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Original Research Article

Neutrophil–Lymphocyte and Platelet–Lymphocyte Ratios are Predictors of Lung Malignancy

Yusup S. Sutanto[1,3*], Muhammad Rudiannor[1,3], Jatu Aphridasari[1,3], Hendra Kurniawan[2]

[1]*Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Sebelas Maret, Indonesia*
[2]*Department of Public Health and Community Medicine, Faculty of Medicine, Universitas Syiah Kuala, Indonesia*
[3]*Dr. Moewardi General Hospital, Indonesia*

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Abstract

Background: Inflammatory cells play an essential role in the neoplastic process by stimulating cancer proliferation, survival, and migration. Neutrophil-lymphocyte and platelet-lymphocyte levels can be used as inflammatory tissue damage markers in cancer patients.

Objective: This study aimed to analyze the increase of neutrophil-lymphocyte ratio (NLR) and platelet–lymphocyte ratio (PLR) as the predictive factors for lung malignancy.

Methods: This study was a diagnostic test to compare NLR and PLR ratios in lung tumor patients at Dr. Moewardi Hospital Surakarta from August to October 2018. The subjects (60) were selected with consecutive sampling who took lung cancer diagnostic tests and divided into two groups of patients with lung tumors (30) and healthy (30) as control. The diagnostic procedures and neutrophil-lymphocyte and platelet–lymphocyte ratio calculation were performed on both groups. The optimum cutoff values for the NLR and PLR were calculated from the receiver operating curve analysis.

Results: The statistical test found a significant difference in the neutrophil–lymphocyte and platelet–lymphocyte ratios between cancer patients and control ($p = 0.0000$). There is a significant difference in the NLR and PLR between healthy and cancer patients. The NLR was calculated and it was 6.25 ± 2.88 in cancer patients and 1.84 ± 0.47 in healthy subjects. Meanwhile, the PLR in cancer patients was 254.93 ± 116.59 and 114.33 ± 27.67 in healthy subjects.

Conclusion: The ROC curve for NLR has an AUC value of 0.941 with a p-value of 0.000 ($P < 0.01$), and for PLR has an AUC value of 0.898 ($p = 0.000$). The increase of NLR and PLR can be used as the predictive factors of lung malignancy.

Keywords: *leukocyte; lymphocyte; lung tumor; malignancy; neutrophil; platelet*
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INTRODUCTION

Lung cancer is the leading cause of cancer morbidity and mortality among men worldwide and the second leading cause of cancer-related deaths among women.[1-5] Lung cancer is also the most common cancer for men in Indonesia, with the rate of incidence of 19.4 per 100.000 men and an average death rate of 10.9 per 100.000 men.[1-6] By contrast, around 200.000 subjects were diagnosed with lung cancer in 2010 in the United States, and nearly 160.000 subjects died of it. The patients diagnosed with lung cancer have an average age of 68–70 years.

The early discovery of lung malignancy is the most encouraging approach to improve the treatment results. Early detection of lung cancer using different serum biomarkers has been tested, but there is no single biomarker that can reliably detect lung cancer.

* Corresponding author:
E-mail: *dr_yusupsubagio@yahoo.com*
(Yusup S. Sutanto)

Table 1. Characteristics of Study Subjects

Characteristics	Lung malignancy diagnosis		p-value
	Positive (n = 30)	Negative (n = 30)	
Age	54.13 ± 16.50	44.53 ± 7.68	0.005[1]
Gender			
Male	17 (56.7%)	17 (56.7%)	
Female	13 (43.3%)	13 (43.3%)	
Employment			0.005[2]
Not working	19 (63.3%)	28 (93.3%)	
Working	11 (36.7%)	2 (6.7%)	
Education			0.000[3]
Primary school	11 (36.7%)	0 (0.0%)	
Secondary school	8 (26.7%)	5 (16.7%)	
High school	9 (30.0%)	16 (53.3%)	
University	2 (6.7%)	9 (30.0%)	
Brinkman index			0.022[3]
Non-smoker	14 (46.7%)	22 (73.3%)	
Mild smoker	5 (16.7%)	4 (13.3%)	
Moderate smoker	8 (26.7%)	4 (13.3%)	
Heavy smoker	3 (10.0%)	0 (0.0%)	
BMI			0.000[3]
underweight	22 (73.3%)	1 (3.3%)	
normal	5 (16.7%)	8 (26.7%)	
overweight	3 (10.0%)	21 (70.0%)	
Clinical symptom			
cough	14 (46.7%)		
chest pain	7 (23.3%)		
dyspnea	9 (30.0%)		

Notes: BMI = body mass index; [1] *Independent t-test*, [2] Chi-Squared/Fischer's exact test, [3] Mann–Whitney U test

Table 2. The difference between NLR and PLR in patients with lung cancer and healthy subjects

Variable	Lung cancer Diagnosis		p-value
	Positive	Healthy	
Neutrophil	75.47 ± 8.30	56.41 ±5.74	0.000[2]
Lymphocyte	15.20 ± 8.01	31.82 ± 5.11	0.000[2]
Platelet	373.70 ± 109.90	313.40 ± 44.93	0.007[1]
Leukocyte	11693.33 ± 3692.20	9020.00 ± 1558.82	0.003[2]
NLR	6.25 ± 2.88	1.84 ± 0.47	0.000[2]
PLR	254.93 ± 116.59	114.33 ± 27.67	0.000[2]

Note: NLR = neutrophil–lymphocyte ratio; PLR = platelet–lymphocyte ratio; [1]Independent t-test; [2]Mann–Whitney test

Combining the tumor's systemic inflammatory factors could be the primary technique to diagnose lung cancer because inflammation is an essential component in cancer development. Cancer mostly develops at the site of infection, chronic irritation, and inflammation. The tumor microenvironment is largely regulated by inflammatory cells. Moreover, tumor cells produce various cytokines and chemokines that can attract leukocytes. The inflammatory component of neoplasms includes different leukocyte subtypes such as neutrophils, macrophages, and dendritic cells producing inflammatory cytokines and mediators.[7-9]

Platelets are increasing in lung cancer cases. They release angiogenesis factor and attach to micro tumor vessels.[10] The presence of macrophage colony-stimulating factor (M-CSF) and granulocyte colony-stimulating factor (G-CSF) cytokines causes neutrophilia in lung cancer patients.[11] Lung cancer cells release TGF-β and IL-10, causing the suppression of lymphocytes. Neutrophils also secrete endothelial vascular growth factors and pro-angiogenic factors involved in tumor formation, which is also essential for tumor growth and metastase.[10-12]

Inflammation plays a vital role in the neoplastic process by stimulating cancer proliferation, survival, and migration. The neutrophil–lymphocyte ratio (NLR) and the platelet–lymphocyte ratio (PLR) can be used as the inflammatory markers of tissue damage in cancer

patients.[8,9]. Until now, the researchers have not found a similar study conducted in Indonesia. The purpose of this study was to analyze the possibility of patients' NLR and PLR values to predict lung malignancy. The study hypothesizes that the increase of NLR and PLR can be used as the predictive factors of lung malignancy.

MATERIALS AND METHODS

Experimental design

This study was a diagnostic test to compare NLR and PLR ratios. NLR was measured by dividing the number of neutrophils and lymphocytes in the peripheral blood. Meanwhile, PLR was measured by dividing the number of thrombocytes and lymphocytes. The diagnostic value of NLR and PLR was evaluated by calculating the area under the curve (AUC) from receiver operating characteristic (ROC) curves for lung malignancy prediction. The baseline characteristics including age, sex, occupation, education, Brinkman index, body mass index (BMI), and clinical symptoms were collected. This study was ethically reviewed and approved by Dr. Moewardi Hospital Committee for Research on Human Subjects (Medical) (approval number: 705/IX/HREC/2018).

Study subjects

The study was performed at Dr. Moewardi Hospital Surakarta from September 2018 until the number of samples was fulfilled. The study population was 60 subjects, that divided into 2 groups, 30 patients with lung tumors and 30 healthy subjects as control. The inclusion criteria for lung tumor patients were the subjects who had lung tumors and undergone diagnostic procedures at Dr. Moewardi Hospital Surakarta, willing to participate in the study by giving informed consent, aged ≥18 years, and have not undergone any chemotherapy treatment. The inclusion criteria for the control group were healthy subjects without lung tumor, willing to follow the study by signing informed consent, aged ≥ 18 years, and have not undergone any chemotherapy. Lung tumor patients with symptoms of acute infection, COPD, diabetes mellitus, acute or chronic kidney failure, clinical HIV, liver disease, and heart failure and those using corticosteroids were excluded from the study. While the exclusion criteria for the control subject were similar to the lung tumor patients.

NLR and PLR measurements

The subjects were subjected to anamnesis, physical examination, laboratory analysis for blood testing, NLR and PLR values calculation, contrast thoracic CT scanning, and diagnostic procedures. The tests were intended to check the compatibility between diagnostic results with NLR and PLR values.

Data analysis

The data analysis was performed using SPSS 21 (IBM) for Windows. A descriptive univariate analysis was presented with frequency and percentage distribution. The data was analyzed with One Way Anova and Mann-Whitney test. This study used diagnostic procedures based on clinical, radiological, transthoracic needle aspiration (cytology), and bronchoscopy. It determined the point of intersection with a receiver operating characteristic (ROC) curve. Fisher's exact test and Pearson's chi-squared test were used to determining the difference between the baseline data parameters.

RESULTS

Study subjects' characteristics

The subjects' general characteristics include age, sex, occupation, education, degree of smoking, BMI, and complaints were showed in Table 1. The average age of patients with a positive cancer diagnosis was 54.13 ± 16.50 years old while the healthy subjects had an average age of 44.53 ± 7.68 years old. The statistical test obtained a p-value = 0.005 ($p < 0.05$), which means that there were significant differences in patient characteristics based on age.

The majority of patients with a cancer diagnosis were male (56.7%) but the statistical test showed no significant difference in patient characteristics based on gender (p-value = 1.000). As much as 63.3% of cancer patients were working while 93.3% of healthy patients were working, and the statistical test showed significant differences in the characteristics of patients based on work (p-value = 0.005). The majority of the subjects with a cancer diagnosis were elementary school graduates (36.7%) and the majority of healthy subjects were in high school (53.3%). Based on the p-value (0.000), there were significant differences in the education characteristics, where cancer-positive subjects tend to have low education.

The number of smokers in cancer patients was 46.7%, so the majority did not smoke. On the other hand, the majority of healthy subjects also did not smoke (73.3%). The statistical test obtained a p-value = 0.022 ($p < 0.05$), which means that there are significant differences in the subjects' characteristics based on the degree of smoking, where cancer-positive subjects tend to smoke. Most of the cancer patients had low BMI (73.3%) while the majority of healthy subjects with excess nutritional status were 70.0%. The statistical test showed significant differences in the subjects' BMI (p-value = 0.000). As much as 46.7% of complaints were from lung cancer patients while the healthy subjects had no complaint and it was significantly different ($p = 0.000$).

NLR and PLR differences in subjects

The results of NLR and PLR calculation in both groups were listed in Table 2. The average number of neutrophils was significantly lower in healthy patients (p-value = 0.000) with the average number was 75.47 ± 8.30 in cancer patients and 56.41 ± 5.74 in healthy subjects. Interestingly, the average lymphocytes were significantly higher in healthy subjects (p-value = 0.000) with the average number 15.20 ± 8.01 in cancer patients and 31.82 ± 5.11 in healthy subjects. On the other hand, the platelets number was significantly lower in healthy subjects ($p = 0.007$), with an average of 373.70 ± 109.90 in cancer patients and 313.40 ± 44.93 in healthy subjects. The leukocytes were also significantly lower in healthy subjects (p-value = 0.003) with an average number of 11693.33 ± 3692.20 in cancer patients and 9020.00 ± 1558.82 in healthy subjects.

From the blood test results, the NLR was calculated and it was 6.25 ± 2.88 in cancer patients and 1.84 ± 0.47

in healthy subjects. As the p-value = 0.000 ($p < 0.05$) so the difference was significant where healthy subjects have lower NLR. Meanwhile, the PLR in cancer patients was 254.93 ± 116.59 and 114.33 ± 27.67 in healthy subjects. The PLR difference between cancer patients and healthy subjects was significantly different (p-value = 0.000).

The diagnostic test of the neutrophil–lymphocyte ratio

Based on the comparison of diagnostic results from both groups with the NLR results. The ROC curve results were illustrated in Figure 1.

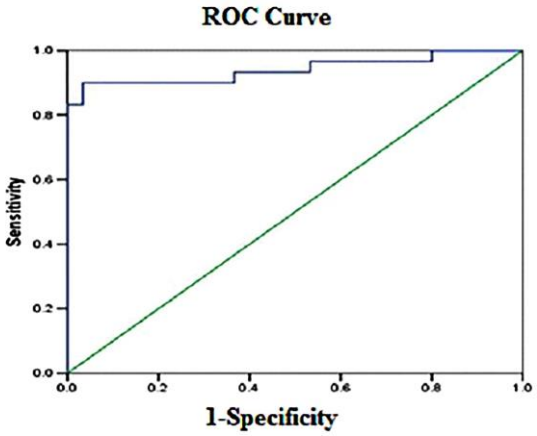

Figure 1. ROC curve test and NLR test

Based on the ROC curve, an AUC value of 0.941 with a p-value of 0.000 ($P < 0.01$) was obtained. The cutoff value for NLR was 2.705 at 90.0% sensitivity and 96.7% specificity. It means that 90.0% of lung cancer patients can be detected by NLR examination. The specificity value of NLR measurements was 96.7%, meaning that it is likely to be healthy, which can be excluded in patients who have NLR > 2.705 of 96.7% (Table 3).

Table 3. NLR and PLR cutoff determination in lung cancer

AUC	Sensitivity	Specificit	Cutoff Value	P
		NLR		
0.941	90.0%	96.7%	2.705	0.000
		PLR		
0.898	83.3%	80.0%	136.63	0.000

The diagnostic test of the platelet–lymphocyte ratio

Similar to NLR measurement, the diagnostic results from both groups were compared with the PLR results to obtain the ROC curve results (Figure 2).

As presented in Table 3, the AUC value of 0.898 ($p = 0.000$) was obtained based on the ROC curve. The cutoff value of PLR was 136.63 at 83.3% sensitivity and 80.0 % specificity. The obtained specificity value suggested that 83.3% of lung cancer patients can be detected by PLR examination. Meanwhile, the obtained specificity value suggested that the probability of a healthy person being excluded in patients who have a PLR > 136.63 is large (80.0%).

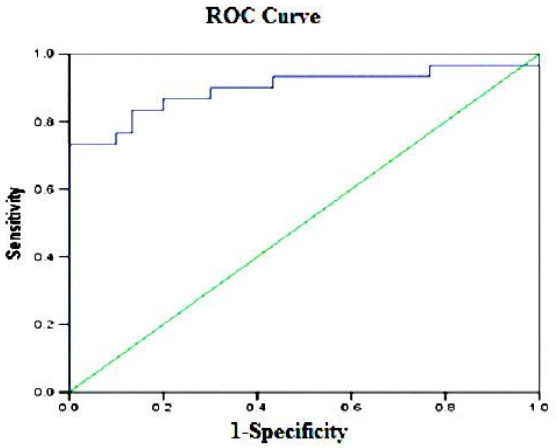

Figure 2. ROC curve for the PLR diagnostic test

DISCUSSION

This study found that the number of males with lung cancer compared with females with lung cancer is in accordance with the study by the World Health Organization. In 2014, lung cancer was the most common type of cancer in Indonesian males. The present study found cancer patients with an average age of 54.13 years[13]. Youlden et al.[14] (2008) reported that in 2002, globally, 5% of patients diagnosed with lung cancer were between the ages of 0 to 44 years; 14% were 45–54 years; 25% were 55–64 years; and 55% among those aged 65 years and older.

The majority of patients with cancer were a worker (63.3%). Also, the majority (53.3%) of patients with a negative diagnosis of cancer have a senior high-school level of education and 36.7% of cancer patients only have a primary school education. Hruba et al.[15] reported that in 2009, there was a 39% increase in the lung cancer risk in unskilled workers compared to office workers and a 31% risk increase for those with lower education compared to those with tertiary education, both after adjusting for the effects of smoking and occupational exposure to carcinogens. The degree of passive smoking by non-smoking healthy patients was 73.3% and 46.7% of the cancer patients were non-smoking. Smoking increases the risk of lung cancer and smokers still show a higher risk than non-smokers because the risk never returns to the baseline or normal. This is consistent with the study of Young et al.[16] in 2009 who reported 85% of lung cancer diagnoses were made in smokers or former smokers. Approximately 50% of lung cancer cases are diagnosed in former smokers. Thus, there are more than 500 million smokers worldwide who are at high risk of lung disease, including lung cancer, and lung cancer occurs in around 15% of smokers.[17]

The majority of patients (73.3%) had a positive diagnosis of cancer and poor nutritional status. In 2018, Zhu et al.[18] reported that high BMI was associated with a low risk of lung cancer. Most of the complaints (46.7%) from patients with lung cancer were the cough. In 2014, Iyer et al.[19] found that the most common symptoms of lung cancer patients were coughing, shortness of breath, and chest pain.

There is a significant difference in neutrophils count between patients with a negative cancer diagnosis and

those with a positive one. Patients with advanced cancer have an increased number of neutrophils in the blood. Tumors inducing neutrophilia can be caused by the production of the granulocyte-macrophage colony-stimulating factor (GM-CSF). Cytokines, such as the granulocyte colony-stimulating factor (G-CSF), interleukin-1 (IL-1), and IL-6, produced by tumors contribute to the increase of neutrophils in the blood. There are significant differences in lymphocytes between healthy subjects and cancer subjects, with a decrease was observed in cancer patients.[20-24] According to Kargl et al.[25] (2008), increased neutrophil count and lymphocyte suppression were obtained in patients with lung cancer.

There is a significant difference in platelet count between healthy and cancer patients. A study conducted by Karagoz et al.[10] found that the number of platelets in lung cancer patients was not different from that in healthy subjects. Another study found thrombocytosis in pulmonary patients was associated with the presence of metastasis.[23]

There is a significant difference in the NLR and PLR between healthy and cancer patients. The relationship between the increased NLR and PLR in various tumors is not yet fully understood, several pathways allow various cancers to grow at the site of infection and inflammation. Inflammation is an essential process in the development and progression of cancer.[24] A study conducted by Kemal et al.[26] supported the predictive value of NLR and PLR markers, reflecting the relationship between cancer and inflammation. This study also supports the results of previous studies in various types of cancer. Nikolic et al. (2016) found a significantly higher NLR and PLR in patients with different histopathological lung cancer subtypes than in the control group.[5] The study also demonstrated that NLR and PLR have a satisfactory diagnostic value in the diagnosis of lung cancer.

The neutrophil–lymphocyte ratio as a predictive factor for lung malignancy

It was observed that the average count of neutrophils was significantly different between groups (p-value = 0.000), with a mean value of 56.41 in healthy controls and 75.47 in cancer patients. It was similar with the lymphocytes number; a significant difference between groups (p-value = 0.000) with the mean value of 31.82 in healthy controls and 15.20 in cancer patients. These results are consistent with Kargl et al.,[25] where the increased neutrophil count and lymphocyte suppression were obtained in patients with lung cancer.

The mean NLR was significantly lower in healthy subjects (p-value = 0.000), with a mean value of 1.84 in healthy controls and 6.25 in patients with a positive diagnosis of cancer. The ROC curve showed the cutoff value of 2.70 for NLR. This is in accordance with a study conducted by Nicolic et al.[5], where there was an increase in the value of NLR in lung cancer patients, which is 2.71. Kemal et al.[26] also showed a significant increase in NLR in patients with lung cancer compared to healthy subjects; 4.42 in lung cancer patients and 2.45 in healthy subjects.

The platelet–lymphocyte ratio as a predictive factor for lung malignancy

The results showed significantly more platelets in cancer subjects (p-value = 0.007), with the mean value of 313.40 in healthy subjects and 373.70 in patients with a positive diagnosis of cancer. However, the lymphocytes were significantly lower in cancer subjects (p-value = 0.000), with an average of 31.82 in healthy controls and 15.20 in patients with a positive cancer diagnosis. Consequently, the result of PLR showed significantly lower values in healthy subjects (p= 0.000) with a mean value of 114.33, while it was 254.33 in patients with a positive cancer diagnosis. In this study, the examination of lung cancer with PLR samples obtained a cutoff value of 136.63 based on the ROC curve. Nicolic et al.[5] found that there is an increase in the PLR value in lung cancer patients, which was 182.31. A study conducted by Kemal et al.[26] also demonstrated a significant PLR increase in cancer patients compared to healthy subjects; 245.1 in lung cancer patients and 148.2 in healthy subjects.

In summary, NLR and PLR are cheap, modest, and readily available biomarkers as predictive information to identify lung malignancy. The limitations of this study are that it cannot distinguish the types of adenocarcinoma lung cancer, squamous cell carcinoma, small cell carcinoma, or large cell carcinoma while helping with the diagnosis. Considering the limitations, the reported results may not give more information for a wide range of lung malignancy types.

CONCLUSION

The increase of NLR and PLR can be used as the predictive factors of lung malignancy. The receiver operating characteristic (ROC) curve for NLR was estimated to have an AUC value of 0.941 ($P < 0.01$), and for PLR, it has an AUC value of 0.898 ($p = 0.000$). The suggestion for further study is the increased number of samples to allow the distinction of lung cancer types.

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