ARAŞTIRMA MAKALESİ/ORIGINAL RESEARCH

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Can Peripheral Blood Parameters Be a Prognostic Factor in Patients with EGFR Positive Lung Adenocarcinoma?

EGFR Pozitif Akciğer Adenokarsinomlu Hastalarda Periferik Kan Parametreleri Prognostik Faktör Olabilir mi?

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ABSTRACT

Introduction: Complete blood count (CBC) is the most commonly used laboratory test in the clinic. The number and distribution of neutrophils, lymphocytes and monocytes are tests that reflect the inflammatory response and the general immune status of the body. In other types of cancer, the status of the peripheral blood prognostic inflammatory markers; neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), platelet-lymphocyte ratio (PLR), and red cell distribution width (RDW), which were determined to be associated with prognosis and treatment, is still unclear in patients with EGFR mutation-positive lung cancer. This study aims to investigate the prognostic value of NLR, LMR, PLR, and RDW in terms of PFS and OS in EGFR positive adenocarcinoma cases.

Methods: Among the patients with EGFR sensitizing mutations, those who were older than 18 years of age, who were treated with EGFR-TKI in primary care or the secondary care after series 1 chemotherapy, those with pre-treatment complete blood count (CBC) and those who were evaluated by computed tomography every three months were included in the study.

Results: We found that only the high-PLR parameter was a significant independent negative prognostic factor for the OS in EGFR-positive NSCLC patients treated with EGFR TKI (HR 2.18, 95% CI 1.17-4.07, p=0.014).

Dsicussion and Conclusion: In our cohort of patients with EGFR-positive NSCLC treated with EGFR TKIs, a high PLR level (>322) was detected as an independent, poor prognostic factor for OS. However, new and multi-center studies are needed to define theprecise prognostic role of other parameters and PLR in this group of patients.

Keywords: adenocarcinoma, EGFR, blood parameters

ÖZ

Giriş ve Amaç: Akciğer kanseri en agresif tümörlerden biridir ve dünyada kanser ölümünün en önemli nedenidir. Küçük hücreli olmayan akciger kanseri (KHDAK) tüm akciğer kanserinin yaklaşık % 85'ini oluşturur ve KHDAK' li hastaların yaklaşık % 70'i başlangıçta kötü prognozla giden ileri evre hastalık teşhisi ile sonuçlanır. Epidermal büyüme faktörü reseptör tirozin kinaz inhibitörleri (EGFR-TKIs) EGFR mutasyonu pozitif KHDAK hastaları için yeni bir tedavi stratejisi oldu ve progresyonsuz sağkalımı (PFS), ortalama sağkalımı (OS) ve hastalardaki yaşam kalitesini standart platin bazlı kombinasyon kemoterapilerine kıyasla arttırdı. Diğer kanser türlerinde, prognozda etkisi belirlenmiş periferal kan prognostik enflamatuar belirteçlerinin; nötrofil-lenfosit oranı (NLR), lenfosit-monosit oranı (LMR), trombosit-lenfosit oranı (PLR) ve kırmızı hücre dağılım genişliği (RDW), EGFR mutasyonu pozitif akciğer kanseri hastalarındaki durumu halen belirsizdir. Bu çalışma, EGFR pozitif adenokarsinom olgularında PFS ve OS açısından NLO, LMR, PLR ve RDW'nin prognostik değerini araştırmayı amaçlamaktadır.

Yöntem ve Gereçler: EGFR mutasyou saptanan hastalar arasında, 18 yaşından büyük olanlar, birinci basamakta veya bir seri kemoterapi sonrası ikinci basamakta EGFR-TKI ile tedavi edilenler, tedavi öncesi tamkan sayımı (CBC) olanlar ve 3 ayda bir bilgisayarlı tomografi ile değerlendirilenler çalışmaya alındı..

Bulgular: EGFR TKI ile tedavi edilen EGFR pozitif KHDAK hastalarında sadece yüksek PLR parametresinin OS için anlamlı bir bağımsız negatif prognostik faktör olduğunu bulduk (HR 2.18,% 95 CI 1.17-4.07, p = 0.014).

Tartışma ve Sonuç: EGFR TKI'lerle tedavi edilen EGFR pozitif KHDAK hastalarından oluşan kohortumuzda, OS için bağımsız, kötüprognostik faktör olarak yüksek bir PLR seviyesi (> 322) tespit edildi. Bununla birlikte, bu hasta grubunda diğer parametrelerinve PLR'nin kesin prognostik rolünü tanımlamak için yeni ve çok merkezli çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: adenokarsinom, EGFR, kan parametreleri

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INTRODUCTION

Lung cancer is one of the most aggressive tumors and the leading cause of cancer-related deaths in the world (1). Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers. Approximately 70% of patients with NSCLC are at the advanced stage at the time of diagnosis and the prognosis is usually not good (2). In patients with epidermal growth factor receptors (EGFR) sensitizing mutation-positive tumors, better results are obtained with EGFR tyrosine kinase inhibitors (TKIs) in progression-free survival (PFS), overall survival (OS) and quality of life compared to standard platinum-based combination chemotherapies (3-6). However, even in patients with positive EGFR sensitizing mutations, the response rate with EGFR-TKIs is around 70%, and approximately 20-30% of pa- tients have primary resistance to EGFR-TKIs. Therefore, additional predictive markers may be needed to estimate the effectiveness of EG- FR-TKIs (7). According to studies evaluating the relationship between the tumor and the pa- tient's immune system, the inflammatory and immune response roles that occur are import- ant in the emergence, proliferation, and pre- vention of the spread of tumor cells and have seen to be effective in response to treatment and prognosis (8-11).

Complete blood count (CBC) is the most com- monly used laboratory test in the clinic. The number and distribution of neutrophils, lymphocytes and monocytes are tests that reflect the inflammatory response and the general immune status of the body. In other types of cancer, the status of the peripheral blood prognostic inflammatory markers; neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), platelet-lymphocyte ratio (PLR), and red cell distribution width (RDW), which were determined to be associated with prognosis and treatment, is still unclear in patients with EGFR mutation-positive lung cancer (12- 15).

This study aims to investigate the prognostic value of NLR, LMR, PLR, and RDW in terms of PFS and OS in EGFR positive adenocarcioma cases.

MATERIAL - METHODS

Between January 2008 and December 2018, stage IV patients who were histologically or cytologically diagnosed with adenocarcinoma, and examined for the presence of EGFR mutation at the Health Sciences University, Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital, were retrospectively analyzed. EGFR mutation analysis was performed using the Cobas® EGFR Mutation Test. Among the patients with EGFR sensitizing mutations, those who were older than 18 years of age, who were treated with EGFR-TKI in primary care or the secondary care after series 1 chemotherapy, those with pre-treatment complete blood count (CBC) and those who were evaluated by computed tomography every three months were included in the study. Patients with an active infection, inflammatory disorders and those who received systemic steroids before treatment with EGFR-TKI were excluded from the study.

Demographic characteristics of the patients such as age, gender, smoking and EGFR mutation type were obtained from their files. The CBC UniCel DxH 800 (Beckman Coulter) device was used in the study, and the NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, the LMR by dividing the absolute lymphocyte count by the absolute number of monocytes, and the PLR by dividing the absolute platelet count by the absolute lymphocyte count. The red blood cell distribution width (RDW) was recorded from the complete blood count. The treatment with EGFR-TKI was continued until the disease progressed or unacceptable toxicity occurred. The study was approved by the eth-ics committee of the University of Health Sci-

ences Dr. Suat Seren Chest Diseases and Surgery Training and Research Hospital with the 6th decision number at the 8th TUEK meeting dated 10.05.2019 and was conducted under the 1964 Declaration of Helsinki and subsequent amendments as well as Good Clinical Practice Guidelines.

Statistical Analysis

OS was defined as the duration from the start of TKI therapy to death or the last follow-up visit. PFS was defined as the duration from the start of TKI therapy to disease progression, death, or the last follow-up visit. Receiver operating characteristic (ROC), curve analysis and the Youden index were performed to determine the optimal NLR, LMR, PLR and RDW cut-off value associated with the best sensitivity and specificity for the average operating system. The best cut-off values determined by the ROC curve were NLR:2.82 (AUC=0.569, p=0.337), LMR:1.71 (AUC=0.570, p=0.332), PLR:322 (AUC=0.501, p=0.987) and RDW: 14.6 (AUC=0.656, p=0.021). Cases with a value equal to or higher than the specified cut-off value were defined as the "high-value group," and cases with lower values, as the "low-value group". The OS curves were formed using the Kaplan-Meier method and the comparisons between high NLR, LMR, PLR, and RDW versus low NRL, LMR, PLR, and RDW were made using the log-rank test. Univariate and multivariate analyzes were performed to assess the prognostic significance of clinical variables, including NLR. The Kaplan-Meier method and Cox regression were used for survival analysis. Variables with $p<0.2$ in the univariate analysis were entered into the multivariate analysis using a stepwise selection method. A two-tailed $p<0.05$ was considered statistically significant. The statistical analyzes were performed using the MedCalc Statistical Software version 15.8.

RESULTS

The EGFR mutation was detected in 82 (9.09%) of 902 stage 4 lung adenocarcinoma patients (exon 19 deletion, n=43; exon 21 L858R point mutation, n=14; and exon 20, n=2, other, n=23). All cases were included in the study because no cases met the exclusion criteria. Seventeen (20.7%) patients received EGFR TKI treatment in Series 2. 46 (56.1%) of the patients were female, and 52 (63.4%) of them had never smoked. The general characteristics of the patients are given in Tables 1aand b.

Table 1a. The General Characteristics of the Patients

GENDER	n	%
Male	36	43.5
Female	46	56.1
SMOKING STATUS		
Never	52	63.4
Quitted	29	35.4
Active Smoker	1	1.2
EGFR TYPE		
Exon 19	43	52.4
Exon 20	2	2.4
Exon 21	14	17.1
Other	23	28
SURVIVAL		
Alive	22	26.8
Exitus	60	73.2
RDW		
<=14.6	31	37.8
>14.6	51	62.2
NLR		
>2.82	58	70.7
>=2.82	24	29.3
LMR		
>1.71	56	68.3
<=1.71	26	31.7
PLR		
<=322	67	81.7
>322	15	18.3

EGFR: Epidermal Growth Factor Receptors
RDW: Red Cell Distribution Width
NLR: Neutrophil-Lymphocyte Ratio
LMR: Lymphocyte-Monocyte Ratio
PLR: PlateletLymphocyte ratio

Table 1b. The General Characteristics of the Patients

	Median	Min.	Max.
AGE	66.0	36.0	85.0
PFS	11.73	1.0	33.0
OS	21.95	1.0	97.15
RDW	14.75	12.20	22.20
NLR	3.59	0.41	46.67
LMR	2.46	0.05	8.0
PLR	189.11	14.43	905.0

PFS: Progression-Free Survival
OS: Overall Survival

The median PFS of the patients was 11 months (95% CI 1-33) and the median OS was 21.95 months (95% CI 1-97.15). The median OS was 25.16 months (95% CI 16.27-34.06) for the low-NLR group, 25.79 months (95% CI 16.56-35.01) for the high-NLR group, and no significant difference was found (log-rank test, p=0.569). The median OS was 18.53 months for the low-LMR group (95% CI 10.70-26.35) and 28.58 months (95% CI 20.33-36.76) for the high LMR group. When the two values were compared, no significant difference was found (log-rank test, p=0.08). The median OS was 30.06 months (95% CI 21.70-38.42) for the low-PLR group and 20.66 months (95% CI 12.15-29.17) for the high-PLR group (log-rank test, p=0.01). The median OS was 34.26 months for the low-RDW group (95% CI 21.05-47.47) and 23.19 months (95% CI 16.67-29.71) for the high-RDW group (log-rank test, p=0.23) (Figure 1).

In the multivariate analysis, we found that only the high-PLR parameter was a significant in-dependent negative prognostic factor for the OS in EGFR-positive NSCLC patients treated with EGFR TKI (HR 2.18, 95% CI 1.17-4.07, p=0.014) (Table 2).

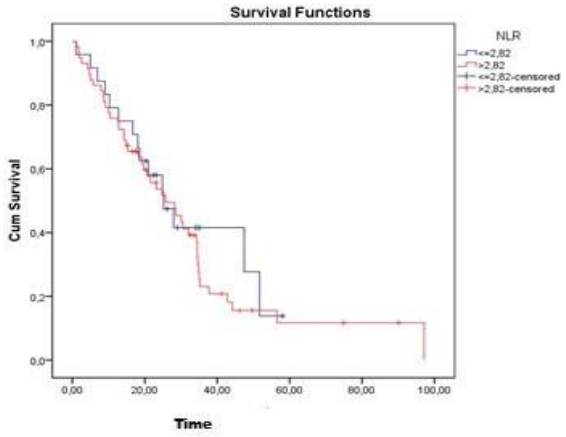


Figure 1A: Overall Survival of NSCLC Patients according to the Retreatment Levels of NLR

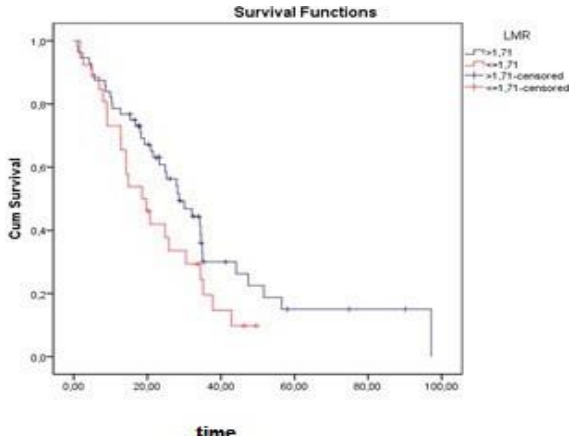


Figure 1B: Overall Survival of NSCLC Patients accordingto the Retreatment Levels of LMR

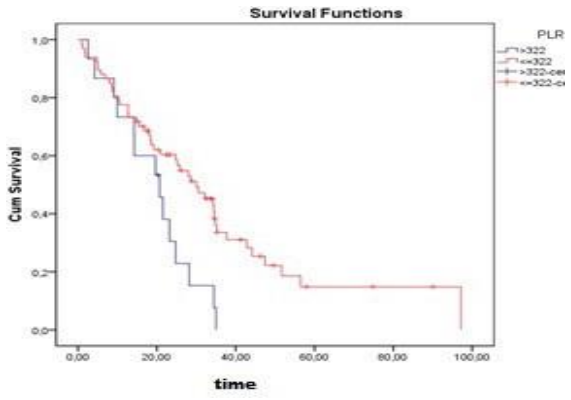


Figure 1C: Overall Survival of NSCLC Patients accordingto the Retreatment Levels of PLR

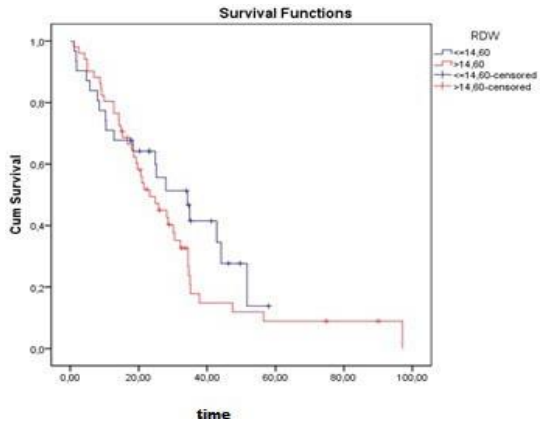


Figure 1D: Overall Survival of NSCLC Patients according to the Retreatment Levels of RD

Table 2. Multivariate Regression Analysis for Overall Survival

		P	HR	% 95 CI	
				Min.	Max.
Step 1	LMR	0.23	1.40	0.80	2.44
	PLR	0.04	1.97	1.03	3.77
Step 2	PLR	0.01	2.18	1.17	4.07

DISCUSSION

There is evidence that easy and cheap peripheral blood parameters reflecting inflammation such as high NLR, low LMR, and high TLR show poor prognosis in many types of cancer(16,17). For lung cancer, it has been shown by many studies that NLR can be a prognostic factor for both early-stage and advanced-stage disease (18-21). However, its prognostic significance in EGFR-positive advanced NSCLC has not been fully addressed, and almost all stuies published to date have been conducted in Asian populations (22-24).

Lin GN et al., in their study including a retrospective analysis of 81 Chinese patients treat- ed with primary care EGFR-TKI (erlotinib or gefitinib), found that high pretreatment NLR values were associated with low PFS and OS (23). Sim SH et al. retrospectively analyzed 85 patients treated with EGFR-TKI and 165 pa- tients receiving chemotherapy in primary care.

In the multivariate analysis, NLR was found to be associated with PFS in the patient group treated with chemotherapy. However, in the patients treated with TKI, NLR was not found to be associated with PFS or ORR (24). Although the number of patients in our study was similar to these studies, NLR was not found to be associated with OS in patients treated with TKI. In the multivariate analysis performed in our study, we determined that the PLR parameter, one of the peripheral blood parameters examined other than the NLR, was a negative prognostic factor for OS in EGFR positive NSCLC patients treated with EGFR TKI. The reason why the NLR did not differ between studies may be ethnic differences.

Berardi et al. (25), in their retrospective study in which they analyzed 401 patients, demonstrated that high NLR is an independent prognostic factor for poor PFS and OS. However, in thisstudy, only a small subset of patients (10%) were EGFR-mutants, so a possible relationshipbetween NLR and survival in mutated patients could not be clearly established. In a study conducted by Thang et al. (26) in 112 patients with advanced-stage EGFR-positive, it was found that NLR and MLR values were significant in evaluating the response to treatment. A positive association between NLR and OS was found in a retrospective study of 152 patients from Japan. (27). In our study, we thought that a significant difference may not have been determined since the lymphocyte-monocyte ratio was examined.

Although there is abundant evidence supporting the effect of NLR on lung cancer prognosis, there is still a lack of specific randomized studies on this subject. Furthermore, there is no precise cut-off point for NLR that can be applied in clinical practice. Almost every study reports its cut-off value for NLR from 2.11 to 5, although the best cut-off value obtained in the meta-analysis appears to be 4. Since there are very few studies on other hematological pa-

rameters, the average values are not yet clear. More studies are needed on this subject (19, 25). In our study, we found the NLR cut-off point as 2.82, which is in line with the literature, We found the cut-off point of PLR, which was determined as a negative prognosis factor, as 322. However, this value needs to be proven with new studies to be conducted withdifferent ethnic groups.

Our study has some limitations. It is a retro- spective study with a relatively small patient sample. Additionally, all patients in our study were collected from a single-center, even though it was the only chest disease hospital inthe region. Moreover, 17 of these patients werepatients who had previously received standard chemotherapy. We found no significant difference between pre-chemotherapy hemogram values and pre-EGFR TKI hemogram parameters of these patients.

The biggest difference of our study is that although there are relatively more published studies evaluating the role of NLR in EGFR-mutant NSCLC patients treated with TKIs, few studies are addressing LMR, RDW and PLR in this respect.

CONCLUSION

In our cohort of patients with EGFR-positive NSCLC treated with EGFR TKIs, a high PLR level (>322) was detected as an independent, poor prognostic factor for OS. However, new and multi-center studies are needed to define the precise prognostic role of other parame- ters and PLR in this group of patients.

Ethics Committee Approval: It was exami- ned with the 6th decision number at the 8thTUEK meeting dated 10.05.2019; It was deemed appropriate for your study to be done inour hospital.

Authors' contributions:

Contrubution Type	Explanation	Contrubutor
Idea	Creating ideas or hypotheses for research and / or articles	Özgür Batum, Ufuk Yılmaz
Design	Planning methods to achieve results	Özgür Batum, Gülru Polat, Sinem Ermin
Check	Supervision and responsibility of the project and the organization of the article and the audience	Ufuk Yılmaz
Sources	Providing "vital" personnel, space, financial resources, tools and equipment for the project	Özgür Batum, Yasemin Özdoğan, Nimet Aksel, Fatma Üçsular
Equipments	Biological materials, reagents and referral patients	Özgür Batum, Eylem Yıldırım, Fevziye Tuksavul
Data collection and / or processing	Taking responsibility for making experiments, following patients, organizing and reporting data	Özgür Batum, Emel Cireli, Zühre Taymaz
Analysis and / or comment	Take responsibility for logical presentation	Ufuk Yılmaz
Literature screening	Take responsibility for literature screening	Özgür Batum, Gülru Polat, Fatma Üçsular
Writer	Taking responsibility for the creation of the whole or the actual part of the work	Özgür Batum
Critical investigation	Before delivering the article, it is necessary to reopen the premise not only in terms of imitation and language, but also in terms of intellectual content.	Ufuk Yılmaz, Özgür Batum

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