Original Article

Correlation Between Changes in NLR Value and RECIST among Lung Cancer Patients at Saiful Anwar Malang Hospital

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Abstract

Background: In practice, clinicians use Response Evaluation Criteria in Solid Tumors (RECIST) to decide the progressivity of lung tumors. Besides RECIST, there is an inflammatory marker called Neutrophil to Lymphocyte Ratio (NLR), which has prognostic value in cancer patients. Many previous studies have shown that NLR can predict the prognosis because inflammation in cancer patients is part of the tumor progressivity. Therefore, the changes in NLR value have the potency to be one of the ways to decide the progressivity of tumors in lung cancer patients.

Method: This cross-sectional study was conducted to see whether there is a correlation between RECIST and NLR in 95 lung cancer patients at Saiful Anwar Hospital whose data were taken from January 2022 to May 2023. The variable will be tested using the chi-square test to see the correlation and the logistic regression method to obtain the odds ratio.

Results: There is a significant correlation between changes in NLR and RECIST with P=0.041. Through Logistic Regression Analysis, the value of the odds ratio is 2.46 (CI 95%=1.03-5.94). In the group with progressive RECIST, the average NLR value after therapy was higher than the average NLR value after therapy in the non-progressive group.

Conclusion: This study concludes that changes in NLR value have the potency to help the determination process of lung cancer progressivity as RECIST does.

Keywords: lung cancer, lung cancer progressivity, NLR, RECIST

INTRODUCTION

Cancer has become one of the top health problems in the world. Especially in developing countries, such as Indonesia, it is estimated that there will be an increase in cases of cancer by 300% by 2030. In 2020, lung cancer became one of the most frequently fatal malignancy cases and had the highest incidence in Southeast Asia.[1] Based on the World Health Organization (WHO), lung cancer is the largest contributor to cancer

incidence in men. Apart from that, the Indonesia Ministry of Health also stated that 1/3 of cancer deaths in males are caused by lung cancer.[2]

In Indonesia, one of the main factors related to it is the smoking habit. The number of smokers in Indonesia is increasing, especially at the student age. Based on Global Youth Tobacco Survey Data, there are 32.1% of students who smoke in Indonesia. This smoking habit affects not only active smokers but also people around them, passive smokers, with an increased risk of lung cancer by 20-30%.[2]

Nowadays, one of the examinations that is used to diagnose lung cancer is the radiology examination. Computed Tomography Scan (CT-Scan) is one of the methods that is most commonly used.[3] CT- Scan is used to determine the stage of tumors, assess the mass of tumors, assess solitary lung nodules and others.[4]

CT-Scan is not only used for diagnostic but also to assess tumor development and evaluate patient therapy. Response Evaluation Criteria in Solid Tumors (RECIST) is the instrument to help the evaluation process of the CT-Scan result. The RECIST assessment will produce conclusions such as Complete Response (CR), Partial Response (PR), Stable Disease (SD) or Progressive Disease (PD).[5]

Many studies have stated the relationship between inflammation and tumor growth. Systemic inflammation is associated with tumor growth factors such as angiogenesis, tumor growth, invasion and metastasis.[6] There is a marker used in assessing inflammation, called neutrophil-to-lymphocyte ratio (NLR). The neutrophil-to-lymphocyte ratio is a ratio value obtained from calculating the number of neutrophils and lymphocytes of the patient. According to Barret et al, the NLR is found to be higher in patients with cancer conditions.[7]

By looking at the correlation between NLR, as a marker of inflammation, and the role of inflammation, which is associated with the presence of tumors and their growth, an increase in NLR indicates an increase in inflammation which also indicates a worsening body condition due to tumor growth. The NLR test is relatively easy because it only uses the patient's complete blood test result.[8]

With the ease and practicality of NLR in the examination process, the changes of the NLR value could be another method, besides RECIST, in determining the disease progressivity of lung cancer patients. Another advantage is NLR also has a lower risk because there is no radiation effect provided by CT scans.

Many previous studies have discussed the role of NLR as a prognostic value but there are still no studies that discuss the correlation between changes in NLR values and RECIST. Therefore, this study was conducted to see the correlation between changes in NLR values and RECIST as an effort to help the process of determining the disease progressivity of lung cancer patients.

METHOD

This study is an analytic observational study with a cross-sectional approach. There were 95 subjects in this study and the data was obtained from the medical records of lung cancer patients at Saiful Anwar Hospital Malang from January 2022 to May 2023.

The inclusion criteria of this study were subjects who had complete NLR and RECIST data before and after therapy. While the exclusion criteria are subjects with incomplete data. The required data needed in this study are age, sex, neutrophil value, lymphocyte value, type of treatment, and RECIST result gained after one cycle of therapy. In this study, NLR was taken without considering other factors such as gender, age, comorbidities or other co-morbid conditions.

Subjects had a complete blood examination to obtain neutrophil and lymphocyte levels that will be calculated into a ratio. The result of the NLR examination before and after therapy will be compared and categorized into two categories, increased NLR and decreased NLR. It will also show the classification of the NLR value before and after therapy based on the normal value of NLR (0.78–3.52). The cut-off of the NLR was obtained from previous research by Forget et al which the range of NLR in healthy persons is 0.78–3.53.

Meanwhile, RECIST was obtained by comparing CT scan results before and after therapy. The conclusion of RECIST will be categorized into two categories, progressive categories (if the result obtained is Progressive Disease) and non-progressive categories (if the result obtained are Partial Response, Complete Response, or Stable Disease).

The data were processed and analyzed using the Statistical Package for the Social Sciences (SPSS) application. Both variables will be tested using the chi-square test to see the relationship and the logistic regression method to obtain the odds ratio. If the analysis does not fulfill the chi-square analysis criteria, analyze statistics using Fisher exact tests.

RESULTS

From 95 subject data included in the inclusion criteria, the following characteristics were obtained in Table 1.

Table 1. Subject's Characteristics

Characteristics	N	%
Sex		
Male	62	65
Female	33	35
Age		
≥60	51	54
<60	44	46
Therapy		
Chemotherapy	85	89
Targeted Therapy	2	2
Chemotherapy + Radiotherapy	8	9

The average age of the subjects was 59 years and the male gender was the majority of the subjects of this study. There were 3 different types of therapy, the majority of subjects received chemotherapy and the rest received targeted therapy or a combination of

chemotherapy and radiotherapy.

Table 2. NLR Value Result and Changes

NLR Value	N	%
Before Therapy		
<0.78	3	3
0.78-3.53	41	43
>3.53	51	54
After Therapy		
<0.78	1	1
0.78-3.53	63	66
>3.53	31	33
NLR Changes		
Increase	31	33
Decrease	64	67

The result of the NLR test obtained before therapy showed that more than 50% of the subjects had a high NLR (>3.53) while after therapy 66% of the subjects had an NLR value of 0.78-3.53. The table also shows that 67% of subjects experienced a decrease in NLR after therapy.

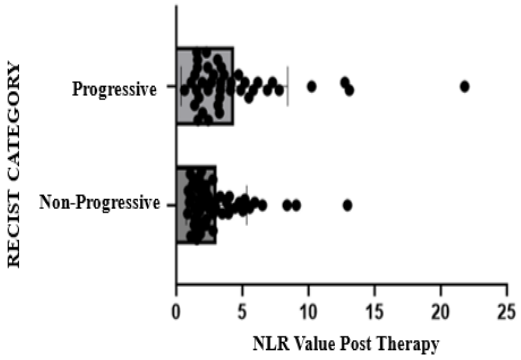
Table 3. RECIST Result (After Therapy) (n=95)

RECIST Result	N
Non-Progressive	
Complete Response	0
Partial Response	16
Stable Disease	38
Progressive	41

According to the RECIST data, after therapy, it showed that 54% of subjects had RECIST conclusions that included a non-progressive category while the rest were included in a progressive category.

The changes in the NLR value variable and RECIST variable were then processed using the chi-square method to produce correlation conclusions and using Logistic Regression to obtain the odds ratio.

Through the chi-square test, the significance value between changes in NLR values and RECIST result is P=0.041 which means there is a significant correlation between changes in NLR values and RECIST result. In addition, after calculating the odds ratio, it was found that OR=2.46 (95% CI=1.03-5.94), which means that patients with increased NLR have a likelihood of lung cancer 2.46 times more progressive than patients with decreased NLR.



Graphic 1. NLR Value After Therapy Data Distribution

Table 4. The Correlation between NLR Changes and RECIST

Variable	RECIST		P	OR (95% CI)
	Progressive	Non-Progressive		
Increased NLR	18	13	0.041	2.46 (1.03–5.94)
Decreased NLR	23	41		

Besides the correlation test, a graph was made to show the distribution of the NLR value after therapy. There is a difference in average NLR value after therapy, where in the progressive RECIST group, the average is 4.394 while in the non-progressive RECIST group, the average is 3.043.

DISCUSSION

From the data of this study subject, it was found that the majority of the subjects' age was above 60 with an average of 59.17. This is in line with the previous study which stated that ages >50 years have a higher risk of developing lung cancer than those <50 years. The age factor is important because, with increasing age, people will be exposed more to the risk factors of lung cancer along with decreasing immunity of the body and regeneration ability of cells.[9]

Other than age, based on the gender data, 65% of the subjects were male. Consistently, incidence and mortality data of lung cancer are found to be lower in women than men.[10] This is because men's smoking behavior is more often than women's, and smoking is the main cause of non-communicable diseases, especially lung cancer.[11]

However, nowadays there is a narrowing gap of smokers between the male and female category. There is a possibility that the mortality rate in women due to lung cancer may exceed men by 2045.[10] The incidence of lung cancer in the subject of this study is certainly not only associated with the risk factors of age and gender, many other factors may affect such as exposure to cigarette smoke, socioeconomic status and others.

One of the variables in this study is the change in NLR value. NLR is a marker that shows the innate immune response played by neutrophils and adaptive immunity plated by lymphocytes. Neutrophils have a role as the first line of the immune system when dealing with pathogens and have a major role when a systemic inflammatory response occurs.[12] Lymphocytes have an important role in suppressing tumor maturation through the process of immunity, one of which is by inducing apoptosis of cancer cells.[13]

In this study, it was found that 54% of subjects have NLR that exceeds normal limits (>3.53). This is in accordance with the results of a previous study which states that there is an increase in NLR in malignancy conditions because inflammatory conditions play an important role in its pathophysiology. Inflammation causes increased tumorigenesis.[12]

There is other proofs state that neutrophils can promote angiogenesis and tumor growth by inducing several factors such as the release of basic fibroblast growth factor, endothelial cell migration and production of reactive oxygen species.[13] However, after undergoing therapy, there was a decrease in the number of subjects who had high NLR (>3.53), which decreased from 54% to 33%. In contrast, there was an increase in subjects who have normal NLR (0.78-3.53)

from 43% to 66%. This is certainly related to the therapy that was given.

Three types of therapy were given to the subjects in this study. Among chemotherapy, radiotherapy combined with chemotherapy, and targeted therapy, the majority of subjects (89%) received chemotherapy. The goal of chemotherapy is to inhibit tumor proliferation and multiplication which will avoid invasion and metastasis. Chemotherapeutic agents generally affect the macromolecular synthesis and function of neoplasm cells by interfering with DNA, RNA, and protein synthesis.[14]

The next therapy is targeted therapy, 2 subjects of this study received targeted therapy which works by delivering drugs specifically to genes or proteins in cancer cells or tissues that support cancer growth.[15] The last type of therapy given to the 8 subjects of this study was a combination of chemotherapy and radiotherapy. This combination therapy is given to patients with good condition, minimal weight loss and elderly patients with severe comorbidities or contraindications to surgery.[14] Chemotherapy can help the radiotherapy process by shrinking the tumor before therapy and destroying the cancer cells that still exist after radiation therapy so that the therapy can work better.[16]

After receiving therapy, there were changes in the subject's blood profile. In this study, changes in blood profile can be seen from neutrophils and lymphocytes in the NLR value. In 67% of subjects who received chemotherapy, 100% of subjects who received combination therapy and 62% of subjects who received targeted therapy had a decrease in NLR.[13]

This decrease is possible because the administration of chemotherapy agents aims to reduce the growth or even eliminate the tumor, which is a source of chemotactic cytokines that will attract neutrophils to migrate to the tumor, causing an increase in neutrophils. Then the decrease in neutrophil production in the body can be reduced due to the absence of neutrophil chemotaxis activity.[13] In addition, chemotherapy itself affects the bone marrow, namely hematopoietic suppression. This effect will cause a decrease in blood cells, one of which is neutrophils.[17]

Although this study did not analyze the relationship of NLR with age and comorbid conditions, these factors also have an impact based on previous studies. Based on the study by Li et al on 3,262 healthy populations, the older age group tends to have a higher NLR value than the younger groups.[18]

This may happen since older people are more likely to be affected by chronic infections or malignant conditions, which as described earlier, increased inflammatory conditions can increase NLR as well. This reason may also explain the condition of increased NLR in people with comorbidities. On the other hand, the previous study shows that there is no significantly different NLR was found between the female and male population at each age group.[18]

This study states that there is a significant relationship between changes in

NLR values and RECIST. The role of RECIST in assessing the progression of lung cancer is very important because RECIST is a standard criteria rule that shows therapeutic response based on tumor growth or shrinkage through radiographic modalities that have been used globally. The results of RECIST can show the presence or absence of progressivity in tumor growth. By having a significant relationship with NLR, it can be said that changes in NLR values can predict the growth of lung tumors, whether progressive or not. Based on the results of the analysis, it was also found that an increased NLR was 2.46 times more likely to have a progressive result than a decreased NLR.[8]

In addition, after therapy, the group with progressive RECIST results had a higher average of NLR compared to the non-progressive group. These results are in line with various other sources that have stated the role of NLR as a predictor of cancer disease outcome. Based on a meta-analysis study, it was concluded that there is an association between poor prognosis and increased NLR in cancer patients.[8] Another similar study also stated that if the NLR value is >4 before therapy, it indicates poor Overall Survival (OS) and Progression-Free Survival (PFS) in lung cancer patients.[6]

The relationship between NLR and RECIST can be understood by looking at the role of neutrophils and lymphocytes, which indicate the inflammatory state in the body, especially due to tumors. In the case of malignancy, the increase of NLR is due to the development and spread of cancer.[13] With the presence of neutrophilia and/or lymphopenia in inflammatory conditions due to tumors, the NLR result will be higher. This inflammation itself is associated with various tumor growth factors, ranging from angiogenesis, progressiveness, and invasion to metastatic tumors.[6] Similarly, RECIST can also show tumor growth or shrinkage through radiographic modalities.

CONCLUSION

Among the 95 subjects of this study, lung cancer patients at Saiful Anwar Hospital Malang, 54 of them had non-progressive RECIST conclusion results Complete Response/Partial Response/ Stable Disease (CR/PR/SD) after undergoing therapy, while 41 of them had progressive results. Then, 64 subjects had a decrease in NLR value after therapy and the remaining 31 had an increase in NLR value.

Based on these two types of data, it was found that there was a significant relationship between changes in NLR values and RECIST in lung cancer patients at Saiful Anwar Hospital Malang. It was found that subjects with increased NLR had a likelihood of lung cancer 2.46 times more progressive than patients with decreased NLR. This result is also supported by previous journals that examine the role of NLR as a prognosis value in cancer patients.

Further research is needed to determine the NLR cut-off value used to

assess the progressivity of lung cancer patients and can be used for further research on NLR in lung cancer patients. In addition, future studies are needed to have more specific subjects such as patient age, patient lung cancer stage and patient therapy data.

REFERENCES

1. Purnamawati P, Tandrian C, Sumbayak EM, Kertadjaja W. Tinjauan Pustaka: Analisis Kejadian Kanker Paru Primer di Indonesia pada Tahun 2014-2019. Jurnal Kedokteran Meditek. 2021;27(2):164–72.
2. Mustafa M, Azizi ARJ, IIIzam EL, Nazirah A, Sharifa S, Abbas SA. Lung Cancer: Risk Factors, Management, And Prognosis. IOSR Journal of Dental and Medical Sciences. 2016;15(10):94–101.
3. Wulandari L, Faot NE. Problem Penegakkan Diagnostik Pasien dengan Massa di Paru. Jurnal Respirasi. 2019;3(2):41–6.
4. Tandi M, Tubagus VN, Simanjuntak ML. Gambaran CT-scan tumor paru di Bagian/SMF Radiologi FK Unsrat RSUP Prof. Dr. R. D. Kandou Manado Periode Oktober 2014 – September 2015. e-CliniC. 2016 Jan 27;4(1):140–5.
5. Schwartz LH, Litière S, de Vries E, Ford R, Gwyther S, Mandrekar S, et al. RECIST 1.1—Update and clarification: From the RECIST committee. Eur J Cancer. 2016;62:132–7.
6. Yu Y, Qian L, Cui J. Value of neutrophil-to-lymphocyte ratio for predicting lung cancer prognosis: A meta-analysis of 7,219 patients. Mol Clin Oncol. 2017;7(3):498–506.
7. Bartlett EK, Flynn JR, Panageas KS, Ferraro RA, Sta.Cruz JM, Postow MA, et al. High neutrophil-to-lymphocyte ratio (NLR) is associated with treatment failure and death in patients who have melanoma treated with PD-1 inhibitor monotherapy. Cancer. 2020;126(1):76–85.
8. Cupp MA, Cariolou M, Tzoulaki I, Aune D, Evangelou E, Berlanga-Taylor AJ. Neutrophil to lymphocyte ratio and cancer prognosis: an umbrella review of systematic reviews and meta-analyses of observational studies. BMC Med. 2020;18(1):360.
9. Pritami AA, Soemarwoto RAS, Wintoko R. Faktor Risiko Kanker Paru: Tinjauan Pustaka. Agromedicine. 2022;9(2):120–3.
10. Bade BC, Dela Cruz CS. Lung Cancer 2020. Clin Chest Med. 2020;41(1):1–24.
11. Arumsari D, Artanti KD, Martini S, Widati S. The Description of Smoking Degree Based on Brinkman Index in Patients With Lung Cancer. Jurnal Berkala Epidemiologi. 2019;7(3):249–56.
12. Buonacera A, Stancanelli B, Colaci M, Malatino L. Neutrophil to Lymphocyte Ratio: An Emerging Marker of the Relationships between the Immune System and Diseases. Int J Mol Sci. 2022;23(7):3636.

13. Hartono B, Pontoh VS, Merung MA. Penilaian Jumlah Neutrofil, Limfosit Dan Trombosit, Kadar Protein Reaktif C, Kadar Albumin, Rasio Neutrofil Limfosit, Serta Rasio Trombosit Limfosit Sebelum Dan Setelah Terapi Pada Penderita Karsinoma Payudara. Jurnal Biomedik (JBM). 2015 Oct 16;7(3):163–70.
14. Kementrian Kesehatan RI. Pedoman Pengendalian Faktor Risiko Kanker Paru. Jakarta: Kementrian Kesehatan RI; 2018.
15. Padma VV. An overview of targeted cancer therapy. Biomedicine (Taipei). 2015;5(4):19.
16. Andayani N, Suryawati S, Salsabila N, Salwani D, Kurniawan H. Effect of Chemotherapy on Quality of Life of Lung Cancer Patients: Scoping Review. Respiratory Science. 2022;3(1):72–84.
17. Budiana ING, Febiani M. Febrile Neutropenia pada Pasien Pascakemoterapi. Indonesian Journal of Cancer. 2017;11(2):77–82.
18. Li J, Chen Q, Luo X, Hong J, Pan K, Lin X, et al. Neutrophil-to-Lymphocyte Ratio Positively Correlates to Age in Healthy Population. J Clin Lab Anal. 2015;29(6):437–43.