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Original Research Article

High Pre-treatment Neutrophil-to-Lymphocyte ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) Show Lower Progressive-free Survival and Overall Survival in Tyrosine Kinase Inhibitor-treated Lung Adenocarcinoma

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Abstract

Background: The role of Neutrophil-to-Lymphocyte ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) as an easy and inexpensive prognostic examination modality has different results. While the combination of the two has never been done.

Objective: This study investigated the association between NLR/PLR and outcomes in advanced lung adenocarcinoma Epidermal Growth Factor Receptor (EGFR) mutation-positive with Tyrosine Kinase Inhibitor (TKI) treatment.

Methods: This retrospective study enrolled 40 medical records of lung adenocarcinoma patients treated with TKI in Ulin General Hospital from 2017-2019, with follow-up until April 1, 2021. A receiver operating curve (ROC) was performed to determine the optimal cut-off and parallel tests of NLR/PLR combination. The Kaplan-Meier was used to evaluate the impact on progressive-free survival (PFS) and overall survival (OS).

Results: The optimal cut-off was 6.25 for NLR and 451.5 for PLR with sensitivity and specificity of PFS (31.6%, 100%, and 18.4%, 100%) and OS (32.4%, 100% and 8.9%, 100%) (AUC 0.362, 0.329 and 0.482, 0.477) respectively. Patients in NLR <6.25 and PLR <451.5 groups presented longer PFS (10 months, 95% CI:7.783 -12.217, vs. 8 months, 2.908-13.092, p=0.821; 10 months, 7.508 – 12.492 vs. 9 months, 6.434-11.566, p=0.513) and OS (20 months, 14.017-25.983 vs.16 months, 11.474-20.526, p=0.378; 20 months, 14.629-25.371 vs. 14 months, 3.735-24.265, p=0.382) but not significantly correlated.

Conclusion: High pre-treatment NLR and PLR showed shorter PFS and OS, although not significant as a prognostic marker for PFS and OS of EGFR-mutant lung adenocarcinoma treated with TKI.

Keywords:
Lung Adenocarcinoma; NLR; PLR; progressive-free survival; and overall survival
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INTRODUCTION

About 85% of new lung cancer cases are non-small cell lung cancer (NSCLC). One of the most typical forms of NSCLC is adenocarcinoma.[1] One type of adenocarcinoma is with an Epidermal Growth Factor Receptor (EGFR) mutation. The highest frequency of EGFR mutations was found in Asia (51.4%). This mutation is most commonly found in women who are not smokers. Consideration for examining mutations in never-smoker Asian females diagnosed with lung adenocarcinoma was recommended before initiation of first-line therapy for advanced NSCLC.[2,3]

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EGFR-Tyrosine Kinase Inhibitor (TKI) is the first-line therapy in NSCLC patients with EGFR mutations. EGFR-TKI offers a better quality of life in lung cancer patients than chemotherapy.[4] Treatment with EGFR TKI will provide a more prolonged overall survival (OS) if the type of lung cancer is adenocarcinoma, younger ageless advanced clinical stage, and there are fewer comorbidities. It was suggested that adenocarcinoma with EGFR TKI has a better life expectancy.[5] However, more research is needed regarding the modalities of prognostic examinations that are easy and cheap to determine the best intervention.

A routine haematological examination has become necessary in patient management. Assessment of Neutrophil-to-Lymphocyte ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) as inflammatory markers are often used to assess stratification and prognostic in patients with malignancies. The development and tumor growth was highly indicated by marker driven by inflammation, such as NLR and PLR. A large cohort study in Korea found a relationship between NLR and lung cancer deaths in lung cancer-free adults.[6] Some studies on different subjects have been done. A study in NSCLC advanced patients, not specific to any therapeutic modalities,[7] and with modalities of immune checkpoint inhibitor therapy (nivolumab and pembrolizumab),[8,9] found that NLR and PLR were significantly related to PFS and OS. Research on NSCLC with surgically resected non-small cell lung cancer found that NLR and PLR were associated with OS.[11] Several studies that assessed NLR and PLR as prognostic markers in NSCLC showed different results.[6–8]

There has been limited research on lung adenocarcinoma treated by EGFR TKI. A study in adenocarcinoma treated with TKI found NLR related to PFS.[9] The combination of NLR and PLR against PFS and OS in EGFR-TKI-treated lung adenocarcinoma patients has not been conducted in previous studies.[10] This study investigated the association between NLR, PLR, and parallel test of both the PFS and OS in advanced lung adenocarcinoma EGFR mutation-positive with TKI treatment. This study was essential to maximize the management of lung adenocarcinoma patients.

MATERIALS AND METHODS

Study Design and Subjects

This is observational analytic research with cohort retrospective design. The sample population was 40 adenocarcinoma lung cancer patients newly diagnosed with positive EGFR mutations who will undergo TKI therapy at Ulin General Hospital. This study data was from outpatient and inpatient medical records of patients treated at Ulin General Hospital from January 2017 to December 2019. This study was conducted with the subject's inclusion: adenocarcinoma lung cancer patients with positive EGFR mutations who received TKI target therapy at Ulin General Hospital from January 1, 2017, to December 1, 2019, and followed until April 1, 2021. The exclusion criteria were (1) Adenocarcinoma lung cancer patients with positive EGFR mutations who had previously undergone targeted TKI therapy or received chemotherapy. (2) Diagnosed with hematological malignancies (3) Diagnosed with infection (4) Got additional corticosteroid therapy or other immunosuppressant drugs.

Table 1. Characteristicsof Subjects

Characteristic	N (%)
Age	
<50	8 (20)
≥50	32 (80)
Gender	
Male	28 (70)
Female	12 (30)
Smoking Status	
Smokers	25 (62.5)
Non-smokers	15 (37.5)
Tumor Stage	
IIIC	1 (2.5)
IVA	39 (97.5)
EGFR Mutation status	
18	0 (0)
19	26 (65)
20	0 (0)
21	14 (35)
ECOG Performance Status	
0	2 (5)
1	37 (92.5)
2	1 (2.5)
TKI	
Afatinib	12 (30)
Erlotinib	2 (5)
Gefitinib	26 (65)

ECOG, Eastern Cooperative Oncology Group; TKI, Tyrosine Kinase Inhibitor.

Data Collection

Positive EGFR Mutation was defined by the detection of EGFR mutations based on PCR test from Formalin-Fixed Paraffin-Embedded (FFPE) blocks or cytology specimens of the patients with lung adenocarcinoma. DNA was assayed using Polymerase Chain Reaction (PCR) Rotor-Gene Q system (Qiagen, Hilden, Germany) with Qiagen therascreen® EGFR RGQ PCR kit (Qiagen, Manchester, UK) to qualitatively detect the following 29 somatic mutation on exon 18, 19, 20, and 21 mutations. NLR was determined by the count of neutrophils divided by the count of lymphocytes. PLR was determined by the total number of platelets divided by lymphocytes. Progression-free survival (PFS) was defined as the length of time during and after the treatment that the condition does not worsen or progressive. Overall Survival (OS) was the length of time from either the date of diagnosis and the patients are still alive.

Table 2. Cut-Off Value, Sensitivity and Specificity of NLR and PLR with ROC Curve Analysis

Variable	*Cut Off*	PFS				OS			
		Sensitivity (%)	**Specificity (%)**	***AUC***	**P-Value 95% CI**	**Sensitivity (%)**	**Specificity (%)**	***AUC***	**P-Value 95% CI**
NLR	6.25	31.6	100	0.362	0.515 (0.200-0.524)	32.4	100	0.482	0.918 (0.253-0.711)
PLR	451.5	18.4	100	0.329	0.420 (0.088-0.569)	18.9	100	0.477	0.898 (0.187-0.768)
NLR+ PLR	-	31.6	100	0.395	0.620 (0.211-0.579)	32.4	100	0.523	0.898 (0.280-0.765)

CI, Confidence Interval

Table 3. Clinicopathology Characteristic based on NLR and PLR

Variable	NLR			PLR		
	<6.25	**≥6.25**	***P Value***	**<451.5**	**≥451.5**	***P Value***
Age						
<50	7	1	0.369	7	1	1.0
≥50	21	11		26	6	
Gender						
Male	8	4	1.0	10	2	1.0
Female	20	8		23	5	
Smoking Status						
Non-smokers	11	4	1.0	13	2	0.691
Smokers	17	8		20	5	
Mutation Status						
Del – 19	19	7	0.720	21	5	1.0
Exon 21 L858R	9	5		12	2	

Fisher exact test

Data Analysis

The normality of data was analyzed using the Shapiro-Wilk test. Determination of the optimal cut-off value of NLR and PLR for PFS and OS uses Receiving Operating Characteristics (ROC) Curves. A parallel test of NLR and PLR was also performed against PFS and OS using ROC curves. NLR and PLR are categorized according to the cut-off point and tested with chi-square or Fisher exact test. NLR and PLR's relationship with Median Survival Time (MST) in PFS and OS were analyzed using Kaplan–Meier's analysis. The difference in each survival time is assessed based on the log-rank test.

This research was approved by Health Research Ethics Committee of Ulin General Hospital, Universitas Lambung Mangkurat (No.50/VII-Reg Riset/RSUDU/2021).

RESULTS

There were a total of 40 subjects included in this study with clinical characteristics in table 1 showed that the majority of the sample was over 50 years old (80%), male (70%), smoker (62.5%), stage IVA (97.5%) with exon mutation 19 (65%), and has Eastern Cooperative Oncology Group Performance Status (ECOG PS) 1 (92.5%). The most frequent use of TKI was gefitinib at 65%, afatinib at 30%, and erlotinib at 5%.

As seen in table 2, we found the same cut-off value of NLR for PFS and OS, 62.5, while PLR for PFS and OS is also the same, which is 451.5. In parallel tests, showing concurrent assessment of NLR and PLR values can increase sensitivity and specificity to PFS and OS.

Analysis of clinicopathological characteristics associated with NLR, PLR and PFS, and OS

Patients with high NLR and high PLR were found at age ≥50, male sex, smoker, and exon mutation 19 (table 3). However, there were no significant differences in NLR and PLR values based on clinicopathological characteristics.

Based on table 4, ages over 50 years, females, smokers, exon deletion mutation 19, and treated with erlotinib were found to have a longer PFS time, but there was no significant difference. Meanwhile, the longer OS was obtained in female patients, smoking and using the erlotinib type of TKI but did not significantly different.

Analysis of NLR and PLR with PFS and OS

The analysis of NLR and PLR values with PFS was described in table 5. Kaplan Meier's curve analysis in figure 1 (A) and (B) showed median PFS in the group with NLR <6.25 was 10 months (95% CI: 7.783 – 12.217), and the group with NLR ≥ 6.25 was eight months (95% CI: 2.908–13.092). PFS in groups with PLR <451. 5 was 10 months (95% CI: 7.508–12.492),

Table 4. Potential Factor of Characteristic Clinicopathology related to PFS and OS

Variable	*Progression-Free Survival*			*Overall Survival*		
	N	**MST(months)**	**P**	**N**	**MST (months)**	**P**
Age						
<50	8	9	0.952	8	19	0.777
≥50	32	10		32	19	
Gender						
Male	28	8	0.774	12	14	0.944
Female	12	10		28	20	
Smoking Status						
Non-smokers	15	9	0.944	15	15	0.826
Smokers	25	12		25	23	
Mutation Status						
Del – 19	26	12	0.221	26	19	0.286
Exon 21	14	7		14	19	
TKI						
Afatinib	12	10	0.099	12	24	0.494
Gefitinib	26	8		26	19	
Erlotinib	2	13		2	25	

MST, *Median Survival Time.* TKI, *Tyrosine Kinase Inhibitor*

Table 5. The Univariate Analysis between NLR and PLR for PFS and OS

Variables	*Progression-Free Survival*			*Overall Survival*		
	Median	**95% CI**	***P value***	**Median**	**95% CI**	***P value***
NLR < 6.25	10 months	7.783 – 12.217	0.821	20	14.017-25.983	0.378
NLR ≥ 6.25	8 months	2.908 – 13.092		16	11.474-20.526	
PLR < 451.5	10 months	7.508 – 12.492	0.513	20	14.629-25.371	0.382
PLR ≥ 451.5	9 months	6.434 – 11.566		14	3.735-24.265	

CI, Confidence Interval

and the group with PLR ≥ 451.5 was 9 months (95% CI: 6.434–11.566). The difference in PFS between high and low NLR and PLR is not significant.

The analysis of NLR and PLR with median OS was in table 5, with Kaplan Meier in Figure 1 (C) and (D). Groups with NLR <6.25 obtained median OS 20 months (95% CI: 14.017-25.983), the group with NLR ≥6.25 obtained the median OS 16 months (95% CI: 11.474-20.526). A group with PLR ≥451.5 obtained an median OS of 14 months (95% CI: 3.735-24.265), while PLR <451.5 had a longer median OS of 20 months (95% CI: 14.629-25.371). However, the difference in the length of OS between the two NLR and two PLR groups was not significant.

DISCUSSION

Based on sample characteristics in adenocarcinoma patients with positive EGFR mutations who underwent TKI therapy in the period 2017 to 2019, this study was, on average, over 50 years old. In accordance with other research, lung adenocarcinoma patients with EGFR mutations were more common in the population of patients ≥ age 50 years.[13] The findings of the present study was also in accordance with a study conducted in dr. Soetomo General Hospital which found that most adenocarcinoma patients were male active smokers with age ≥ 50 years.[11] In this study, the most common type of mutation was the deletion of Exon 19 in both men and women.

Several studies on NLR and PLR as prognostic biomarkers in NSCLC treated with different therapeutic modalities have been conducted. Prognostic biomarkers studied in advanced NSCLC patients, not specific in therapeutic modalities, found that high NLR and PLR are significantly associated with poor OS. High NLR is significantly associated with poor OS post-treatment.[7] Another study on NSCLC subjects treated with immune checkpoint inhibitors (nivolumab and pembrolizumab) found that high NLR and PLR pre-treatment values were independently associated with shortening PFS and OS.[9] In NSCLC patients treated with nivolumab, it was found that the increase in NLR and PLR was associated with shorter PFS and OS. While patients with surgically resected NSCLC found that NLR and PLR were associated with OS, only Systemic Inflammation Index (SII) was promising as a prognostic predictor for patients with surgically resected, and its significance persisted only in subgroups of pulmonary adenocarcinoma. [12] In NSCLC with dominant subtype epidermoid carcinoma on the sample, NLR values were independently associated only with survival disease, and PLR was associated with only overall survival.

There was only one study on the subjects of EGFR mutation lung adenocarcinoma treated with EGFR TKI and found NLR, PLR, and SII were predictors of PFS; however, only SII was a predictor in the OS. The cut-off values found in the study were ≥4.40 (NLR) and ≥182.595 (PLR).

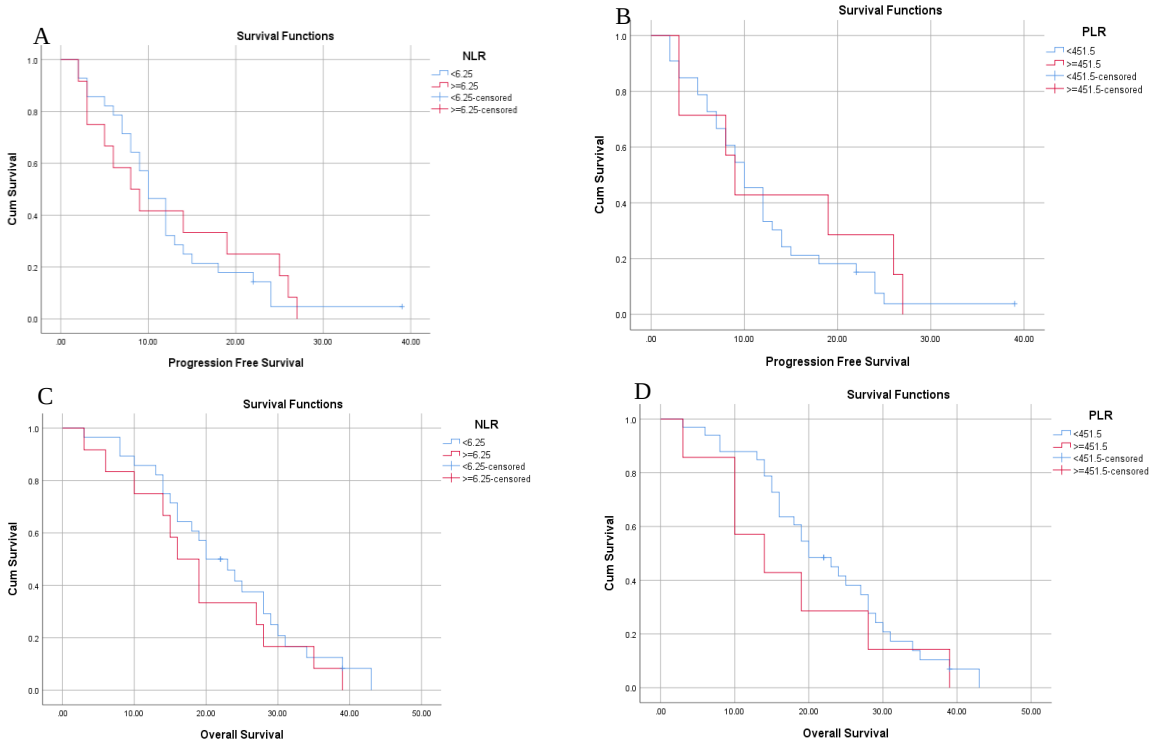

Figure 1. *Kaplan–Meier* curves of PFS according to NLR (A) and PLR (B), and OS according to NLR (C) and PLR (D).

Several characteristic variables in NSCLC subjects affect NLR and PLR values, including ECOG PS related to higher NLR and smoking history related to higher PLR.[10]

The present study found that the characteristics of subjects, such as age, gender, smoking status, and mutation status, were not significantly associated with high NLR and high PLR. With the cut-off values of ≥6.25 (NLR) and ≥451.5 (PLR) that we found, Kaplan Meier analyzed log-rank tests and found no significant differences in PFS and OS. However, both show shorter median values in high NLR groups and high PLR. So far, there are minimal publications of research on lung adenocarcinoma subjects with EGFR mutations.

In this study, a parallel test combining NLR and PLR values in adenocarcinoma patients found an increase in Area Under the Curve (AUC) to 0.523 (sensitivity=31.6%, specificity=100%), higher than the use of NLR or PLR alone. A study combining prognostic NLR and PLR scores in NSCLC subjects found that higher NLR was associated with poor prognosis. Low to normal NLR with high PLR was related to moderate risk, while lower NLR and lower PLR were an excellent prognosis.[12]

The relationship between NLR and PLR to the OS showed no significant relationship. Lower and higher NLR has OS 20 and 16 months, respectively. Meanwhile, lower and higher PLR had OS of 20 and 14 months, respectively. In a previous study, a significant relation was not found in PLR with OS, 29 months in low PLR and 17.3 months in high PLR. There were significant results in NLR and SII with longer OS in low-value groups. There have not been many other studies with similar research subjects compared to this study.[10] The difference in the results of this study compared with the previous studies could be caused by several factors. As is known, NSCLC is a type of 85% of lung cancer, and adenocarcinoma is the most common NSCLC. The incidence of EGFR mutations in the lung cancer subgroup adenocarcinoma in Asia-Pacific also has the highest frequency of 47%, and many factors can affect prognostic patients.[13] However, the characteristics of clinicopathology (age, gender, smoking status, type of mutation, and type of TKI therapy) in this study showed no meaningful relationship with the PFS and OS, indicating that it was not significant to interfere with the research.

Another factor related to PFS and OS but not assessed in this study was the nutritional status of subjects where systemic inflammation due to cancer is known to affect immune status while inducing metabolic disorders and resulting in malnutrition. Cancer-related cachexia also affected prognosis.[14] Cachexia was frequent in advanced cancer patients, corresponding with reduced life and bad prognosis.[15] As a complication of cancer, cachexia manifests as a loss of muscle and fat mass.[16] Another study examining immune-inflammation-nutritional parameters (PNI) was significantly associated with overall survival.[17]

Another factor that can be related to prognosis is the type of mutation; a *multi-centre* study in Korea showed that the most EGFR mutations were Exon-19 (51%) followed by Exon-21 (42%). Deletion of Exon-19 is the only significant factor that decreases mortality, while mutation of Exon-21 is associated with the highest increase in mortality.[18] In this study, all samples that did not experience progressiveness in this study also had a type of deletion exon-19 only. Although the type of lung cancer has been homogeneous in previous studies, the kind of mutation with a different potential effect on prognosis may be one factor affecting the outcomes.

Other studies showed a prognosis link with genes and protein markers that play an essential role in lung adenocarcinoma, i.e.: UBE2C, MCM2, MCM6, FEN1, and TPX.[18] Other research on gene *signatures* demonstrates strong prognostic abilities and can be an independent predictor for lung adenocarcinoma patients in all datasets except GSE31210. In addition, the gene *signature* can predict lung adenocarcinoma patients' overall survival (OS) in different subgroups.[19] The identification of numerous inactivating mutations in genes that regulate the epigenome was a recent result of whole exome sequencing of thousands of patient malignancies. These mutations may affect nucleosome placement, histone modifications, and DNA methylation patterns, altering gene expression. Given that epigenomes play a significant part in the hierarchy of gene regulatory mechanisms, mutations may affect various pathways connected to the cancer phenotype.[20] These gene protein markers were also associated with poor prognoses; we have not studied them further. More research about other related factors like nutritional state and genetic factors needs to be done to confirm further research.

CONCLUSION

In conclusion, high pre-treatment NLR and PLR showed slightly shorter PFS and OS, although they were not significant as a prognostic marker for PFS and OS of EGFR-mutant lung adenocarcinoma treated with TKI.

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