

PLATELET-TO-LYMPHOCYTE RATIO (PLR) PROFILE AND NEUTROPHIL-TO-LYMPHOCYTE RATIO (NLR) IN LUNG CANCER PATIENTS IN ULIN GENERAL HOSPITAL BANJARMASIN 2017-2018

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Abstract: Lung cancer is the leading cause of malignancy in the world reaching up to 13% of all cancer diagnoses. Platelet-to-Lymphocyte Ratio (PLR) and Neutrophil-to-Lymphocyte Ratio (NLR), are promising markers of inflammatory prognosis, clinical decisions for proper management of lung cancer patients. The research used a retrospective analytic observational study as its research method. Samples were taken from Pathology Anatomy Laboratory, and the medical record data of lung cancer patients in Ulin General Hospital Banjarmasin from 2017 to 2018. Male lung cancer patients have percentage of 72% with PLR NLR values by sex are not much different $p>0.05$. 23% of patients were aged ≥ 65 years and 77% were aged ≤ 65 years with value $p>0.05$. Adenocarcinoma reaches 65% with $p>0.05$. Most metastases are 44% pleural effusion with value $p>0.05$. Percentage of advanced stage is 90% with a higher PLR NLR value at the end stage. There is a meaningful relationship of NLR with lung cancer stage $p<0.05$, but no relationship with PLR $p>0.05$. PRL and NRL are increased at advanced stage. NRL and PRL did not differ significantly based on age, sex and histology of lung cancer.

Keywords: Platelet-to-lymphocyte ratio (PLR), Neutrophil-to-lymphocyte ratio (NLR), lung cancer

INTRODUCTION

Lung cancer is the leading cause of malignancy in the world reaching up to 13% of all cancer diagnoses. In addition, lung cancer also causes 1/3 of all cancer deaths, especially in men. The incidence of lung cancer is quite high in Indonesia, which is ranked 3rd of all malignant neoplasms in inpatients and outpatients in hospitals, in 2012, lung cancer accounted for about 23.1% of all new cancer cases and was the cause of 19.7 % of all cancer deaths in Indonesia.¹

Cancer begins with an inflammatory response which has a significant role in tumor initiation and progression and the predictive value of inflammatory markers in tumor prognosis. Various parameters to measure inflammatory parameters, including Platelet lymphocyte ratio (PLR) Neutrophil to Lymphocyte Ratio (NLR). PLR is calculated as a ratio of the platelets number to the lymphocytes number. Meanwhile, NLR is calculated as the ratio of the neutrophils number to the lymphocytes number.^{2,3}

In recent decades the number of platelets, neutrophils and lymphocytes has been the focus of research in relation to the prognosis of various types of cancer. Therefore in this study the PLR and NLR profiles of lung cancer patients in the Ulin General Hospital Banjarmasin in the January 2017-December 2018 period will be explained.

RESEARCH METHOD

This research is an analytic observational design. The study was conducted at Ulin General Hospital Banjarmasin. The parameters observed were neutrophil, platelet and lymphocyte values. Inclusion criteria include all patients diagnosed with histological lung cancer, inpatients at Ulin General Hospital Banjarmasin from 1 January 2017 to 31 December 2018 and not having hematological abnormalities such as: diseases that affect the production of blood cells in the bone marrow and Pulmonary infection diseases such as: Pulmonary TB, Pneumonia, Bronchitis, Lung Abscess and Lung Mycosis. Exclusion criteria included medical record data that did not include inclusion criteria, which were not diagnosed with histological lung cancer, data of tumor, incomplete laboratory data and patients who had received chemotherapy before. The obtained data was recorded and processed using SPSS 16.0.

RESULTS AND DISCUSSION

In this research, samples distribution based on gender, from 78 samples, there were 56 men patients (72%) and 22 women patients (28%). This result meant the incidence of lung cancer is higher in men than women.

Table 1. NLR and PLR value based on samples gender

Parameter	Gender		p value
	Man	Woman	
Total (person)	56	22	
NLR	7.09±6.89	9.68±1.52	0.33
PLR	333.2±349.5	344.7±190.2	0.7

Based on the data in table 1, the mean of NLR value in men is almost the same as in women: 7.09 ± 6.89 in men and 9.68 ±

1.52 in women. Likewise the PLR values for men and women were not much different (333.2 ± 349.5 in men and 344.7 ± 190.2 in

women). Based on the results of statistical analysis showed no significant relationship between gender with PLR and NLR values where the values of $p = 0.7$ and $p = 0.33$ ($p > 0.05$).

From the research, the age distribution of lung cancer sufferers is more at the age of

≤ 65 years (60 patients or 77%) compared to the age of ≥ 65 years (18 patients or 23%). The mean age of lung cancer patients based on these results was 57.43 ± 9.91 years.

Table 2. NLR and PLR value based on the samples age

Parameter	Age		p value
	≤ 65 y.o	≥ 65 y.o	
Total (person)	60	18	
NLR	7.9 ± 10.5	6.94 ± 7.58	0.77
PLR	354.5 ± 348	272.4 ± 117	0.36

PLR and NLR values in these two age groups were found to be not much different, i.e PLR: 354.5 ± 348 at age ≤ 65 years and PLR: 272.4 ± 117 in the age group ≥ 65 years. NLR value: 7.9 ± 10.5 at age ≤ 65 years and NLR: 6.94 ± 7.58 in the age group ≥ 65 years. The results obtained $p = 0.36$ for the relationship between PLR and age, and $p = 0.77$ for the relationship between NLR and age. Based on the results of this statistical analysis it was concluded that there was no

significant relationship between PLR and NLR values with age in lung cancer patients.

The number of patients based on the stage of cancer for this research were divided into early and advanced stage of lung cancer stage. In this research, advanced lung cancer patients were 56 patients (71.7%) and those who were still in the early stages were only 22 patients (28.3%). The advanced lung cancer patients were more than early stage of lung cancer.

Table 3. NLR and PLR value based on the stage of cancer

Parameter	Stage of Cancer		p value
	Early Group (IA, IB, IIA, IIB, IIIA)	Advanced Group (IIIB, IIIC, IVA, IVB)	
Total (person)	22	56	
NLR	3.86 ± 2.22	8.33 ± 1.04	0.013
PLR	260.3 ± 140.9	343.9 ± 325.1	0.39

Based on the data in table 3 it can be concluded that the PLR in these 2 groups show different values, where the early stage has a lower PLR value than the advanced stage group. The PLR in the early stage group was 260.3 ± 140.9 and at the advanced stage was 343.9 ± 325.1 . However, based on statistical analysis there was no significant relationship between PLR values and the

stage of lung cancer where $p = 0.39$ ($p > 0.05$).

The NLR values in both groups of stages also showed an increase from the normal value of > 3.53 . In the table 3 the NLR in the early stage is higher than the advanced stage group, i.e, 3.86 ± 2.22 in the early stage patients and 8.33 ± 1.04 in the advanced stage patients. This was further

strengthened by the results of statistical analysis which showed that a significant relationship was found between the NLR

value and the stage of lung cancer $p = 0.013$ ($p < 0.05$).

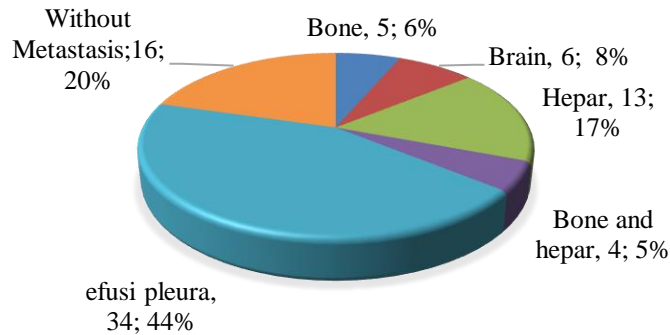


Figure 1. The comparison of lung cancer metastasis

Table 4. NLR and PLR value based on lung cancer metastasis profile

Parameter	Metastasis Profile		Nilai <i>p</i>
	Metastasis	Without Metastasis	
Total (person)	62	16	
PLR	311.4±162.4	266±139	0.67
NLR	8.34±1.09	5.18±4.49	0.38

Based on figure 1, the most often lung cancer metastasis is pleural effusion with a percentage of 44% (34 patients), from the total of 62 patients (79%) who had metastasis of lung cancer. Lung cancer patients without metastasis as much as 21% (16 patients), with PLR values in bone, brain, liver, liver and bone metastases, pleural effusion, and those without metastasis in order as follows: 301.4 ± 83.2 , 282.1 ± 105.6 , 322.6 ± 140 , 284 ± 218.1 , 318.1 ± 188.4 , 266 ± 139 . The NLR values for bone, brain, liver, liver and bone metastases, pleural effusion, and those

without metastases are as follows: 19.9 ± 3.13 , 5.67 ± 3.77 , 8.9 ± 8.5 , 6.45 ± 2.3 , 7.12 ± 6.83 , 5.18 ± 4.49 . Based on Table 5, it shows that the PLR and NLR values are higher in lung cancer with metastasis compared to lung cancer without metastasis. From the statistical analysis it was concluded that there was no significant relationship between PLR and NLR values with lung cancer metastasis ($p > 0.05$), where $p = 0.67$ for the relationship with PLR and $p = 0.38$ for the relationship with NLR.

Table 6. NLR and PLR value based on histological type

Parameter	NSCLC Type		<i>p value</i>
	Adenocarcinoma	Squamous Cell Carcinoma	
Total (person)	51	27	
NLR	7.84±6.85	7.72±1.41	0.23
PLR	324.3±166.8	356.1±483.2	0.6

Adenocarcinoma and squamous cell carcinoma are types of Non-Small Cell Lung Cancer (NSCLC). This research found 65% (51 patients) of adenocarcinoma lung cancer, while squamous cell carcinoma was 35% (27 patients). The mean NLR and PLR results in the two types of histology were not much different and both showed an increase. The adenocarcinoma type showed PLR value 324.3 ± 166.8 and the squamous cell carcinoma type showed PLR value of 356.1 ± 483.2 . In accordance with the NLR values that did not show a large difference between the 2 types of histology of lung cancer i.e., 7.84 ± 6.85 for adenocarcinoma types and 7.72 ± 1.41 for NLR values for squamous cell carcinoma types. The results of statistical analysis showed the results of $p > 0.05$ ($p = 0.6$ for PLR and $p = 0.23$ for NLR) where it was concluded that there was no significant relationship between PLR and NLR values with the type of lung cancer histopathology.

Based on the description of the result, lung cancer patients are more men than women. This is as stated in previous studies that man patients have a 4.64 times greater risk of experiencing lung cancer compared to patients who are women. The relationship between gender and lung cancer is often associated with smoking.¹

The PLR and NLR values based on gender in this study are not much different. This is consistent with studies conducted by Alexander that found NLR values were not influenced by gender, education, and marital status.^{4,5}

Based on the age of lung cancer patients in this study found more at age ≤ 65 years than at age ≥ 65 years. This result is in line with research conducted by Chiang T.A which states that the majority of sufferers are found at the age of less than 65 years by 66% compared with age over 65 years which is as much as 34%.⁶

Based on research conducted by Endang, the normal PLR value is 155 and the normal NLR value is between 0.78-3.53.⁷ The PLR value based on the stage in

this study showed a higher value at an advanced stage than the initial stage. This is in line with the theory which states that platelets play an important role in tumor growth. Platelets can stimulate tumor development by increasing the process of angiogenesis through the cytokine Vascular Endothelial Growth Factor (VEGF). There is a direct correlation between the number of circulating platelets and VEGF levels in plasma serum. Tumor cells tend to aggregate to form lump in circulation with adhesion. Platelet aggregation with tumor cells causes tumor cells to live longer.⁸

Thrombocytes and tumor cells have heterogeneous outer protective functions protecting the tumor cells themselves from attacks in the blood circulation, especially attacks from leukocytes. According to Nieswandt, platelets will undergo lysis and this process is mediated by Natural Killer (NK) tumor cells in his research using mice, causing thrombocytopenia. Then, this hypothesis was confirmed by Palumbo et al. That there was a decrease in the expression of fibrinogen or α protein and it turned out that this protein played an important role for thrombocytes activation. In this study also showed that thrombocytes and fibrinogen protect tumor cells in blood vessels from Natural Killer (NK) cells.⁹

Rachidi found that thrombocytes are the main source of TGF- β with TGF- β -docking Glycoprotein A Reiterations Predominant (GARP) receptor expression. The function of GARP is to activate TGF- β near the thrombocytes. The GARP-TGF β complex with lactate secreted by thrombocytes can inhibit T cell immunity. This data consolidates the evidence that thrombocytes can interfere the adaptive immune system to deal with cancer cells.⁹

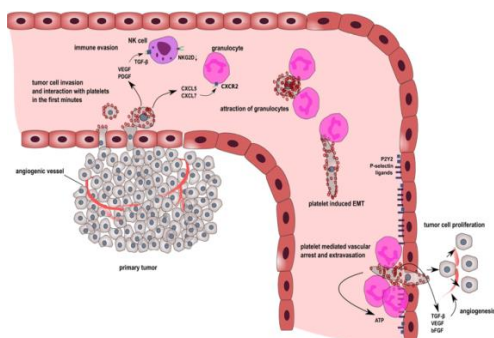


Figure 2. Platelet role in Angiogenesis and Tumor Metastasis¹¹

It can be concluded that the higher the platelet value will increase the PLR which means that the lymphocyte value will decrease with the severity of the cancer stage. The decrease in the number of T helper lymphocytes occurs through the mechanism of cancer cells that damage the antigen presentation. In addition these cells also produce immunosuppressed mediators such as IL-10, Nitrite Oxide (NO) and Transforming Growth Factor- β (TGF- β) which have a role in the mechanism of reducing the number of lymphocytes, so it is consistent with the results of this study that the ratio of platelets and lymphocytes will be higher along with the increasingly severe stage of lung cancer.⁹ However, based on statistical analysis in this study it was found that the p value > 0.05 which showed that there was no significant relationship between the PLR value with the stage of lung cancer. This is suitable with other studies by Xiaobin Gu which was also carried out in Asian populations such as the sample in this study. In that study Xiaobin Gu explained that PLR increase was associated with poor Overall Survival (OS) and Disease Free Survival (DFS) or Progress Free Survival (PFS), especially in NSCLC. In addition, high PLR values have a significant relationship with poor OS and DFS or PFS in Caucasians but do not have a significant relationship with poor OS and DFS or PFS in Asian populations.¹⁰ Komurgoclu research in Asian populations also explains the same thing, PLR does not show a significant relationship in predicting the

outcome of NSCLC. In contrast, the NLR shows a significant relationship in predicting the outcome of NSCLC.¹¹

The NLR values in the two staging groups in this study also both showed an increase from the normal value with a p value < 0.05 where there was a significant relationship between the NLR values and the stage in lung cancer. This is consistent with the theory that the increase in neutrophils is an indicator of poor prognosis. In many patients with advanced stage of cancer, an increase in the number of neutrophils in the blood is found.¹²

Neutrophils can exclude factors that cause localized immunosuppression by interfering with T cell responses, inducing T cell apoptosis that allows tumor development to occur.^{13,14}

Neutrophils can directly work on pralalignant epithelial cells to accelerate the tumorigenicity process. Neutrophils produce ROS (through the action of myeloperoxidase and NADPH oxidase) which are known to cause DNA damage, genomic instability, and gene mutations in pramalignant epithelial cells and encourage oncogenic transformation. This observation shows that neutrophils can promote tumorigenesis through various mechanisms, especially in chronic inflammation.¹²

In this study it is also known that pleural and hepatic effusions are organs with the most presentations as sites for metastases in lung cancer. This was explained by Jing Li in his study that the most common metastases were in patients diagnosed with advanced lung cancer. The data is also strengthened by Milovanovic who explained in his research that the most frequent hematogenous metastasis is in the liver and adrenal glands.^{15,16}

Based on the histology type of pathology anatomy in lung cancer, this study reported that the type of adenocarcinoma was the most histological type of pathology anatomy. PLR and NLR values both show an increase but the value is not much different between the types of

adenocarcinoma with squamous cell carcinoma types.

Zhang Xiaoli et al found that most NSCLC type lung cancer patients had an increased neutrophil lymphocyte ratio. This is similar to the results of previous studies where the average value of NLR increased. Increased NLR is associated with poor prognosis and treatment and a low 5-year survival rate in these patients. High or increased NLR can be explained by increased neutrophils and reduced lymphocytes.^{7,17}

CONCLUSION

Based on research conducted obtained results with the number of male sufferers more than women. The mean NLR and PLR between men and women is not much different from the value of $p > 0.05$. The mean age of patients with lung cancer was 57.43 ± 9.91 years. There was 23% of patients were aged ≥ 65 years and 77% of patients aged ≤ 65 years and had a PLR NLR value that was not much different from $p > 0.05$. Based on the type of lung cancer histopathology, the percentage of adenocarcinoma is 65% with PLR and NLR values between the two histology types of pathology anatomy which are not much different from $p > 0.05$. Most metastases are pleural effusion (44%). Based on statistical analysis, it can be concluded that there is no significant relationship between PLR and NLR values with lung cancer metastasis ($p > 0.05$), where $p = 0.67$ for relationship with PLR and $p = 0.38$ for relation with NLR. The percentage at the advanced stage of lung cancer is 90% with an average PLR-NLR value that is higher than the average value of an early stage PLR-NLR; which obtained NLR value with lung cancer stage p value < 0.05 and between PLR value with lung cancer stage p value > 0.05 .

For further research required a larger sample size and a longer period. Therefore, for the future progress of research, a complete medical record data support is needed for each health facility.

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