EJMI

DOI: 10.14744/ejmi.2022.53326
EJMI 2022;6(1):33–37

Research Article

Could Pretreatment Neutrophil/Lymphosit Ratio and Derived Neutrophil/Lymphosit Ratio Predict Overall Survival of Patients With Extensive Stage Small Cell Lung Cancer?

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Abstract

Objectives: We designed this study to evaluate the prognostic significance of basal neutrophil / lymphocyte ratio (NLR), derived NLR (dNLR) and systemic immune inflammation index (SII) in patients with extensive stage (ES) SCLC treated with platinum-based combination regimen.

Methods: This study was a hospital-based retrospective observational case-series study. 145 ES SCLC patients were included the study from Dr. Ersin Arslan Education and Research Hospital Departments of Medical Oncology and Radiation Oncology between the years of 2011-2018.

Results: The median age of the patients was 61 (range 31-81) years and 131 (90.3%) patients were male. 144 (99,3 %) patients were treated with the platinum etoposide combination regimen and 134 patients (92,4 %) received cisplatin in combination. The median follow-up time was 10 months and 116 (80%) patients died. Progression-free survival (PFS) and overall survival (OS) were estimated, respectively, as 8 and 12 months. Patients in the low NLR and low dNLR scores had better overall survival than those with high NLR and high dNLR (14 versus 10 months respectively and p=0,01).

Conclusion: This study showed that basal NLR and dNLR may have prognostic biological value in patients with ES SCLC treated with cisplatin + etoposide.

Keywords: Derived neutrophil/lymphosit ratio, extensive stage, neutrophil/lymphosit ratio, overall survival, small cell lung cancer.

Cite This Article: *Bahceci A, Kotek Sedef A. Could Pretreatment Neutrophil/Lymphosit Ratio and Derived Neutrophil/Lymphosit Ratio Predict Overall Survival of Patients With Extensive Stage Small Cell Lung Cancer? EJMI 2022;6(1):33–37.*

Despite improvements in early diagnosis and cancer treatments in recent years, lung cancer remains the leading cause of cancer-related deaths worldwide.[1] Small cell lung cancer (SCLC) constitutes approximately 15% of all lung cancers.[1] Although SCLC is a chemosensitive disease, it is characterized by very rapid deterioration, early metastasis and poor prognosis.

Various prognostic indices have been developed in order to predict the course of the disease in many types of cancer and sometimes make the choice of treatment easier, and new indices are still being investigated. These prognostic indices need to be easy and simple to be put into routine use.

Inflammation plays an important role in cancer development. Systemic inflammation increases tumor proliferation, invasion, and angiogenesis.[2] Neutrophil, lymphocyte, monocyte and platelet are markers of systemic inflam-

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Submitted Date: September 02, 2021 **Accepted Date:** January 16, 2022 **Available Online Date:** February 28, 2022

mation. Neutrophil / lymphocyte ratio (NLR), derived NLR (dNLR) and systemic immune inflammation index (SII) are newly developed inflammatory indexes in various cancer types that can be easily calculated by blood count.

The aim of this study is to evaluate the prognostic and predictive significance of pre-treatment NLR, dNLR and SII scores in SCLC patients with extensive stage at the time of diagnosis given platinum-based combination chemotherapy.

Methods

Patients

We designed this study to evaluate the prognostic significance of basal NLR, dNLR and SII in patients with ES SCLC treated with platinum-based combination regimen. This study was a hospital-based retrospective observational case-series study. Among 1500 newly diagnosed lung cancer patients at Dr Ersin Arslan Education and Research Hospital Departments of Medical Oncology and Radiation Oncology between the years of 2011-2018. There were 145 ES SCLC patients. Basal NLR, dNLR and SII and demographic data were collected, together with the outcome of chemotherapy. Kaplan-Meier survival analyses and Cox proportional hazard models were used to examine the effects of basal NLR, dNLR and SII on overall survival.

The NLR was calculated as follows: Neutrophil/lymphocyte

The dNLR was calculated as follows: Neutrophil/(White blood cell – neutrophil)

The SII was also calculated with formula as follows: (Neutrophil x Platelets)/Lymphocyte.

Ethical Approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Gaziantep University Ethical Comittee: 07.10.2020; Number 2020/260.

Statistical Analysis

All results were presented as the rate for categorical values or mean and median for continuous variables. Clinical and statistical significant correlation between continuous variables was calculated by Spearman's rank correlation test, rs (spearman's correlation coefficient) and p value (2-tailed) were noted. Overall Survival (OS) was defined by the time from the date of death and last control minus the first day of the chemotherapy. Survival curves were estimated according to the Kaplan-Meier method, and log-rank tests were used for univariate statistical comparisons. Adjusted Hazard Ratio (HR) and 95% confidence interval (95% CIs) were used for estimation. Receiver operating characteristic curve analysis was performed to determine the NLR, dNLR and SII cut-off values. The cut-off values for NLR, dNLR and SII was determined for whole group and patients were dichotomized into high and low groups for each parameter with roc analysis. All statistical data were analyzed using the SPSS version 17.0, and a p value of <0.05 was considered statistically significant.

Results

Study Patients

Patient characteristics are shown in Table 1. The median age of the patients was 61 (range 31-81) years and 131 (90.3%) patients were male. All of the patients (n=145) were stage 4. Majority of patients had European Cooperative Oncology Group (ECOG) performance score 0 and 1 (n=65, 44,8% and n=75, 51,7% respectively). 31 (21,4%) patients had cranial metastasis, 83 (57,2%) patients had bone metastasis and 50 (34,5%) patients had liver metastasis. 144 (99,3%) patients were treated with the platinum etoposide combination regi-

Table 1. Patient and Tumor Characteristics

Characteristics	n (%)
Median age	61 (31-81) years old
Gender	
Men	131 (90.3)
Women	14 (9.7)
ECOG Performance Score	
0	65 (44.8)
1	75 (51,7)
2	4 (2,8)
4	1 (0,7)
NLR Value	
Low (<3,275)	74 (51)
High (≥3,275)	71 (49)
dNLR Value	
Low (<1,98)	68 (46,9)
High (≥1,98)	77 (53.1)
SII Value	
Low (<895,3)	67 (46,2)
High (≥895,3)	78 (53,8)
Metastasis Zones	
Liver	50 (34,5)
Cranium	31 (21,4)
Bone	83 (57,2)
Pleura	13 (9)
Adrenal	32 (22.1)
Distant Lymph Node	109 (75,2)

men and 134 patients (92,4%) received cisplatin in combination. The cut-off values for NLR, dNLR and SII was determined for whole group and patients were dichotomized into high and low groups for each parameter. 74 (51%) patients had low NLR score and 71 (49%) patients had high NLR score. 68 (46,9%) patients had low dNLR score and 77 (53,1%) patients had high dNLR score. 67 (46,2%) patients had low SII score and 78 (53,8%) patients had high SII score.

Treatment and Outcomes

The median follow-up time was 10 months and 116 (80%) patients died. Progression-free survival (PFS) and overall survival (OS) were estimated, respectively, as 8 and 12 months (Figs. 1, 2). 70 (48,3%) patients had complete response (CR) at the end of first line platin-etoposide combination treatment. 52 (74,3%) patients had CR at the end of treatment and 18 (25,7%) patients had CR at the interim analysis (after 3 cycle chemotherapy).Treatment outcomes was shown in Table 2.

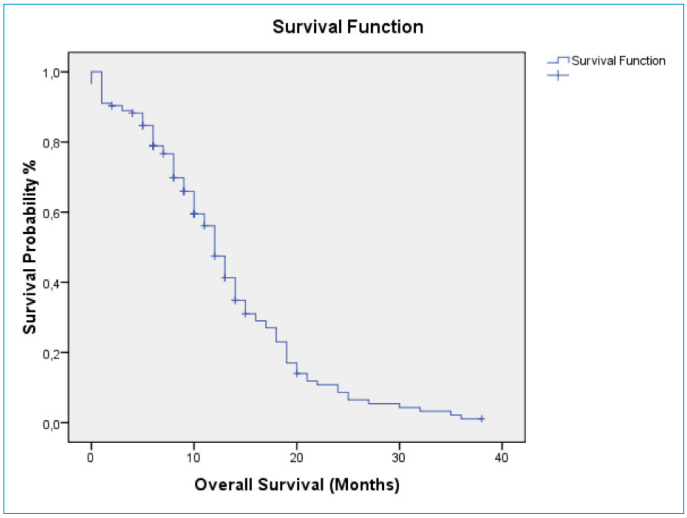

Figure 1. Kaplan–Meier survival curve for overall survival.

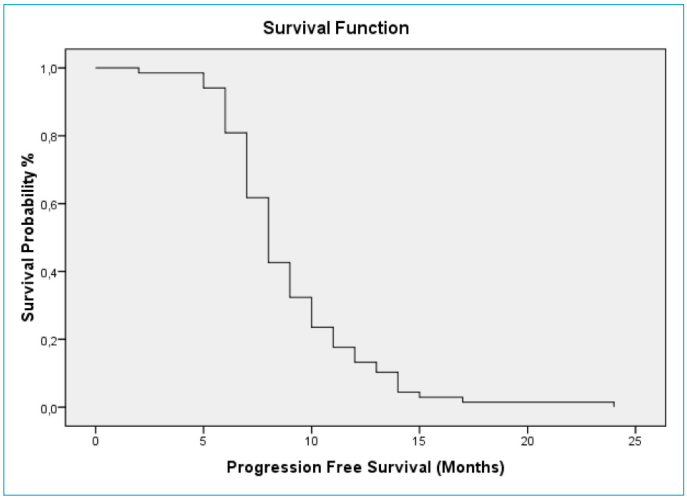

Figure 2. Kaplan–Meier survival curve for progression-free survival.

Table 2. Treatment and Outcomes

Characteristics	n (%)
Chemotherapy Regimen	
Cisplatin-Etoposide	135 (93.1)
Carboplatin-Etoposide	10 (6.9)
Complete Response of 1st line	
Yes	70 (48.3)
No	75 (51.7)
Complete Response Time	
Interim Analysis	18 (25.7)
End of Treatment	52 (74.3)
Disease Recurrence After CR	
Yes	68 (46.9)
No	2 (1.3)
Final Status	
Died	116 (80)
Alive	29 (20)

Patients in the low NLR and low dNLR scores had better overall survival than those with high NLR and high dNLR (14 versus 10 months respectively and p=0,01) (Figs. 3, 4). There was no statistically significant difference in median OS between patients with high SII and those with low SII (13 versus 12 months respectively and p=0,15). There was no statistically significant relationship in terms of PFS for all three inflammatory markers (NLR, dNLR and SII; p=0,40, p=0,83 and p=0,19 respectively). The relationship between NLR, dNLR and SII with survival analysis (OS and PFS) was shown in Table 3 and Table 4. There was no statistically significant relationship between the complete response rates and inflammatory markers (NLR, dNLR and SII; p=0,15, p=0,08 and p=0,37 respectively).

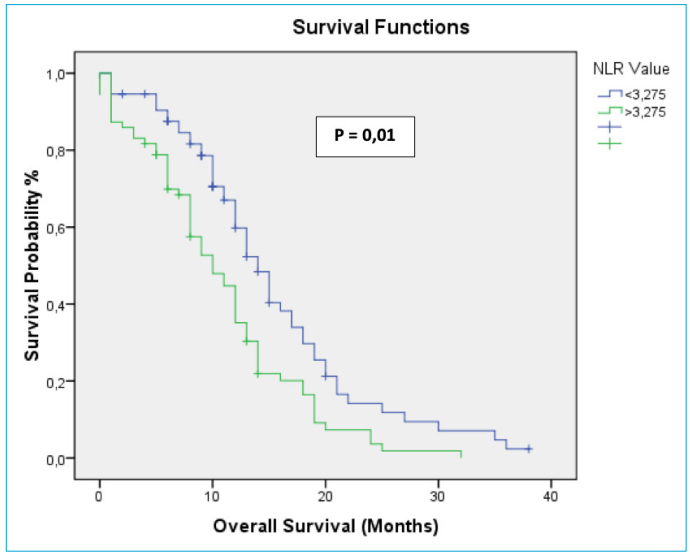

Figure 3. According to NLR value, Kaplan–Meier survival estimates for overall survival.

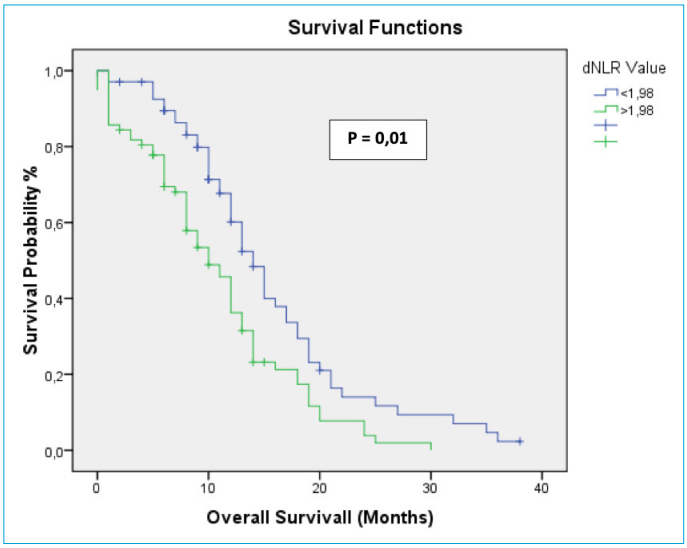

Figure 4. According to dNLR value, Kaplan–Meier survival estimates for overall survival.

Discussion

Most cancers are caused by areas of infection, chronic irritation, and inflammation. In 1863, Rudolf Virchow noticed leukocytes in neoplastic tissues and suggested that the origin of cancer was in sites of chronic inflammation.[3] Today, it is known that inflammation increases the risk of tumor development, triggers the initiation of genetic mutations, and is an important mechanism in tumor progression and metastasis.[4] However, lymphocytes are an essential element of the cell-mediated immune response against cancers.[5] It has been reported that low lymphocyte count is associated with the poor prognosis of cancer patients.[6-8] Since the decrease in lymphocyte count means higher NLR and dNLR scores, the relation of high scores in these scores with decreased survival can be easily understood. In our study, the overall survival of patients with high NLR and dNLR scores was statistically significantly less than those with low scores.

Therefore, it is thought that inflammatory parameters may be good prognostic markers of cancer in recent years. In this study, the pre-treatment NLR, dNLR and SII scores of 145 patients with ES SCLC and their response to platinum-based chemotherapy were analyzed retrospectively. The results showed that the pre-treatment NLR, dNLR score is an independent prognostic factor in patients with SCLC. We have demonstrated that these simple and user-friendly prognostic tools are useful for ES SCLC patients treated with chemotherapy alone.

In a study by Yilmaz et al., NLR was found to be prognostic in terms of overall survival in gastrointestinal stromal tumors.[9] In a study conducted by Capone et al. in patients with advanced malignant melanoma, both NLR and dNLR were shown to be prognostic.[10] Likewise, a meta-analysis by Duan et al., including 21 studies, showed that high NLR and dNLR were associated with poor survival.[11]

There are some limitations such as the retrospective nature of the study and the follow-up of all patients in a single center. Due to the retrospective design, it was not possible to obtain information about whether some patients had comorbid diseases and weight loss. In addition, although the number of patients included in this study was relatively small, these inflammatory indexes were found to be statistically significant. However, multi-center, prospective, large-scale studies should be conducted to verify this result. Second, patient selection was based on the availability of pre-treatment blood tests.

In conclusion, the results of our study show that NLR and dNLR score, which are indicators of systemic inflammation, are useful in evaluating the overall survival of patients with Es SCLC. These inflammatory indices are cost-effective prognostic markers and can be calculated easily. Therefore, it should be included in routine clinical practice.

Disclosures

Ethics Committee Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Gaziantep University Ethical Comittee: 07.10.2020; Number 2020/260.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – A.B.; Design – A.B.; Supervision – A.B.; Materials – A.B.; Data collection &/or processing – A.B., A.K.S.; Analysis and/or interpretation – A.B., A.K.S.; Literature search – A.B.; Writing – A.B.; Critical review – A.B., A.K.S.

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