ORIGINAL ARTICLE

Prognostic Value of the Systemic Immune-Inflammation Index in EGFR Mutation-Positive Lung Adenocarcinoma Patients Treated with Tyrosine Kinase Inhibitors

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ARTICLE INFO

Article history:
Received 21 May 2022
Received in revised form
13 September 2022
Accepted 28 September 2022
Available online 30 September 2022

Keywords:
Cancer,
Lung adenocarcinoma,
Systemic immune-inflammatory index,
Tyrosine kinase inhibitors.

ABSTRACT

Introduction: Inflammatory parameters calculated from complete blood counts such as neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and systemic immune-inflammatory index (SII) are related to poor prognosis in lung cancer patients. This study aimed to explore a correlation between NLR, PLR, and SII to survival rates in advanced lung adenocarcinoma with tyrosine kinase inhibitors (TKIs) as the main treatment choice.

Methods: This was a retrospective observational study of patients with epidermal growth factor receptor (EGFR) mutation-positive lung adenocarcinoma treated by TKIs at Ulin General Hospital Banjarmasin from January 2017 to December 2019. The optimal cut-off values for NLR, PLR, and SII were obtained using the receiver operating characteristic curve (ROC). Kaplan–Meier analyses were used to assess the prognostic value of inflammation parameters in overall survival (OS) and progression-free survival (PFS).

Results: This study involved 50 samples, 62% male, with an average age of 55.98 years old, 94% in stage IVA, EGFE mutation in exon 19 (58%) and exon 21 (42%). About 58% of patients have a smoking history. The optimal cut-off value for NLR, PLR, and SII was 6.095, 356.935, and 1767.0, respectively. However, only the SII was significantly associated with survival; SII ≥ 1767.0 correlated with shorter OS (18 months vs. 28 months, p = 0.014) and PFS (7 months vs. 12 months, p = 0.004).

Conclusion: Pre-treatment SII can be a prognostic factor for survival in EGFR mutation-positive lung adenocarcinoma patients receiving TKIs.

INTRODUCTION

Lung cancer is the main cause of death from cancer cases worldwide, with the incidence rate being ranked first in 2020.[1] Non-small cell lung carcinoma (NSCLC) cases are found in approximately 85%, with adenocarcinoma being the most common type. NSCLC cases have a low survival rate because they are often diagnosed late.[2] Epidermal growth factor receptor (EGFR) mutation-positive are found in 10-35% of patients with tyrosine kinase inhibitors (TKI) treatment as the main choice. It was strongly associated with Asians, non-smokers, and females.[3–5] The two main types of mutations are deletions at exon 19 and point mutations L858R at exon 21.[2,3] In Indonesia, especially at Ulin General Hospital Banjarmasin, 40% positive EGFR mutations were found in 2017-2018.[6] However, the most challenging in using TKI is that all patients who initially improve with the treatment can develop resistance and indicate disease progression later in life.[4,6]

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Jurnal Respirasi (Journal of Respirology), p-ISSN: 2407-0831; e-ISSN: 2621-8372.
Accredited No. 200/M/KPT/2020; Available at https://e-journal.unair.ac.id/JR. DOI: 10.20473/jr.v8-I.3.2022.133-139

The role of cytokines has been known to be a major contributor to tumorigenesis, especially in cancer cells. Several previous studies have found a correlation between inflammatory parameters and NSCLC. Specifically, previous studies have found that the inflammatory parameters calculated from complete blood counts (CBC), such as neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), as prognostic factors of survival rates in cancer patients.[7,8] Neutrophils have pro-oncogenic behavior. They also act as an important mediator of local inflammation in cancer and promote tumorigenesis and metastasis. Interleukin (IL)- 1, IL-8, growth-related oncogene protein-alpha/chemokine (C-X-C motif) ligand 1 (GRO- α/CXCL1), and macrophage inflammatory protein-1 alpha/chemokine (C-C motif) ligand 3 (MIP-1α/CCL3) are several cytokines that have been shown to increase neutrophil recruitment (neutrophilia) and suppress systemic lymphocyte counts (lymphopenia).[9,10] Systemic neutrophilia and lymphopenia are correlated with a poorer prognosis in cancer patients.[10–12] Thrombopoietin (TPO) is overproduced by tumor cells and indirectly mediated by IL-6 and other cytokines. Furthermore, TPO will stimulate the production of platelets and then release them into the systemic circulation. The activated platelets attach to tumor cells to protect tumors from Natural Killer cells (NK cells) attack and help the process of metastasis.[13]

Inflammatory parameters such as NLR and PLR only combine two kinds of inflammatory cells. Therefore, SII, which combines lymphocytes, neutrophils, and platelets, has a better value than NLR and PLR. Several previous studies have also concluded that SII is an independent prognostic marker in NSCLC patients.[8,14] The SII is an easy test, inexpensive, and widely available as part of a CBC. We have not encountered any study in the literature observing the relation between NLR, PLR, and SII with survival in EGFR mutation-positive lung adenocarcinoma patients receiving TKIs in Indonesia during our literature research. As far as we know, this study is the first in Indonesia.

METHODS

Patient Selection

This was a retrospective study of EGFR mutation-positive lung adenocarcinoma patients receiving TKIs at Ulin Regional General Hospital Banjarmasin, Indonesia, between January 2017 and December 2019. We collected data from medical records or contacted by phone. The patients harboring EGFR-positive mutation exon 19 and 21 and complete data of pre-treatment CBC results were included in this study. The exclusion criteria were clinical evidence of acute infection and a history of hematological malignancy. Consequently, 50 patients were analyzed in this study. The Ethics Committee of Ulin General Hospital approved this study (No. 30/VI-Reg Riset/RSUDU/21).

Data Collection

We extracted the patient's characteristics from medical records, including age, gender, stage of disease, EGFR mutation status, Eastern Cooperative Oncology Group Performance Status (ECOG PS) score, smoking history, type of EGFR-TKIs, and CBC before TKIs therapy. We calculated the NLR, PLR, and SII as follows: NLR = neutrophil count/lymphocyte count, PLR = platelet count/lymphocyte count, and SII = neutrophil count × platelet count/lymphocyte count. The period from the patient's first diagnosis to death from any cause or last follow-up was defined as overall survival (OS). Meanwhile, the period from the date of the first diagnosis to the date of disease progression or last follow-up was defined as progression-free survival (PFS).

Statistical Analysis

The optimal cut-off values for NLR, PLR, and SII were obtained using the receiver operating characteristic (ROC) curve. The Kaplan-Meier method was used to analyze survival rates (OF, PFS), and differences among the curves were compared using log-rank tests. p values <0,05 were considered significant. All analyses were performed using SPSS software 25.0.

RESULTS

Patient Characteristics

There were 50 patients included. The majority of the study subjects consisted of 31 (62.0%) males and 19 (38.0%) females. The median age was 56.5 years old (range: 33–73 years old). In this study, it was dominated by exon 19 deletion mutations (58.0%), with stage IVA (94.0%) and ECOG score 1 (84.0%). There were 29 (58.0%) patients with a smoking history and 32 (64.0%) patients who received gefitinib treatment.

The Cut-Off Value of NLR, PLR, and SII and Their Correlation with Patient Characteristics

The median NLR was 5.7 (1.7-2.0), the median PLR was 381.45 (107.64-1474), and the median SII was 1674.65 (470–6782.07). The areas under the ROC curves (AUCs) were 0.511, 0.373, and 0.653 for the NLR, PLR, and SII. The cut-off value was 6.09 for NLR, 356.93 for PLR, and 1.767.0 for SII (Figure 1).

In this study, NLR, PLR, and SII did not significantly associate with age, gender, stage of disease, EGFR mutation status, ECOG score, smoking status, and type of EGFR-TKI using the previously obtained cut-off values (Table 2).

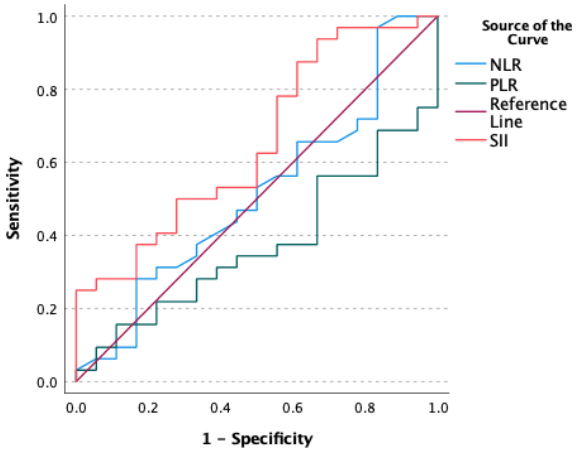

Figure 1. ROC analysis of the optimal cut-off value of NLR, PLR, and SII

Table 1. The characteristics of the patients

Variable	Data
Total	50
Age (years old) mean ± SD (median; range)	55.98 ± 9.51 (56.5 ;33 – 73)
Gender	
Male	31 (62.0%)
Female	19 (38.0%)
Stage	
III C	1 (2.0%)
IV A	47 (94.0%)
IV B	2 (4.0%)
EGFR mutation	
19	29 (58.0%)
21	21 (42.0%)
ECOG PS	
0	2 (4.0%)
1	42 (84.0 %)
2	6 (12.0 %)
Smoking history	
Yes	29 (58.0%)
No	21 (42.0%)
EGFR-TKIs	
Gefitinib	32 (64.0%)
Erlotinib	4 (8.0%)
Afatinib	14 (28.0)
NLR mean ± SD (median; range)	6.7 ± 3.8 (5.7;1.7 – 20)
PLR mean ± SD (median; range)	514.18 ± 198.14 (381.45; 107.64 – 1474)
SII mean ± SD (median; range)	2162.55 ± 1555.69 (1674.65;470 – 6782.07)
OS (months) mean ± SD (median; range)	24.60 ± 8.56 (29.8;1 – 44)
PFS (months) mean ± SD (median; range)	11.68 ± 8.47 (10;1 – 44)

Table 2. Characteristics of study subjects based on NLR, PLR, and SII value

Characteristics	NLR		p	PLR		p	SII		p
	(≥ 6.09)	(<6.09)		(≥ 356.93)	(<356.93)		(≥ 1.767)	(<1.767)	
Age (years old)									
<65	11 (22%)	28 (56%)	0.22	19 (38%)	20 (40%)	0.538	18 (36%)	21 (42%)	0.845
≥65	3 (6%)	8 (16%)		6 (12%)	5 (10%)		6 (12%)	5 (10%)	
Gender									
Male	29 (58%)	2 (4%)	0.844	26 (52%)	5 (10%)	0.141	16 (32%)	15 (30%)	0.992
Female	10 (20%)	9 (18%)		11 (22%)	8 (16%)		8 (16%)	11 (22%)	
Stage									
IIIC	0	1 (2%)		1 (2%)	0		0	1 (2%)	
IVA	38 (76%)	9 (18%)	0.689	36 (72%)	11 (22%)	0.068	23 (46%)	24 (48%)	0.659
IVB	1 (2%)	1 (2%)		0	2 (4%)		1 (2%)	1 (2%)	
EGFR mutation									
19	23 (46%)	6 (12%)	0.479	24 (48%)	5 (10%)	0.744	14 (28%)	15 (30%)	0.706
21	16 (32%)	5 (10%)		13 (26%)	8 (16%)		10 (20%)	11 (22%)	
ECOG PS									
1-2	36 (72%)	8 (16%)	0.379	36 (72%)	8 (16%)	0.987	19 (38%)	25 (50%)	0.646
3	3 (6%)	3 (6%)		1 (2%)	5 (10%)		5 (10%)	1 (2%)	
Smoking history									
Yes	23 (46%)	9 (18%)	0.905	26 (52%)	6 (12%)	0.347	17 (34%)	15 (30%)	0.78
No	13 (26%)	5 (10%)		12 (24%)	6 (12%)		7 (14%)	11 (22%)	
EGFR-TKIs									
Gefitinib	24 (48%)	8 (16%)		23 (46%)	9 (18%)		16 (32%)	16 (32%)	
Erlotinib	2 (4%)	2 (4%)	0.77	3 (6%)	1 (2%)	0.516	1 (2%)	3 (6%)	0.741
Afatinib	13 (26%)	1 (2%)		11 (22%)	3 (6%)		6 (12%)	8 (16%)	

Table 3. Univariate analysis of patient characteristics correlated with OS and PFS

Characteristics	Total (n)	OS		PFS	
		median	p	median	p
Age (years old)					
<65	39	23.5	0.314	9	0.639
≥65	11	34		14	
Gender					
Male	31	19	0.874	10	0.249
Female	19	15		9	
Stage					
IIIC	1	9	0.721	10	0.495
IVA	47	19		10	
IVB	2	10		13.5	
EGFR Mutation					
19	29	19	0.387	12	0.289
21	21	18		7	
ECOG PS					
0-1	44	19.5	0.591	9.5	0.734
2	6	6.5		8	
Smoking history					
Yes	29	19.5	0.452	11	0.873
No	21	14.5		9.5	
EGFR-TKIs					
Gefitinib	32	16	0.632	8.5	0.488
Erlotinib	4	27.5		15.5	
Afatinib	14	24.5		11	
NLR					
High (≥ 6.09)	23	24	0.665	7	0.792
Low (<6.09)	27	26		10	
PLR					
High (≥ 356.93)	20	24	0.259	10	0.581
Low (<356.93)	30	27		13	
SII					
High (≥ 1767)	24	18	**0.014***	7	**0.003***
Low (<1767)	26	26		12	

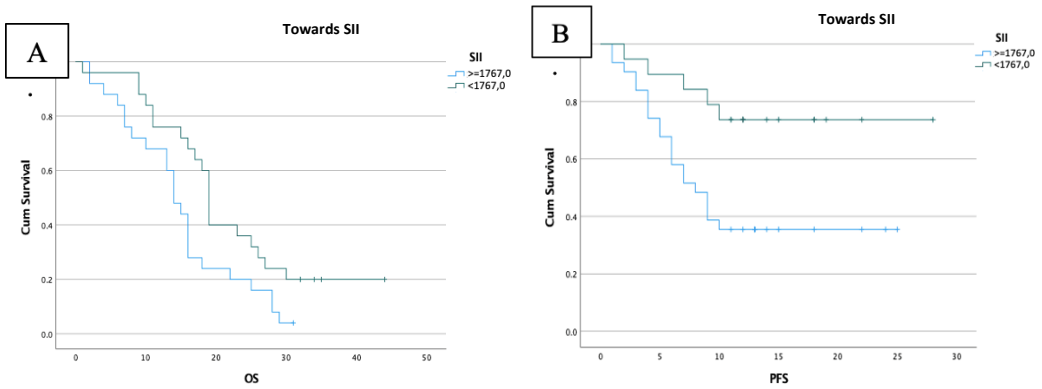

Figure 2. Kaplan Meier analysis for OS (A) and PFS (B) according to SII

Univariate Analysis between Patient Clinicopathological Characteristics and Survival

Univariate cox regression analysis (Table 3) showed that only the SII score had a prognostic factor for OS and PFS. All other clinicopathological characteristics, including NLR and PLR, were statistically insignificant.

Survival Outcomes

We calculated the association between OS and PFS with SII by the Kaplan–Meier method. Median OS and median PFS in the low SII group (28 months; 12 months) were longer than in the high SII group (18 months; 7 months), as shown in Figures 2A and 2B.

DISCUSSION

The role of inflammation has been widely studied and described in various stages of cancer development. Cancer cells will produce pro-inflammatory factors and activate peripheral leukocyte cells (e.g., neutrophils, lymphocytes, macrophages, and dendritic cells) that have a role in invasion, metastasis, and angiogenesis.[15,16] In the microenvironment of a tumor, neutrophils, platelets, and lymphocytes will also produce cytokines that can facilitate tumor development and metastasis, such as IL-1, IL-6, and tumor necrosis factor (TNF). In addition, leukocyte infiltration has also been shown to be associated with tumor angiogenesis.[8,17]

Neutrophilia is usually accompanied by relative lymphocytopenia, which indicates a significant reduction in the cell-mediated adaptive immune response. This can occur because cancer cells will induce tumor-associated neutrophils (TAN) through the formation of transforming growth factor–ß (TGF-ß). Therefore, they can produce cytokines that suppress lymphocyte activity. The presence of systemic neutrophilia and lymphopenia before starting chemotherapy is correlated with a poorer prognosis in lung cancer patients.[8,10–12,18]

Tumor cells also produce TPO excessively and indirectly mediated by IL-6 and other cytokines. Furthermore, TPO will stimulate the bone marrow to produce platelets. Platelets actively influence the behavior of cancer cells, but conversely, the physiology and phenotype of platelets are also influenced by tumor cells. In the process of metastasis, tumor cells will affect the synthesis of platelets and the release of chemical mediators that cause activation and aggregation of platelets in cancer patients.[14,19]

Previous studies found that the higher the inflammatory parameters (e.g., NLR, PLR, SII), the worse the prognosis for adenocarcinoma patients. This study assessed the prognostic value of inflammatory parameters (NLR, PLR, SII) in predicting survival in EGFR mutation-positive lung adenocarcinoma patients receiving EGFR-TKIs. Almost all of the characteristics of the subjects, including NLR and PLR, were not significant as prognostic factors for survival. This result is in line with a study by Chao Deng, *et al*., who also found no significant association between age, sex, smoking status, ECOG score, and type of mutation with survival in 200 Chinese patients with EGFR mutation-positive receiving TKIs.[7]

We obtained the cut-off value of 6.095 for NLR, 356.935 for PLR, and 1.767 for SII. This study found that NLR ≥6.095, PLR ≥356.935, and SII ≥1767.0 had shorter OS values with a median of 23 months, 24 months, and 18 months, respectively.

Meanwhile, NLR ≥6.095, PLR ≥356.935, and SII ≥1.767 had shorter PFS values with a median of 7 months, 10 months, and 7 months, respectively. However, only the SII was significantly associated with survival. SII was a significant prognostic factor for OS ifSII ≥1.767 (median value = 18 months vs. 28 months) and for PFS if SII ≥1.767 (median value = 7 months vs. 12 months).

SII markers integrate neutrophils, lymphocytes, and platelets, thus providing an overview of better inflammatory and immune status than NLR and PLR. This marker can be a simple and non-invasive prognostic indicator to be performed in lung cancer patients. Pre-treatment systemic inflammation, characterized by elevated SII values, has been known to be a prognostic marker of survival in lung cancer patients.[11,17]

Based on previous studies, it was found that the cut-off value of each previous study had different values. Chao Deng, *et al*. found that SII >1.066.935 had a shorter survival in adenocarcinoma patients receiving EGFR-TKIs.[7] Li, *et al*. also said that SII <1.218.81 had a longer OS in adenocarcinoma patients with brain metastases.[20] In addition, Tomita, *et al*. found that SII <471.2 had a better OS.[21]

LIMITATION

This study found the SII value as a prognostic marker of survival rates in adenocarcinoma patients receiving EGFR-TKIs. However, we found some limitations. First, this study was taken from one center with limited samples. Second, data were obtained from medical records retrospectively. This makes it difficult to obtain complete data on comorbidities, metabolic conditions, metastatic status, cumulative smoking dose, job history, and nutritional status influencing the outcome. In addition, the type of EGFR-TKIs used by the subjects in this study also has an effect. Therefore, it is recommended that the study be conducted prospectively with a larger sample size from a multicenter.

CONCLUSION

In this study, the optimal cut-off value for NLR, PLR, and SII was 6.095, 356.935, and 1.767, respectively. We found that the SII value ≥ 1.767 was correlated with shorter OS and PFS. The pre-treatment SII value was correlated with survival in EGFR mutation-positive lung adenocarcinoma patients receiving TKIs and could be used as a prognostic marker.

Acknowledgments
None declared.

Conflict of Interest
The author declared there is no conflict of interest.

Funding
This study did not receive any funding.

Authors' Contributions
Collecting and extracting data, searching for literature, and writing the manuscript: MR. Analyzing statistics and interpreting the results: MR, H, ES. Concepting, designing, and supervising: H, ES. Revising the manuscript: MR, H, ES, TAW. All authors contributed and approved the final version of the manuscript.

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