies, including esophageal and lung cancer.[6] Systemic inflammation response index (SIRI), another inflammatory indicator, has been defined as a prognostic and predictive factor for various types of cancer, including pancreatic cancer and non-small cell lung cancer (NSCLC).[7,8] The ratio of hemoglobin (Hb) and red cell distribution width (RDW) (HRR) are novel prognostic markers in SCLC, and in this study, it has been shown that each unit increase in HRR reduces death and survival by 1.6 times.[9] Another study in NSCLC showed that low HRR was associated with shorter survival.[10] Recently, the lymphocyte-to-C-reactive protein ratio (LCR), a novel marker, was shown to exert prognostic significance for lung cancer.[11] Another study reported the prognostic significance of many inflammatory markers in extensive-stage SCLC.[12] A decrease in lymphocyte/monocyte ratio (LMR) was found to be a poor prognostic indicator in extensive-stage SCLC.[13] Despite growing evidence of the impact of these inflammation-based scores on the prognosis of SCLC patients, there is limited information on the prognostic significance of the novel parameters. The aim of this study was to determine whether the easily measurable LCR value is an independent prognostic factor for OS, with the number of patients that may be sufficient considering this deficiency.

## METHODS

All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki and approved by Ankara Atatürk Sanatorium Training and Research Hospital Clinical Researches Ethics Committee (Date: 22.03.2023, Decision No: 2012-KAEK-15/2676) for studies involving humans and the study was

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designed retrospectively, no written informed consent form was obtained from patients. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

### Patients

Extensive-stage SCLC patients diagnosed between January 2010 and January 2020 at Chest Diseases Clinics were included in the study. Inclusion criteria: (i) histopathologically diagnosed extensive-stage SCLC; (ii) adequate imaging data for computed tomography (CT), magnetic resonance imaging device (MRI), and PET-CT tumor staging; (iii) no previous antitumor therapy (including radiotherapy, chemotherapy, immunotherapy and targeted therapy); (iv) routine blood and blood biochemistry findings based on hospital laboratory test results. Exclusion criteria: (i) patients younger than 18 years of age; (ii) patients with limited stage SCLC and non-small cell lung carcinoma (NSCLC) confined to one lung and regional lymph nodes only and can be included in a safe radiotherapy field; (iii) patients with secondary carcinoma; (iv) patients with concomitant infections, inflammatory diseases, lymphoproliferative diseases.

1039 SCLC patients were screened. A total of 514 patients were included in the study after the exclusion of 199 patients without PET-CT results and 326 patients with limited stage.

### Clinical Data

Clinical data such as age, gender, smoking history, staging, treatment regimens (chemotherapy, radiotherapy, adjuvant therapy, neoadjuvant therapy, operation), and pre-treatment LCR values were recorded. LCR value was calculated using CBC values as follows: Lymphocyte x 1000/ CRP (mg/l).

### Tumor Staging

Tumor staging was performed based on the eighth edition of the staging criteria published by the International Association for the Study of Lung Cancer.14

### Observation Indicators

Median overall survival (OS) was defined as the time interval between initiation of treatment and final follow-up and/or death.

### Statistical Analysis

Descriptive statistics were used to express continuous variables (mean, standard deviation, minimum, median, maximum).

Conformity of continuous variables to normal distribution was analyzed by the Shapiro-Wilk test.

Overall survival was examined by Kaplan-Meier method.

The effect of blood parameters on survival was examined by Cox Regression analysis.

Measurement of blood parameters and predictive power of progression and death were examined by ROC analysis.

The value of statistical significance was determined as 0.05. The analyses were performed using the MedCalc® Statistical Software version 19.7.2 (MedCalc Software Ltd, Ostend, Belgium; 2021) Program.

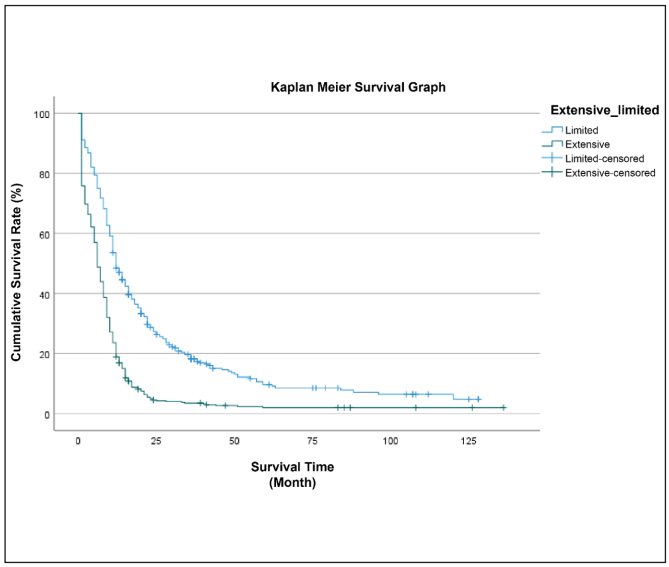
## RESULTS

514 patients were included in the study. Of the patients participating in the study, 461 (89.6%) were male and 53 (10.3%) were female. The mean age was 62.7. 211 (41%) patients had a history of smoking. 326 patients (38.9%) were in the limited stage and 514 patients (61.1%) were in the extensive stage. 111 (13.2%) patients had bone metastasis, 22 (2.6%) lung, 16 (1.9%) liver, 25 (3%) adrenal gland, 10 (1.2%) brain, and 328 (39.1%) more than two organs. The clinical characteristics of the participating patients are listed in Table 1. The mean survival time for extensive-stage SCLC is 6 months (5.3-6.7). A statistically significant difference exists between limited and extensive disease stages in terms of OS ($p<0.001$) (Figure 1). The initial LCR value of the patients was 0.5 (0-361), and there was a statistical difference between the limited and extensive disease groups. NLR value was 3.7 (0.8-157.1) and CRP/Alb value was 0.6 (0-65.7) in the extensive stage group while statistical significance was noted in the limited stage group. Laboratory parameters are shown in Table 2. LCR exerts a statistically significant effect on overall survival in the extensive group. A 1-unit increase in LCR reduces death by 1.004 times (Table 3). As shown by the ROC analysis, LCR was not found to be effective in predicting death, and the baseline cut-off value could not be determined (Figure 2).

**Table 1.** Demographic data and laboratory parameters

| | n (%) |
|---|---|
| Gender | |
| Male | 461(89.6) |
| Female | 53 (10.3) |
| Age (years) | 62.7 |
| Smoking | 211 (41) |
| Smoking consumption amount (pack/year) | 48.9 (+25.5)* |
| Disease Stage: | |
| Limited Stage | 326 (38.9) |
| Extensive Stage | 514 (61.1) |
| Metastasis localizations: | |
| Bone | 111 (13.2) |
| Opposite Lung | 22 (2.6) |
| Liver | 16 (1.9) |
| Surrenal | 25 (3) |
| Brain | 10 (1.2) |
| > Two organs | 328 (39.1) |

*: Mean ± SD




| | Median | St. Error | 95% Confidence Interval-Lower limit | 95% Confidence Interval-Upper limit |
|---|---|---|---|---|
| Limited | 12.0 | 0.7 | 10.54 | 13.46 |
| Extensive | 6 | 0.3 | 5.3 | 6.7 |

**Figure 1.** Effect of limited/extensive involvement on overall survival

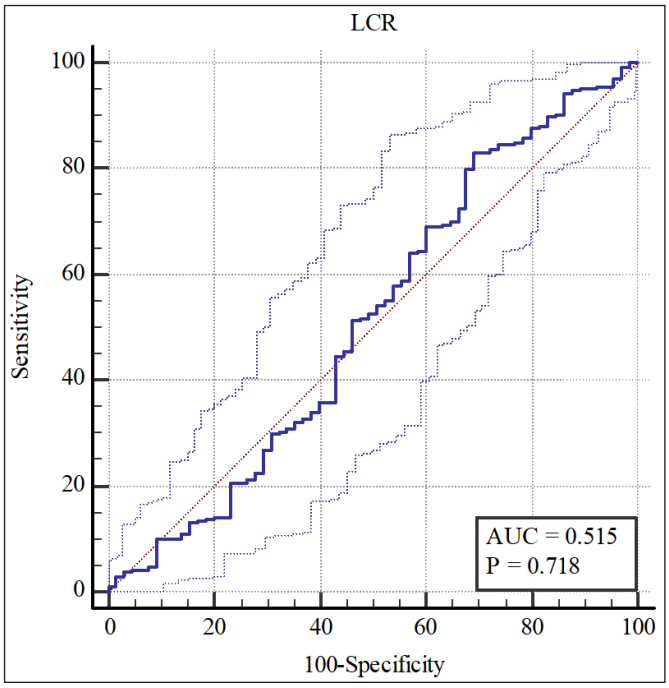



**Figure 2:** LCR ROC analysis graph

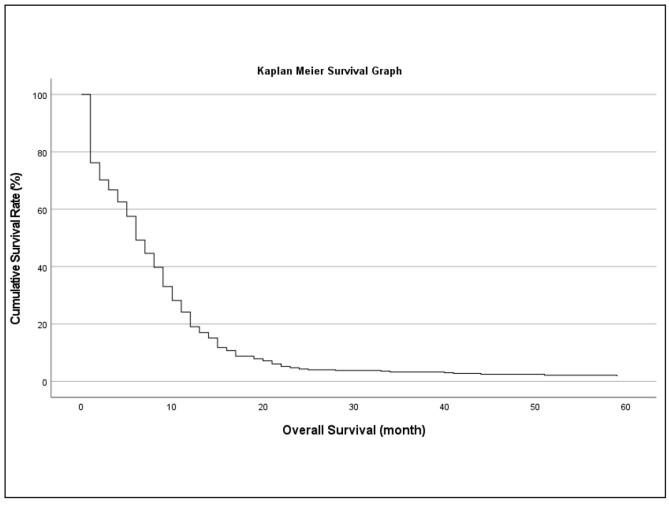
**Table 2.** Evaluation of Parameters by Limited and Extentive Stages

| | Limited | Extensive | p |
|---|---|---|---|
| LCR | 0.7 (0-361) | 0.5 (0-311) | 0.002 |
| NLR | 3.1 (12684.7-687.7) | 3.7 (0.8-157.1) | <0.001 |
| Platelet/Alb. | 57.7 (3.2-219.1) | 62.2 (1.0-44.6) | 0.337 |
| PLR | 18.2 (2.6-42.9) | 18.9 (2.3-60.8) | 0.542 |
| CRP/Alb. | 0.4 (0-14.7) | 0.6 (0-65.7) | <0.001 |
| HRR | 1 (0.4-1.4) | 1 (0.3-1.4) | 0.533 |

CRP: C-reactive protein, HRR: Hemoglobin/Red cell distribution width ratio LCR: lymphocyte/CRP ratio, NLR: neutrophil/lymphocyte ratio PLR: Platelet/lymphocyte ratio

**Table 3.** Effect of LCR Values on Overall Survival in the Extensive Group

| | p | HR | 95% CI |
|---|---|---|---|
| LCR | 0.025 | 0.996 | 0.993-1.00 |




## DISCUSSION

In small cell lung cancer, survival time has not been improved due to the lack of novel treatment options and simple and effective parameters for assessing prognosis. Extensive-stage SCLC especially displays an aggressive course, and the median overall survival (OS) is averagely 6 to 8 months.[2] OS was 6 months in our study, which was consistent with the literature.

In a study by Yuan He et al.[11] consistent with the findings of previous studies, LCR was determined as an independent prognostic marker for both PFS and OS, whereas decreased LCR was found to be a poor prognostic marker. A study by Yılmaz H et al.[12] which is the first publication in our country demonstrating the prognostic significance of novel inflammatory markers in extensive small cell lung cancer, showed that LCR is an independent prognostic marker for both PFS and OS. In this study, PFS ($p < 0.001$) and OS ($p < 0.001$) were found to be longer in the patient group with high LCR than in the low LCR group. In our study, the LCR value was not found to be significant in predicting death, and the basal cut-off value could not be determined. Again, in the study conducted by Iriagac et al.[13] in Turkey, OS was 8.78 (1.07-54.80) months and PFS was 5.6 (1.07-44.03) months in extensive-stage SCLC patients. In their study, PFS was 4.5 months and OS was 7.5 months in the low lymphocyte/monocyte ratio (LMR) group, whereas the median PFS was 6.5 months and OS 10.1 months in the high LMR group. It was thought that high LMR might have good prognostic value for survival (HR: 0.54 95% CI 0.38-0.77. p=0.001). In our study, LCR exerted

a statistically significant effect on overall survival in the extensive group. It was determined that every 1-unit increase in LCR reduced the death by 1.004 times, however, the LCR value was not found to be effective in predicting death according to the result of the ROC analysis, and the lower and upper group analysis could not be performed since the basal cut-off value could not be determined.

## CONCLUSION

In this study, we revealed that LCR was associated with overall survival in extensive-stage SCLC patients, which suggests that LCR can be used as a prognostic marker.

Nonetheless, the fact that it is a single-center retrospective study and there is no standard cut-off value that can be compared is among the limitations of our study. Prospective studies including all factors affecting LCR value are needed to reveal the relationship of LCR with OS as an independent factor.

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** The study was carried out with the permission of Ankara Atatürk Sanatorium Training and Research Hospital Clinical Researches Ethics Committee (Date: 22.03.2023, Decision No: 2012-KAEK-15/2676).

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

**Referee Evaluation Process:** Externally peer-reviewed.

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

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**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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