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RESEARCH ARTICLE

Association of mean platelet volume (MPV), MPV/PLATELET (PLT) ratio, and lymphocyte/monocyte ratio (LMR) as poor prognostic factor in EGFR-mutant lung adenocarcinoma treated with EGFR tyrosine kinase inhibitor

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ABSTRACT

Association of mean platelet volume (MPV), MPV/PLATELET (PLT) ratio, and lymphocyte/monocyte ratio (LMR) as poor prognostic factor in EGFR-mutant lung adenocarcinoma treated with EGFR tyrosine kinase inhibitor

Introduction: *Platelets (PLT) and host systemic inflammatory response (SIR) are known to be effective in the aggregation of cancer cells and the formation of metastasis. There are studies pointing out to the prognostic efficacy of lymphocyte-monocyte ratio (LMR) showing SIR activation and mean platelet volume (MPV) values indicating platelet activation in various cancer types. We predict that easy-to-access hemogram parameters such as MPV, MPV/PLT, and LMR can be guiding in the clinical follow-up period of patients with epidermal growth factor receptor (EGFR) positive mutation and who received EGFR, tyrosine kinase inhibitor (TKI) in the first-line treatment in predicting the progression of the disease, predicting the survival time of the patients, and evaluating the response to treatment.*

Materials and Methods: *The study is retrospective and included patients with stage III and stage IV pulmonary adenocarcinoma with positive EGFR mutations and for whom TKI was used in the first-line treatment between January 2011 and January 2021. MPV, MPV/PLT, and LMR values of the patients were calculated before treatment. Age, sex, comorbidity, smoking history, TNM stage, metastasis localizations, EGFR mutation types, TKI treatments used in first-line treatment, and MPV, MPV/PLT, and LMR values at the 1st month of treatment were recorded. With Kaplan-Meier, six-month, one-year, three-year, and five-year survival rates, average life expectancy, and 95% confidence intervals for these periods were calculated. Variables that may affect progression and overall survival (OS) were determined by performing univariate and multivariate Cox regression analysis.*

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Results: *One hundred and two patients were included in the study. The mean age of the patients was 64.30 ± 12.6 years. Eighty-four patients were in stage IV at the time of diagnosis. The expected mean progression-free survival (PFS) period of the cases was found to be 13.3 months. The mean life expectancy of the cases was found to be 35.1 months. Web-based Cutoff Finder algorithm written in the R program (http://molpath.charite.de/cutoff) was used to determine the ideal cut points for MPV, MPV/PLT, and LMR. The cut-off values were found to be 7.55 fL for MPV, 0.251 for MPV/PLT, and 2.615 for LMR, respectively. In univariate Cox regression analysis, LMR level lower than 2.615 increased the rate of progression 1.747 times (95% confidence interval: 1.129-2.705) and the death rate 2.056 times (95% confidence interval: 1.217-3.475) (p= 0.012, p= 0.007). The mean PFS LMR cut-off value was 10.3 months, and 15.3 months, and mean OS durations were 25.1 months and 40.8 months for the groups with low and high cut-off values respectively (p= 0.011, p= 0.006 log-rank test). According to the results of multivariate Cox regression analysis, MPV/PLT< 0.251, smoking, presence of pleural and adrenal metastases, and gefitinib treatment were independent factors in determining PFS. The independent factors determining OS in multivariate Cox regression analysis were being male, platelet increase, MPV> 7.55, gefitinib treatment, and smoking.*

Conclusion: *MPV, MPV/PLT, and LMR are potential biomarkers that can be used for the clinical follow-up of lung ADC patients receiving EGFR-TKI treatment.*

Key words: *MPV; MPV/PLT; LMR; PFS; EGFR mutation*

ÖZ

Ortalama trombosit hacmi (MPV), MPV/PLATELET (PLT) oranı, lenfosit/monosit oranının (LMR) EGFR tirozin kinaz inhibitörü ile tedavi edilen ileri evre EGFR-mutant akciğer adenokarsinomunda kötü prognostik faktör ile ilişkisi

Giriş: *Plateletler (PLT) ve konak sistemik inflamatuvar yanıtın (SIR) kanser hücrelerinin agregasyonunda ve metastaz oluşumunda etkili olduğu bilinmektedir. SIR aktivasyonunu gösteren lenfosit-monosit oranı (LMR) ve trombosit aktivasyonunu belirten mean platelet volüm (MPV) değerlerinin, çeşitli kanser türlerinde prognostik etkinliğini gösteren çalışmalar mevcuttur. Epidermal growth factor reseptor (EGFR) mutasyonu pozitif birinci basamak tedavide EGFR tirozin kinaz inhibitörü (TKİ) alan ileri evre akciğer adenokarsinom (ADK) hastalarında, ulaşımı kolay hemogram parametrelerinden MPV, MPV/PLT ve LMR'in; hastaların klinik takip sürecinde hastalığın progresyonunu predikte etmede, sağkalım sürelerini öngörmede, tedaviye yanıt değerlendirmede yol gösterici olabileceklerini öngörmekteyiz.*

Materyal ve Metod: *Bu retrospektif bir çalışmadır. Ocak 2011-Ocak 2021 yılları arasında EGFR mutasyonu pozitif birinci basamak tedavide TKİ kullanılan evre III ve evre IV akciğer adenokarsinom tanılı hastalar çalışmaya dahil edildi. Hastaların tedavi öncesi MPV, MPV/PLT ve LMR değerleri hesaplandı. Hastaların yaş, cinsiyet, ek hastalık, sigara kullanım öyküsü, TNM evresi, metastaz lokalizasyonları, EGFR mutasyon çeşitleri, birinci basamakta kullanılan TKİ tedavileri, tedavinin birinci ayında MPV, MPV/PLT ve LMR değerleri kaydedildi. Kaplan-Meier testiyle altı aylık, bir yıllık, üç yıllık ve beş yıllık sağkalım hızları ve ortalama beklenen yaşam süreleriyle bu sürelere ilişkin %95 güven aralıkları hesaplandı. Progresyon ve genel sağkalıma etkili olabilecek değişkenler, tek değişkenli ve çok değişkenli Cox regresyon analizi ile belirlenmiştir.*

Bulgular: *Çalışmaya 102 hasta dahil edildi. Hastaların yaş ortalamaları 64,30 ± 12,6 yıldı. Seksen dört hasta tanı anında evre IV'tü. Olguların ortalama beklenen progresyonsuz yaşam süresi ise 13,3 aydı. Olguların ortalama beklenen yaşam süresi ise 35,1 aydı. MPV, MPV/PLT ve LMR için en iyi kesim noktalarını belirlemek amacıyla R programında yazılmış web tabanlı Cutoff Finder algoritması (http://molpath.charite.de/cutoff) kullanıldı. Sırasıyla cut-off değerleri MPV için 7,55 fL, MPV/PLT için 0,251 ve LMR için ise 2,615'ti. Tek değişkenli Cox regresyon analizinde LMR düzeyinin 2,615'ten düşük olması progresyon hızını 1,747 kat (%95 güven aralığı: 1,129-2,705), ölüm hızını 2,056 kat (%95 güven aralığı: 1,217-3,475) arttırmaktaydı (p= 0,012, p= 0,007). Ortalama PFS LMR cut-off değerine göre düşük ve yüksek gruplarda sırasıyla 10,3 ay, 15,3 ay, ortalama OS süreleri sırasıyla 25,1 ay, 40,8 ay idi (p= 0,011, p= 0,006 log-rank testi). Çok değişkenli Cox regresyon analizi sonuçlarına göre PFS'yi belirlemede; MPV/PLT< 0,251; sigara kullanımı, plevra ve adrenal metastaz varlığı, gefitinib tedavisi bağımsız faktörlerdir. Çok değişkenli Cox regresyon analizinde OS'yi belirleyen bağımsız faktörler ise; erkek cinsiyet, platelet artışı, MPV> 7,55, gefitinib tedavisi ve sigara kullanımıdır.*

Sonuç: *MPV, MPV/PLT ve LMR, EGFR-TKİ tedavisi alan akciğer ADK hastalarının klinik takiplerinde kullanılabilecek potansiyel biyobelirteçlerdir.*

Anahtar kelimeler: *MPV; MPV/PLT; LMR; PFS; EGFR mutasyonu*

INTRODUCTION

Non-small cell lung cancer (NSCLC) constitutes approximately 80%-85% of all lung cancer cases, with lung adenocarcinoma representing 60% of NSCLC occurrences (1). Pulmonary adenocarcinoma is notably characterized by its aggressive clinical progression. At the time of diagnosis, 47% of lung adenocarcinoma patients are found to be in the metastatic stage, 37% in the locally advanced stage, and only 16% in a stage amenable to surgical intervention (2). Early diagnosis and vigilant clinical follow-up are crucial.

The epidermal growth factor receptor (EGFR) is crucial in mediating angiogenesis, which is essential for

tumor growth and metastasis, as well as regulating fundamental cellular processes such as apoptosis and proliferation (3). EGFR is predominantly expressed in lung adenocarcinoma, and mutations within this receptor serve as significant biomarkers for both the treatment and prognosis of lung cancer (4,5).

The detection of EGFR mutations is pivotal in determining the efficacy of lung adenocarcinoma therapies (6). Over the past 15 years, the development of tyrosine kinase inhibitors (TKIs) targeting EGFR mutations has been shown to extend progression-free survival (PFS) by 10 to 30 months compared to chemotherapy alone (7).

In the context of lung cancer and its subtypes, numerous studies have explored the potential of readily accessible hemogram parameters, along with their inter-parameter ratios, as biomarkers for prognostic assessment. While each hemogram parameter has a distinct association with lung cancer progression, platelets are particularly noteworthy due to their secretion of various cytokines that contribute to cancer cell proliferation, metastasis, and, critically, resistance to EGFR-TKI therapy (8-12).

As first-line EGFR-TKI therapy gains prominence, there is a growing need for readily accessible biomarkers to predict patient prognosis and monitor treatment response. This study aims to evaluate the prognostic value of mean platelet volume (MPV), the MPV/platelet (PLT) ratio, and the lymphocyte-to-monocyte ratio (LMR) in patients with advanced lung adenocarcinoma undergoing first-line EGFR-TKI treatment. The investigation will also consider the roles of platelets and systemic immune-inflammation ratio (SIR) in this context.

MATERIALS and METHODS

This study included patients with advanced-stage lung adenocarcinoma who received TKI therapy as first-line treatment between January 2011 and January 2021 and were confirmed to have positive EGFR mutations at diagnosis. The study was designed retrospectively and was approved by the ethics committee under approval number 2012-KAEK-15/2304, dated May 11, 2021.

EGFR mutation detection was carried out through polymerase chain reaction (PCR) amplification and subsequent DNA sequencing of tumor samples, following standard protocols.

Demographic information, clinical staging according to the 8th edition of the TNM classification system, and the localization of metastases using brain MRI and 18F-FDG PET-CT imaging were systematically recorded. Additionally, data on EGFR gene mutations, including exon deletions and mutation subtypes, as well as the specific TKI treatments administered, were documented.

Laboratory values, including PLT, MPV, lymphocytes, monocytes, C-reactive protein (CRP), lactate dehydrogenase (LDH), and albumin were measured before and after one month of initiating treatment. MPV/PLT ratio and LMR were calculated from these measurements. Statistical analysis was employed to assess whether there were significant changes in these values at the one-month mark.

To identify optimal cut-off points for MPV, MPV/PLT, and LMR, we utilized the web-based Cutoff Finder algorithm (http://molpath.charite.de/cutoff), implemented in the R programming environment. Clinical, demographic, and laboratory data of patients were compared using these established cut-off values to determine their prognostic significance (13).

The total follow-up duration and overall survival (OS) time for each patient were meticulously recorded. Progression-free survival, defined as the interval from diagnosis to the first instance of disease progression or death from any cause, was the primary outcome measure of the study. The secondary endpoint was OS, calculated as the period from diagnosis to death from any cause.

Patients were excluded from the study if they had an active infection at diagnosis, were receiving systemic steroid therapy for any reason, had a concurrent second malignancy, or if their medical records could not be accessed from the file or computer system.

Statistical Analysis

The distribution of continuous and discrete numerical variables was analyzed using the Kolmogorov-Smirnov test and Levene's test, respectively. To assess the impact of the best cut-off points for MPV, MPV/PLT, and LMR on PFS and OS, Kaplan-Meier survival analysis was performed with the log-rank test. This analysis included the calculation of crude survival rates, as well as six-month, one-year, three-year, and five-year survival rates, mean life expectancy, and 95% confidence intervals (CI) for each sub-group.

Cox proportional hazards regression models were employed to investigate the univariate effects of all potential variables on PFS and OS. Subsequently, multivariate Cox proportional hazards models were used to identify the factors with the most significant impact on PFS and OS. All variables with a p≤ 0.10 from the univariate analyses were included in the regression models as potential risk factors. For each variable, the hazard ratio (HR), 95% CI, and Wald statistics were computed.

To determine whether there was a statistically significant change in MPV levels from baseline to the first month, a dependent t-test was conducted. The Wilcoxon signed-rank test was used to assess significant differences in MPV/PLT and LMR levels. Data analysis was performed using IBM SPSS statistics version 25.0 (IBM Corporation, Armonk, NY, USA), with results considered statistically significant at p< 0.05, unless otherwise specified. Additionally, a Bonferroni correction was applied to control for type I error across all multiple comparisons.

RESULTS

In our study, of the 4000 patients diagnosed with lung adenocarcinoma between 2011 and 2021, 102 patients were deemed to meet the inclusion criteria for the study (Figure 1). The mean age of the patients was 64.30 ± 12.6 years, with a median follow-up period of 16.5 months. In the study cohort, 51% (n= 52) were male. Demographic characteristics are detailed in Table 1. MPV minimum-maximum values of the patients were between 5.33 and 12.60 fL (7-11 fL). The minimum and maximum PLT values of the patients were 154 x 10^{-3}/L, -707 x 10^{-3}/L (150 x 10^{-3}/L, -450 x 10^{-3}/L) (Table 2). The optimal cut-off values identified were 7.55 fL for MPV, 0.251 for MPV/PLT ratio, and 2.615 for LMR (http://molpath.charite.de/cutoff). OS rate was 43.1%. The six-month, one-year, three-year, and five-year OS rates were 82.8%, 69.1%, 33.0%, and 26.7%, respectively, with a mean expected OS of 35.1 months. Patients with MPV> 7.55 exhibited significantly shorter OS compared to those with MPV≤ 7.55, with a mean OS of 24.5 months vs 47.3 months (log-rank p= 0.003) (Figure 2). An MPV> 7.55 was associated with a 3.203-fold increase in mortality rate and was identified as an independent adverse prognostic factor for OS (Table 3).

In the multiple regression analysis, additional independent factors influencing OS included the male sex, thrombocytosis, gefitinib treatment, and smoking (Table 3). PFS rate across all cases was 14.7%, with six-month, one-year, and three-year PFS rates of 71.6%, 45.1%, and 6.0%, respectively. The mean PFS duration was 13.3 months.

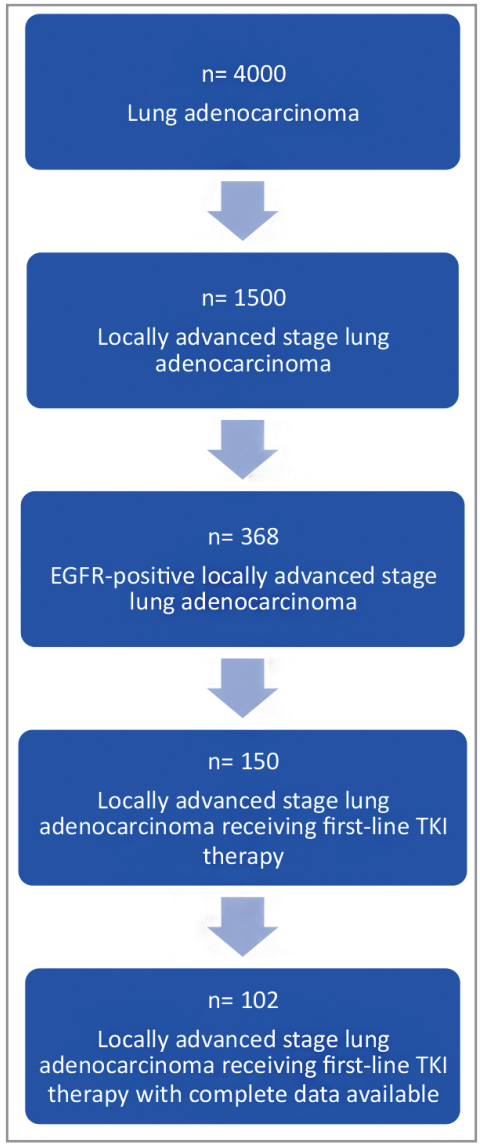

Figure 1. Flow chart.

Univariate Cox regression analysis revealed that patients with an MPV/PLT ratio< 0.251 had a significantly shorter PFS compared to those with higher ratios (mean PFS duration 10.9 months vs. 15.1 months, log-rank p= 0.040) (Figure 3). Multivariate analysis identified a low MPV/PLT ratio as an independent poor prognostic factor for PFS, with an

Table 1. Demographic and clinical characteristics of the cases

	n= 102
Age (year)	64.3 ± 12.6
Age range (years)	31-94
Sex	
Female	50 (49.0%)
Male	52 (51.0%)
Smoking history	
No	44 (43.1%)
Still smoking	21 (20.6%)
Smoked and quitted	37 (36.3%)
Cigarette pack/year	10 (0-120)
Concomitant diseases	
HT	49 (48.0%)
DM	25 (24.5%)
COPD	9 (8.8%)
CAD	9 (8.8%)
Hypothyroidism	5 (4.9%)
Arrhythmia	4 (3.9%)
CHF	3 (2.9%)
Asthma	2 (2.0%)
CKD	2 (2.0%)
CVA	2 (2.0%)
HVD	1 (1.0%)
Progression developing	87 (85.3%)
Mortality	58 (56.9%)
Total follow-up period (month)	16.5 (0.5-84.9)
Stage	
IIIA	5 (4.9%)
IIIB	5 (4.9%)
IIIC	6 (5.9%)
IV	86 (84.3%)
Metastasis sites	
Opposite lung	26 (25.5%)
Pleura	40 (39.2%)
Skeleton	45 (44.1%)
Adrenal gland	12 (11.8%)
Brain	21 (20.6%)
EGFR mutations	
Exon 15	1 (1.0%)
Exon 18	1 (1.0%)
Exon 19	65 (63.7%)
Exon 20	10 (9.8%)
Exon 21	31 (30.4%)
Treatment	
Erlotinib	70 (68.6%)
Afatinib	20 (19.6%)
Gefitinib	10 (9.8%)
Dacomitinib	2 (2.0%)

HT: Hypertension, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, CAD: Coronary artery disease, CHF: Congestive heart failure, CKD: Chronic kidney disease, CVA: Cerebrovascular accident (stroke), HVD: Heart valve disease.

MPV/PLT ratio< 0.251 approximately doubling the risk of progression (Table 4). Other independent adverse prognostic factors for PFS included smoking, gefitinib treatment, pleural metastases, and adrenal metastases (Table 4).

According to univariate Cox regression analysis, patients with a lower LMR than the established cut-off value exhibited worse OS and PFS compared to those with higher LMR (mean OS 25.1 months vs. 40.8 months, log-rank p= 0.006; mean PFS 10.3 months vs. 15.3 months, log-rank p= 0.011). However, in multivariate Cox regression analysis, LMR was not identified as an independent risk factor for either OS or PFS (Tables 3,4).

When comparing clinical characteristics based on cut-off values, CRP levels were significantly higher in the group with MPV> 7.55 compared to those with lower MPV (p< 0.001). Additionally, LDH and CRP levels were elevated in the LMR< 2.615 group (p< 0.001 and p= 0.026, respectively), while albumin levels were reduced (p= 0.011).

A re-evaluation of MPV, MPV/PLT, and LMR levels before the initiation of EGFR-TKI treatment and after one month of treatment revealed a significant decrease in MPV levels (p= 0.030) (Table 5).

DISCUSSION

In our study, we evaluated the prognostic significance of blood parameters (PLT, MPV, lymphocytes, monocytes, CRP, LDH, and albumin) in 102 patients who were identified with an EGFR mutation and received EGFR-TKI therapy. We specifically assessed the MPV/PLT and LMR values before treatment and at the first month of treatment.

Table 2. Descriptive statistics of MPV, MPV/PLT and LMR

					Percentiles		
	Mean	SD	Minimum	Maximum	25	50	75
MPV (fL)	8.4367	1.51046	5.33	12.60	7.2575	8.4500	9.5250
PLT (x10^{-3}/L)	320.5490	109.08282	154.00	707.00	247.2500	300.5000	376.5000
MPV/PLT< 0.251(x10^{-1} %)	0.029384	0.0114407	0.0108	0.0597	0.020292	0.026905	0.036814
Lymphocyte	20.2222	8.60724	2.00	39.00	14.2250	19.8500	26.3000
Monocyte	6.4180	2.14994	1.80	15.30	4.9000	6.2000	7.5000
LMR (%)	3.3379	1.58277	0.51	8.39	2.1469	3.1747	4.2246

PLT: Platelet, MPV: Mean platelet volume, LMR: Lymphocyte-monocyte ratio.

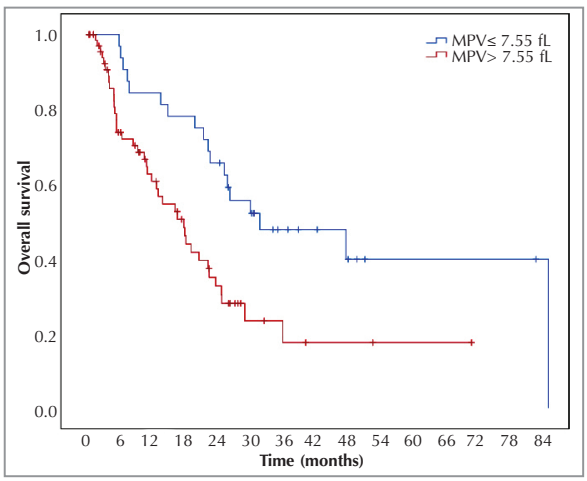

Figure 2. Kaplan-Meier curve of MPV for overall survival.

There is a parallel relationship between platelets and tumor cells. Cytokines secreted by tumors, such as IL-6, IL-1, GM-CSF, and G-CSF, influence the growth and differentiation of megakaryocytes. Activated platelets release vascular endothelial growth factors by activating fibrinolysis and coagulation systems, making platelets more reactive (14). These reactive platelets contribute to the spread of cancer cells and the development of metastasis (8-10). It is also known that the secretion of cytokines such as TGF-β and HGF from these platelets leads to the development of EGFR-TKI resistance (12).

The MPV value, measured in every complete blood count, indicates platelet activation and volume (15). The higher the MPV, the more active and larger the platelets are. The association of high MPV values with systemic inflammation has been established (16). It has also been reported as an indicator of poor prognosis in cardiovascular diseases associated with inflammation (17).

A meta-analysis investigating the relationship between MPV and 12 types of cancer showed that MPV is particularly elevated in endometrial, gastric, thyroid, and lung cancers (18). The relationship between MPV and survival in lung cancer presents varying results in the literature. Some studies have linked low MPV with poor survival, while others have found no association between MPV and survival (19-24).

In our study, we identified high MPV as an independent factor associated with poor OS. Patients with high MPV values had lower survival times.

Omar et al. have reported that patients with elevated MPV levels exhibited shorter PFS and OS in their study of individuals with stage III and stage IV NSCLC (25). Similarly, in a study conducted by Watanabe et al. on patients diagnosed with stage IIIA, stage IIIB, and stage IV lung adenocarcinomas who were receiving first-line TKI treatment for EGFR-positive mutations, an increase in MPV has been found to be associated with reduced PFS (26).

In a study conducted by Shen et al. on patients with NSCLC receiving etoposide-based first-line chemotherapy, high MPV has been identified as an independent factor associated with poor survival (12). The variation in results regarding the relationship between MPV and survival in different types of lung cancer may be attributed to the diversity of patient groups in the studies, differences in genetic mutations, the impact of treatments such as chemotherapy and radiotherapy, and the presence of comorbidities associated with inflammatory processes.

In our study, patients with high MPV levels were observed to have elevated CRP levels. High CRP is an indicator of chronic inflammation, and studies have shown its association with an increased risk of lung cancer (27). Furthermore, a study on NSCLC

Table 3. Effects of all possible factors considered to have an effect on overall survival with univarite and multivariate cox's proportional hazard regression analysis

	Univariate analysis			Multivariate analysis		
	HR (95% CI)	**Wald**	**p**	**HR (95% CI)**	**Wald**	**p**
Age (year)	1.005 (0.985-1.026)	0.252	0.616	-	-	-
Male factor	2.344 (1.365-4.024)	9.541	0.002	3.480 (1.747-6.932)	12.580	**<0.001**
Stage IV	0.909 (0.470-1.760)	0.080	0.778	-	-	-
Distant organ metastases	1.330 (0.785-2.253)	1.121	0.290	-	-	-
Opposite lung metastases	0.949 (0.519-1.736)	0.029	0.865	-	-	-
Pleural metastases	1.468 (0.861-2.502)	1.993	0.158	-	-	-
Skeleton metastases	1.243 (0.734-2.105)	0.656	0.418	-	-	-
Adrenal metastases	1.566 (0.736-3.332)	1.358	0.244	-	-	-
Brain metastases	1.066 (0.564-2.017)	0.039	0.844	-	-	-
Exon 20 mutation	0.509 (0.183-1.414)	1.676	0.195	-	-	-
Erlotinib	1.000	-	-	-	-	-
Afatinib	1.128 (0.555-2.293)	0.111	0.739	0.675 (0.310-1.472)	0.975	0.324
Gefitinib	4.292 (2.021-9.117)	14.365	<0.001	4.143 (1.752-9.800)	10.475	**<0.001**
No smoking history	1.000	-	-	-	-	-
Still smoking	3.151 (1.602-6.199)	11.058	<0.001	2.482 (1.123-5.485)	5.052	0.025
Smoked and quitted	1.143 (0.622-2.100)	0.185	0.667	1.121 (0.561-2.240)	0.104	0.747
PLT($x10^{-3}$/L)	1.003 (1.001-1.005)	6.749	0.009	1.004 (1.002-1.007)	11.808	**<0.001**
MPV (fL)	1.175 (0.993-1.389)	3.541	0.060	-	-	-
MPV> 7.55	2.353 (1.316-4.209)	8.324	0.004	3.141 (1.592-6.194)	10.904	**<0.001**
MPV/PLT ($x10^{-1}$)	0.911 (0.080-10.397)	0.006	0.940	-	-	-
MPV/PLT< 0.251 ($x10^{-1}$ %)	1.298 (0.769-2.190)	0.955	0.328	-	-	-
Lymphocyte	0.982 (0.954-1.010)	1.587	0.208	-	-	-
Monocyte	1.059 (0.957-1.171)	1.238	0.266	-	-	-
LMR (%)	0.847 (0.712-1.007)	3.552	0.059	-	-	-
LMR <2.615 (%)	2.056 (1.217-3.475)	7.251	0.007	1.482 (0.826-2.658)	1.740	0.187

PLT: Platelet, MPV: Mean platelet volume, LMR: Lymphocyte-monocyte ratio HR: Hazard ratio, CI: Confidence interval.

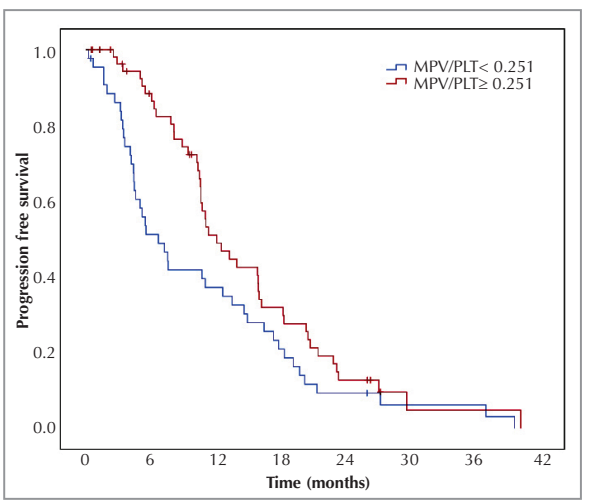

Figure 3. Kaplan-Meier curve of MPV/PLT for progression-free survival.

patients demonstrated that high CRP levels had a negative impact on survival (28). These findings support the inflammatory role of MPV in EGFR-positive lung adenocarcinoma.

In our study, we observed a statistically significant decrease in MPV levels at the first month of EGFR-TKI treatment compared to baseline values. This reduction in MPV after EGFR-TKI therapy has also been noted in the study by Watanabe et al (26). Although the effect of EGFR-TKI therapy on platelets is not well understood, the decrease in MPV values after one month of treatment suggests that MPV may serve as a useful biomarker in evaluating the response to EGFR-TKI therapy.

To minimize the variability in MPV values within groups, some researchers suggest that MPV should

Table 4. Effects of all possible factors considered to have an effect on progression-free survival with univariate and multivariate Cox's proportional hazard regression analysis

	Univariate analysis			Multivariate analysis		
	HR (95% CI)	**Wald**	**p**	**HR (95% CI)**	**Wald**	**p**
Age (year)	0.995 (0.979-1.011)	0.363	0.547	-	-	-
Male factor	1.643 (1.058-2.552)	4.885	0.027	1.605 (0.960-2.682)	3.260	0.071
Stage IV	1.035 (0.600-1.787)	0.015	0.901	-	-	-
Distant organ metastases	1.089 (0.711-1.669)	0.153	0.696	-	-	-
Opposite lung metastases	1.006 (0.614-1.649)	0.001	0.981	-	-	-
Pleural metastases	1.651 (1.057-2.580)	4.846	0.028	2.113 (1.273-3.507)	8.369	**0.004**
Skeleton metastases	1.086 (0.706-1.672)	0.141	0.707	-	-	-
Adrenal metastases	1.775 (0.956-3.296)	3.305	0.069	2.240 (1.162-4.319)	5.796	**0.016**
Brain metastases	1.243 (0.726-2.128)	0.628	0.428	-	-	-
Exon 20 mutation	1.031 (0.515-2.063)	0.007	0.932	-	-	-
Erlotinib	1.000	-	-	1.000	-	-
Afatinib	0.847 (0.477-1.502)	0.324	0.569	0.686 (0.35-1.310)	1.303	0.254
Gefitinib	3.051 (1.478-6.298)	9.099	0.003	3.322 (1.55-7.111)	9.560	**0.002**
No smoking history	1.000	-	-	1.000	-	-
Still smoking	3.057 (1.672-5.590)	13.167	<0.001	2.920 (1.52-5.584)	10.491	**<0.001**
Smoked and quitted	1.241 (0.762-2.022)	0.753	0.386	1.405 (0.81-2.428)	1.483	0.223
PLT ($x10^{-3}$/L)	1.002 (1.001-1.004)	6.658	0.010	-	-	-
MPV (fL)	1.019 (0.890-1.166)	0.071	0.790	-	-	-
MPV> 7.55	1.529 (0.976-2.395)	3.443	0.064	-	-	-
MPV/PLT ($x10^{-1}$)	0.199 (0.028-1.444)	2.548	0.110	-	-	-
MPV/PLT< 0.251 ($x10^{-1}$ %)	1.554 (1.016-2.379)	4.126	0.042	1.735 (1.10-2.737)	5.617	**0.018**
Lymphocyte	0.989 (0.966-1.013)	0.824	0.364	-	-	-
Monocyte	1.043 (0.947-1.149)	0.719	0.396	-	-	-
LMR (%)	0.916 (0.803-1.046)	1.682	0.195	-	-	-
LMR< 2.615 (%)	1.747 (1.129-2.705)	6.264	0.012	1.434 (0.87-2.347)	2.062	0.151

PLT: Platelet, MPV: Mean platelet volume, LMR: Lymphocyte-monocyte ratio, HR: Hazard ratio, CI: Confidence interval.

Table 5. Laboratory measurements of the cases according to follow-up times

	Basal value	**First month of treatment**	**p**
MPV (fL)	8.44 ± 1.51	8.21 ± 1.33	**0.030**†
MPV/PLT ($x10^{-1}$)	0.269 (0.203-0.368)	0.286 (0.212-0.362)	0.663‡
LMR (%)	3.17 (2.15-4.22)	3.22 (2.23-4.08)	0.943‡

PLT: Platelet, MPV: Mean platelet volume, LMR: Lymphocyte-monocyte ratio.
†: Dependent t-test, ‡: Wilcoxon sign test.
Descriptive statistics: Expressed as mean ± standard deviation or median (25^{th} percentile-75^{th} percentile).

always be evaluated in conjunction with platelet count (29). The MPV/PLT ratio has recently been found to be prognostically associated with lung cancer, hepatobiliary cancer, pancreatic cancer, and colorectal cancer (24,26,30).

In a study on NSCLC, the MPV/PLT value was found to be lower compared to the control group, and low MPV/PLT was associated with poor OS (31). Similarly, in our study, we found that low MPV/PLT was associated with poor PFS.

Systemic inflammatory response plays a crucial role in the formation of cancer cells and the progression of metastasis (32). Cytotoxic T lymphocytes are key players in the systemic inflammatory response

against cancer cells, and macrophages derived from monocytes are believed to be associated with tumor progression (33). Chen et al. have demonstrated that a low LMR was correlated with shorter PFS and OS in a study involving EGFR mutation-positive NSCLC patients receiving TKIs as first-line treatment (34). Similarly, Watanabe et al. have found that patients with low LMR values had reduced PFS in a study of individuals with advanced lung adenocarcinoma undergoing first-line TKI therapy for EGFR mutations (26). In our study, although patients with an LMR value below the determined cut-off exhibited an increased rate of death and progression, LMR was not identified as an independent factor in determining these outcomes.

In our study, patients with an LMR value below 2.615 exhibited higher levels of LDH and CRP and lower levels of albumin compared to those with higher LMR values. LDH is recognized as a prognostic marker for tumor burden and distant organ metastasis (35). Hypoalbuminemia is known to be an independent risk factor for prognosis and survival across various cancers, including lung, breast, colorectal, and gastric cancers (36). The elevated CRP, reduced albumin, and increased LDH levels observed in the low LMR group reinforce the association with poor prognosis and high mortality rates.

Our study identified smoking and gefitinib treatment as independent poor prognostic factors for both OS and PFS. Recent research has demonstrated that smoking aberrantly activates the EGFR pathway and contributes to resistance against EGFR-TKI treatments (37). Zhang et al. have conducted a meta-analysis examining the impact of smoking on treatment response in NSCLC patients receiving EGFR-TKI. Their findings indicated that non-smokers had a longer PFS compared to smokers (38).

The limitations of our study include its single-center and retrospective nature, the evaluations being conducted at the first month of EGFR-TKI treatment, and the inclusion of comorbidities associated with inflammatory processes in the study.

The strengths of our study lie in selecting patients with EGFR mutation-positive lung adenocarcinoma who received first-line TKI therapy, thereby minimizing genetic diversity and treatment variability that could affect the parameters (MPV, MPV/PLT, LMR). Additionally, the fact that our center is a reference institution for lung cancer, providing prompt access to TKI therapies, and the management of lung cancer by specialists in pulmonary medicine, are notable strengths of our study.

CONCLUSION

In our study, we identified high MPV and high MPV/PLT as independent prognostic factors in patients with EGFR-positive locally advanced lung adenocarcinoma. We believe that elevated MPV and high MPV/PLT could be useful in indicating poor OS and PFS in these patients and that these metrics may be employed in evaluating responses to TKI therapy.

Ethical Committee Approval: This study was approved by Ankara Keçiören raining and Research Hospital Clinical Research Ethics Committee (Decision no: 2012-KAEK-15/2304, Date: 11.05.2021).

CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: All of authors

Analysis/Interpretation: All of authors

Data acquisition: All of authors

Writing: HGK

Clinical Revision: All of authors

Final Approval: All of authors

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