ORIGINAL ARTICLE

Neutrophil-Lymphocyte Ratio (NLR) as a Prognostic Marker in Advanced Lung Cancer Patients Undergoing First-Line Treatment

Dinda Ary Miranda Dewi[1*], Ungky Agus Setyawan[2], Liana Karliasari[3]
[1]Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia.
[2]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Brawijaya/Dr. Saiful Anwar General Hospital, Malang, Indonesia.
[3]Department of Radiology, Faculty of Medicine, Universitas Brawijaya/Dr. Saiful Anwar General Hospital, Malang, Indonesia.

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ABSTRACT

Introduction: Neutrophil-lymphocyte ratio (NLR) is one of the systemic inflammatory markers that play a role in detecting the degree of sepsis in the cancer microenvironment. A high NLR, with a dominant predominance of neutrophil cells, can release cytokines and chemokines that induce cancer cell proliferation and metastasis. Conversely, a low NLR, predominately of lymphocyte cells, can activate the immune system to handle chronic inflammation. From its mechanism of action, NLR is often used to predict the future prognosis and survival rate of cancer patients. This study aimed to analyze the effect of first-line therapy in lung cancer patients with an alternative prognostic indicator in the form of changes in NLR values confirmed by the response evaluation criteria in solid tumors (RECIST).
Methods: This study used an analytical observational method with a cross-sectional approach and was conducted using secondary data samples from the medical records of lung cancer patients treated at Dr. Saiful Anwar General Hospital, Malang.
Results: Spearman's correlation analysis between NLR and RECIST revealed a relationship (p = 0.001). Determining the NLR cut-off point using the receiver operating characteristic (ROC) curve yielded a value of 3.55, with NLR sensitivity and specificity at 69.44% and 69.76%, respectively. The therapy administration to lung cancer patients significantly decreased NLR (p = 0.032).
Conclusion: NLR is a valuable tool for routinely monitoring therapy outcomes in lung cancer patients and can be considered an alternative prognostic marker due to its promising results.

INTRODUCTION

Lung cancer remains a significant global health concern, with the incidence of cases steadily increasing over the past few decades. In 2020, there were more than 19 million new cases worldwide, resulting in nearly 10 million deaths.[1] In Indonesia, lung cancer accounted for 34,783 cases (8.8%) of all cancer cases.[1] Smoking is the main factor contributing to approximately 80% of lung cancer-related deaths in males and 70% of deaths in females.[2]

Standard treatment modalities for lung cancer include chemotherapy and targeted therapy, both of which can cause side effects such as diarrhea, anemia, neutropenia, nausea, fever, constipation, mucositis, epigastric pain, thrombocytopenia, bone marrow suppression, low sodium and magnesium levels, kidney damage, and peripheral neuropathy.[3,4] The response evaluation criteria in solid tumors (RECIST) is commonly used to monitor changes in cancer size before and after therapy periodically. These changes are then categorized into four conditions: stable disease

*Corresponding author: dindaarymd@student.ub.ac.id

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(SD), progressive disease (PD), complete response (CR), and partial response (PR).[5]

Neutrophil-lymphocyte ratio (NLR) could be an alternative method for evaluating cancer cell development.[6] NLR works by assessing the degree of inflammation in the cancer microenvironment. A high NLR value is associated with a poor prognosis. In this case, one of the advantages of NLR is that it can be easily measured and is accessible even in hospitals with limited facilities.[7]

As explained previously, this study aimed to investigate the potential of NLR as an alternative prognostic marker alongside RECIST to determine the progression of cancer cells, especially in lung cancer patients undergoing first-line therapy at Dr. Saiful Anwar General Hospital, Malang.

METHODS

This study used an analytical observational method with a cross-sectional approach using secondary data obtained from the medical records of lung cancer patients undergoing treatment at Dr. Saiful Anwar General Hospital, Malang, between January 2022 and May 2023.

The subjects were selected based on the inclusion criteria, which included treatment-naive lung cancer patients, those with stage IIIA or higher, and those who had completed three months of first-line therapy. NLR values were calculated from the results of complete blood count tests by dividing the absolute neutrophil count by the absolute lymphocyte count before and after therapy.

The data were analyzed using the International Business Machines Corporation (IBM) Statistical Package for the Social Sciences (SPSS). The first step was to perform a Kolmogorov-Smirnov normality test. Following this, a Pearson correlation test was performed to analyze the relationship between NLR values and RECIST results. Subsequently, the receiver operating characteristic (ROC) curve was employed to determine the NLR cut-off point against cancer cell progression. Finally, the Wilcoxon test was performed to assess the effect of lung cancer therapy on changes in NLR values.

RESULTS

Based on the predetermined inclusion criteria, 82 subjects met the qualifications with the following characteristics (Table 1).

Table 1. Characteristics of the subjects

Characteristic	n = 82	Percentage (%)
Gender		
Female	26	31.7
Male	56	68.3
Age		
40-49 years old	9	11
50-59 years old	27	32.9
60-69 years old	34	41.5
≥ 70 years old	12	14.6
Diagnosis		
Adenocarcinoma	43	52.5
Adenosquamosa cell carcinoma	6	7.3
Small cell carcinoma	6	7.3
Non-small cell carcinoma	1	1.2
Squamous cell carcinoma	25	30.5
Others	1	1.2
Stage		
IIIA	1	1.2
IIIB	5	6.1
IIIC	0	0
IVA	49	59.8
IVB	27	32.9
Therapy		
Chemotherapy	74	90.2
Targeted therapy	8	9.8

The average NLR value of 82 subjects before therapy was 4.54 ± 4.30. After treatment, the average NLR value decreased to 4.09 ± 4.95. Table 2 presents the NLR values before and after therapy, indicating a relative decrease in NLR values after therapy. Table 3 shows the average NLR values after the subjects completed three months of therapy.

Table 2. Neutrophil-lymphocyte ratio values before and after therapy

NLR Values	n (%)	Mean ± SD
Pre-Therapy		
Decreased (< 0.78)	1 (1.22)	0.43
Normal (0.78-3.53)	42 (51.22)	2.69 ± 0.48
Increased (>3.53)	39 (47.56)	6.64 ± 5.52
Post-Therapy		
Decreased (< 0.78)	1 (1.22)	0.63
Normal (0.78-3.53)	54 (65.85)	2.09 ± 0.72
Increased (>3.53)	27 (32.93	8.23 ± 6.97

NLR: neutrophil-lymphocyte ratio, SD: standard deviation

Table 3. Neutrophil-lymphocyte ratio values based on the response evaluation criteria in solid tumors results after therapy

RECIST	n (%)	NLR Values (Mean ± SD)
Non-Progressive		
Complete response	-	-
Partial response	13 (15.85)	2.43 ± 0.29
Progressive		
Stable disease	32 (39.02)	3.41 ± 0.60
Progressive disease	37 (45.12)	6.26 ± 5.96

RECIST: response evaluation criteria in solid tumors, NLR: neutrophil-lymphocyte ratio, SD: standard deviation

The initial analysis involved the Kolmogorov-Smirnov normality test on neutrophil and lymphocyte data to determine data distribution. The p-value was 0.041 ($p < 0.05$), indicating that the data were not normally distributed. Therefore, a box plot analysis was employed to detect outliers, excluding three outliers data. Following this, the p-value changed to 0.2 ($p > 0.05$), indicating that the data were normally distributed. Subsequently, the Pearson correlation test was performed to determine the relationship between the NLR values and the RECIST results. The test yielded a p-value of 0.001 ($p < 0.05$) and a correlation coefficient (r) of 0.381, indicating a significant relationship between NLR and RECIST. The ROC curve analysis revealed an area under curve (AUC) of 0.744 ($p = 0.000$).

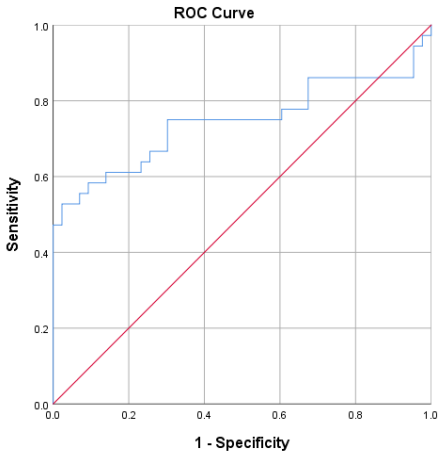

Figure 1. Result of ROC test

Based on the ROC analysis, the NLR cut-off point was 3.55, with a sensitivity of 69.44% and a specificity of 69.76%. According to RECIST results, 69.44% of subjects with NLR values of 3.55 or higher had progressive disease, while 69.76% of subjects with NLR values of 3.55 or lower had non-progressive disease.

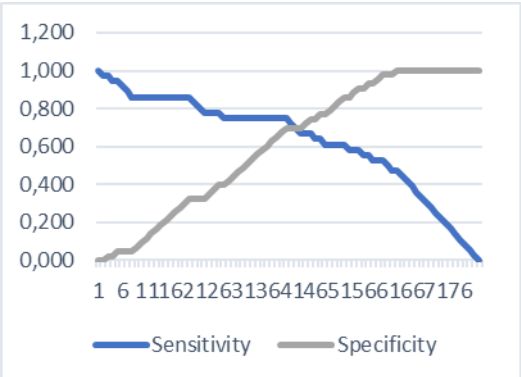

Figure 2. NLR cut-off point

Other parameters derived from the sensitivity and specificity values included a positive presumption value (65.79%), a negative presumption value (73.17%), a positive likelihood ratio (2.3), a negative likelihood ratio (0.44), and accuracy (69.62%).

Table 4. Analysis of neutrophil-lymphocyte ratio cut-off point against response evaluation criteria in solid tumors results

NLR Values	RECIST		Total
	Progressive Disease	Non-Progressive Disease	
≥ 3.55	25	13	38
≤ 3.55	11	30	41
Total	**36**	**43**	79

NLR: neutrophil-lymphocyte ratio, RECIST: response evaluation criteria in solid tumors

Finally, the Wilcoxon test yielded a p-value of 0.032 ($p < 0.05$), indicating a significant change in NLR values after the administration of first-line therapy.

DISCUSSION

Among 82 subjects in this study, the majority were within the age range of 60-69 years old, with the youngest subject being 42 years old. This finding aligns with 2022 Surveillance, Epidemiology, and End Results (SEER) data from the National Cancer Institute (NCI), which reported that the incidence of lung cancer between 2016 and 2020 was dominated by individuals aged 65-74 years old.[8] In addition, the National Guideline on Medical Services (PNPK) for lung cancer treatment highlights that the incidence of lung cancer is low in individuals aged under 40 years old.[4] However, the risk tends to increase in individuals aged 70 years old and older.[4] This can be caused by aging factors, physiological changes that weaken the immune system, gradual cell damage that outpaces cell repair capabilities, and cumulative exposure to carcinogens or other risk factors that trigger cell susceptibility to mutation.[9]

This study also found a higher proportion of male subjects compared to female subjects, with a ratio of 2:1. This is consistent with the findings by May, *et al.* (2023), who found that the higher incidence of lung cancer in males was associated with smoking habits, increased levels of abnormal testosterone, and occupational exposure to carcinogens such as asbestos, which are more common among males.[10] The most common type of cancer cell observed in the subjects was adenocarcinoma, which is thought to be influenced by environmental exposures or genetic abnormalities.[11]

The subjects in this study were patients diagnosed with lung cancer at stages III to IV (advanced stage). A key factor contributing to the majority of cancer diagnoses occurring in the advanced or terminal phase is the delay in seeking medical attention. Hutajulu, *et al.* (2022) concluded that delays in examination for more than three months can significantly increase the risk of mortality (p = 0.030).[12]

The results of data analysis showed a significant correlation between NLR as a prognostic marker and the objective therapy response with a p-value of 0.001 and a correlation coefficient of 0.381. The significance of this relationship was further supported by the fact that the calculated r value exceeded the critical r value (r = 0.2213). The positive r value indicated that higher NLR values were associated with worsening conditions in lung cancer patients, as evidenced by the RECIST results. The meta-analysis by Yang, *et al.* (2021) reported similar findings, where patients with high NLR significantly predicted poor OS (HR = 1.65, 95% CI 1.46 to 1.88; p <0.001) and PFS (HR = 1.38, 95% CI 1.23 to 1.55; p <0.001).[13] However, the correlation strength (r) was low, indicating a weak correlation. Factors that may influence this include potential sampling bias and the influence of comorbid conditions. Sampling bias can be caused by extreme variations in NLR values, leading to abnormally distributed data.[14] Buonacera *et al.* (2022) also noted that in addition to cancer, several other conditions could falsely increase NLR, such as age, gender, obesity, exogenous steroid use, infection, hematological problems, acute myocardial infarction, pulmonary embolism, stroke, type 2 diabetes, and stress.[7]

The AUC value of 0.744, with a p-value of 0.000, indicated that NLR is a fairly effective prognostic marker for assessing cancer cell progression.[15] The cut-off value obtained in this study was 3.55, with NLR sensitivity and specificity at 69.44% and 69.76%, respectively. These results suggested that in lung cancer patients with NLR values 3.55 or higher, 69.44% or 25 out of 36 samples had progressive disease, according to the RECIST results. Conversely, in lung cancer patients with NLR values of 3.55 or lower, 69.76% or 30 out of 41 samples had non-progressive disease. The positive presumption value (PPV) of 65.79% was also obtained, indicating the probability that NLR values of 3.55 or higher accurately predicted progressive disease. On the other hand, the negative presumption value (NP) of 73.17% indicated the true probability that NLR values of 3.55 or lower correctly predicted a non-progressive disease. Based on the sensitivity and specificity values, this study measured the positive and negative likelihood ratios of 2.3 and 0.44, respectively. These ratios suggested that the NLR was adequate in classifying true positive or negative from false positive or negative.[16,17]

A study by Rapoport, *et al.* (2020) showed similar results with an average pre-therapy NLR value of 5.[18] The study found that patients with pre-therapy NLR of 5 or higher had an average overall survival (OS) of 7.02 months.[18] Meanwhile, those with an NLR of 5 or lower had an OS of 14.5 months (p = 0.0026).[18] Based on the Wilcoxon analysis, the study showed that lung cancer patients responded positively to changes in NLR values (p = 0.032).[18] Among the 79 samples tested, the majority showed a decrease in NLR. This decrease is due to the administered therapy, which effectively suppresses systemic inflammation associated with cancer cell growth.[18] Many factors, including a complex network of chemical reactions, DNA repair and tolerance pathways, cell cycle arrest mechanisms, and intra- and extracellular signaling pathways, mediate the relationships between inflammation, DNA damage, and cancer growth. Decreased inflammation can inhibit proliferation, trigger apoptosis of cancer cells, and prevent further DNA damage.[6,19,20]

From the results and discussion, it can be concluded that NLR is a valuable tool for estimating the prognosis of first-line therapy outcomes as validated by the RECIST results. Apart from its sensitivity and specificity, NLR is also cost-effective and more efficient, making it a viable option for routine monitoring in cancer patients, especially those with lung cancer. However, the limitation of this study was the lack of consideration for patient confounding factors or comorbidities that could affect NLR values.

CONCLUSION

Neutrophil-lymphocyte ratio (NLR) significantly correlates with the rate of cancer cell progression. Providing appropriate and early therapy can suppress inflammatory conditions, thereby inhibiting cancer cell progression, as evidenced by a decrease in NLR and RECIST, which refers to non-progressive disease. Lower NLR values are also associated with increased survival rates in cancer patients. Therefore, NLR is a valuable prognostic tool for assessing cancer therapy outcomes, especially in lung cancer.

Given the limitations of this study, the authors recommend further research with a larger sample size and consideration of patient comorbidities to provide a more accurate representation of lung cancer patients across different therapeutic modalities.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Authors' Contributions

Data sampling, analysis, and discussion: DAMD, UAS, LK. All authors contributed and approved the final version of the manuscript.

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