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Prognostic Value of Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio in Lung Cancer

***Seda Beyhan Sagmen, Coskun Dogan, Sevda Comert, Nesrin Kiral, Ali Fidan, Elif Torun Parmaksiz**

Health Science Unv Kartal Dr. Lutfi Kirdar Training and Research Hospital, Department of Pulmonary Medicine, Istanbul, Turkey.
*Email: sedabeyhansagmen@gmail.com
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Abstract: Numerous studies determined that the neutrophil/lymphocyte (NLR) and platelet/lymphocyte ratios (PLR) had prognostic value in several cancer types. This study aimed to evaluate the relationship between NLR and PLR values with the survival time of lung cancer patients. Patients diagnosed with lung cancer between January 2014 and December 2016, were retrospectively evaluated. Demographic characteristics, disease stages, laboratory parameters recorded, and the relationship of NLR and PLR values with the survival time and the disease stage evaluated. NLR and PLR were categorized into two groups. SPSS 17.0 software package was used for the statistical analysis. ROC analysis, Student T-test, Chi-square, and Mann-Whitney U test were used. Mean age of 62±8 years were included in the study. In the NSCLC group, the average NLR and PLR values were 4±3.35 and 194.6±144.4 respectively. Regarding the NSCLC group, the overall survival time was shorter in the subgroup with an NLR >3.43 (13.1 months) compared to the subgroup with an NLR ≤3.43 (24.3 months). The mean survival time was shorter in the group with a PLR > 136.9 compared to the group with a PLR ≤136.9 (15.9 and 24.6 months respectively). Subgroups consisting of survivors and non-survivors in the NSCLC group showed a statistically significant difference considering neutrophil and lymphocyte count, CRP, NLR, and PLR values ($p<0.05$). As NLR and PLR values are easily accessible, they have an essential role in the prognosis of lung cancer as well as other cancer types.
Keywords: lung cancer; neutrophil to lymphocyte ratio; platelet to lymphocyte ratio; prognosis; survival time

INTRODUCTION

Lung cancer is the leading cause of cancer deaths worldwide. Approximately 85% of lung cancer cases constitute of non-small cell lung cancer (NSCLC) and 15% of small cell lung cancer (SCLC). Despite the advances in diagnosis and treatment, lung cancer has still a poor prognosis (Siegel et al., 2013). Was demonstrated that one of the most important determinants of survival was the stage of the tumor. Other factors that affect prognosis are gender, age, and weight loss. In addition, it was found out that specific laboratory parameters measured before the treatment have also an important role in the prognosis (e.g. lactate dehydrogenase (LDH), alkaline phosphatase (ALP), albumin, carcinoembryonic antigen) (Bremnes et al., 2003; Douillard et al., 2010; Tanner et al., 2012) Inflammation also considered as a critical factor with its effects on the tumor development and progression. However, it is also

well known that angiogenesis, metastasis, and the response to the treatment are also important factors.

Neutrophils, T lymphocytes, and B lymphocytes are considered as factors that play a vital role in tumor inflammation. The imbalance between neutrophils and lymphocytes is secondary to the tumor hypoxia or necrosis, which may be related to the anti-apoptotic effects of the neutrophils (Mantovani, 2009; Schreiber et al., 2011). NLR may reflect the imbalance between neutrophils and lymphocytes in patients with the tumor. It functions as a representative index of the systemic inflammation. In various solid tumors, markers such as platelets, neutrophils, lymphocytes, NLR, and PLR have evaluated as indicators of systemic inflammatory response. Findings indicated that neutrophilia, lymphopenia and thrombocytosis were related to malignancies (S. Lee et al., 2013; Y. Lee et al., 2012). Platelets also have an important role in cancer progression. Platelets contribute to tumor growth by stimulating angiogenesis via vascular endothelial growth factor (VEGF). It was demonstrated that high NLR and PLR values are related to short survival time in the group with advanced stage NSCLC (Wu et al., 2015). NLR and PLR were an easily accessible and simple test. NLR and PLR may help to detect prognosis when carefully interpreted. In our study, we investigated the correlation between the NLR and PLR and prognosis in lung cancer patients treated with a standard regimen.

MATERIALS AND METHODS

In this retrospective study, the files of 280 patients, who were diagnosed with lung cancer in our clinic between January 2014 and December 2016, were evaluated. Demographic characteristics such as age, gender, pathological diagnosis, lung cancer cell type, disease stages, date of diagnosis, date of death of deceased patients, complete blood count (neutrophil, lymphocyte, thrombocyte, CRP, eosinophil) NLR, PLR and survival time recorded. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count from a complete blood count and PLR was calculated by dividing the absolute platelet count by the absolute lymphocyte count. NLR and PLR values were categorized into 2 groups (NLR>3.43, NLR≤3.43; PLR>136.9, PLR≤136.9). 60 patients, who had a bacterial infection at that time, were not treated at all, were not treated according to the stage of the disease and had no laboratory results in their files, were excluded from the study. The relationship between NLR and PLR values of patients with survival time and disease stages investigated. The study protocol was approved by Kartal Dr. Lutfi Kirdar Training and Research Hospital institutional review board

Data were analyzed with the SPSS 17.0 software package. For the descriptive data, mean values and percentage used. Student's T-test and Mann-Whitney U test were used for continuous variables. In the NSCLC group, regarding NLR and PLR values, cut-off values over a 1-year time interval were found, and the area under the ROC curve calculated for each of them. For this purpose, "survival ROC" package in R program was used. Youden J index was used for the determination of the cut-off values. NLR and PLR variables divided into two groups according to the calculated cut-off point and the survival probabilities compared between the groups with values over and under the cut-off point with the Log-rank test. $P<0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

A total of 220 (181 NSCLC and 39 SCLC) patients with a mean age of 62±8 years included in the study. 82.3% of the patients were males.

The demographic characteristics of the patients summarized in Table 1.

In the NSCLC group, the mean NLR and PLR values were 4±3.5 and 195.5±153.7, respectively. In the NSCLC group, the overall survival time was shorter in the subgroup with NLR>3.43 at diagnosis (13.1 months) compared to the subgroup with an NLR ≤3.43 (24.3 months). The mean survival time was shorter in the group with a PLR >136.9 compared to the group with a PLR≤136.9 (15.9 and 24.6 months; p<0.0001and p=0.002 respectively) (Figure 2). There was no statistically significant difference between the NLR and PLR groups categorized according to the cut-off value in respect of age and gender (p> 0.05).

Overall mean NLR and PLR values were 4.08±3.35 and PLR 194.6±144.4, respectively. There were statistically significant differences between survivors and non-survivors considering the neutrophil count, lymphocyte count, CRP, NLR and PLR values (p=0.02, p<0.001, p=0.002, p<0.001, p<0.001 respectively).

In the NSCLC group, there was statistically significant difference between survivors and non-survivors in respect of neutrophil count, lymphocyte count, CRP, NLR and PLR values (p=0 .008, p = 0.003, p =0.002, p<0.0001; p=0.001 respectively).

The mean NLR and PLR values were 4.2±2.5 and 190.4±91.3, respectively, in the SCLC group. In the SCLC group, there was a statistically significant difference between survivors and non-survivors regarding lymphocyte count and PLR value (p=0.003; p=0.003, respectively).

There was a statistically significant difference between the subgroups of SCLC group consisting of early and advanced stage patients regarding the CRP, NLR and PLR values (p<0.0001, p=0.001, p=0.028 respectively) (Table 2). The subgroups of the SCLC group consisting of the limited and advanced stages showed a statistically significant difference considering the lymphocyte count and PLR value (p=0.004, p=0.028, respectively) (Table 3).

Table 1. Demographic and clinical characteristics of lung cancer patients

	N	Percentage
CANCER TYPE		
Adenocarcinoma	50	22.7%
Squamous cell	91	41.4%
NOS	40	18,2%
Small cell (SCLC)	39	17.7%
CANCER TYPE-2		
Non-small cell lung cancer (NSCLC)	181	82.3%
Small cell (SCLC)	39	17.7%
STAGE-NSCLC		
Early stage (1,2,3A)	88	48.6%
Advanced stage (3B,4)	93	51,4%
STAGE–SCLC		
Limited disease	10	25.6%
Diffuse disease	29	74.4%
Survivors		
NSCLC	79	43.6%
SCLC	10	25.6%
Non-survivors		
NSCLC	102	56.4%
SCLC	29	74.4%

Table 2. Hematological parameters in early and advanced stage non-small cell lung cancer

NSCLC	ADVANCED STAGE	EARLY STAGE	p-value
N(10^3/uL)	7.12±2.69	5.95±2.13	0.075
L(10^3/mm^3)	1.89±0.69	2.06±0.79	**0.084**
PLT(10^3/uL)	329.4±103.2	306.7±94.2	0.178
CRP (mg/L)	37.87±32.2	19.55±28.9	**0.0001**
N/L	4.49±4.3	3.58±2.6	**0.001**
PLT/L	208.1±191.3	182.9±115.7	**0.028**

Table 3. Hematological parameters in limited and advanced stage small-cell lung cancer

SCLC	ADVANCED STAGE	LIMITED STAGE	P-value
N(10^3/uL)	6.76±2.1	7.73±2.3	0.757
L(10^3/mm^3)	1.76±0.79	2.22±0.91	**0.004**
PLT(10^3/uL)	319.4±94.2	299.4±93.8	0.423
CRP (mg/L)	33.80±28.8	15.52±11.3	0.223
N/L	4.52±4.3	3.50±2.6	0.317
PLT/L	206.9±115.7	136.6±178.7	**0.028**

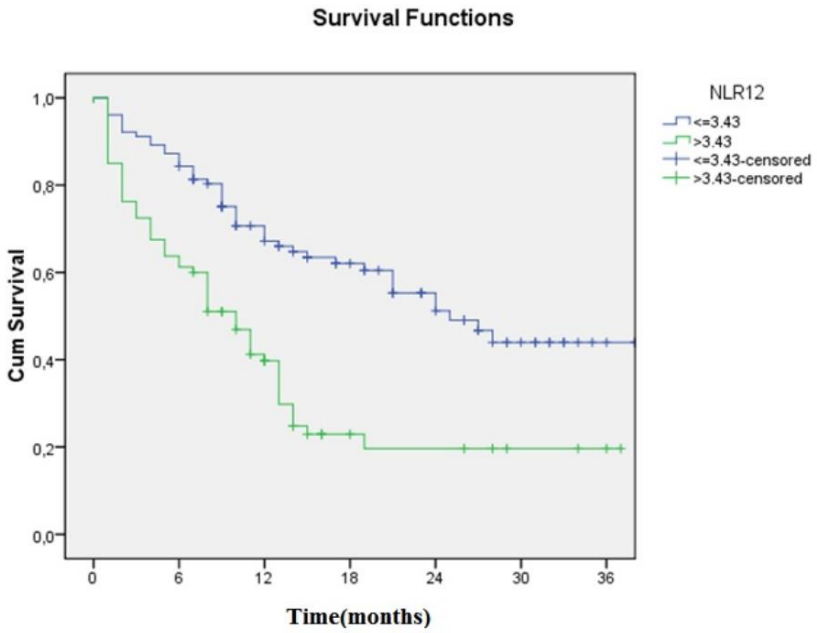

Figure 1: The mean survival time of the groups with NLR>3.43 and NLR≤3.43.

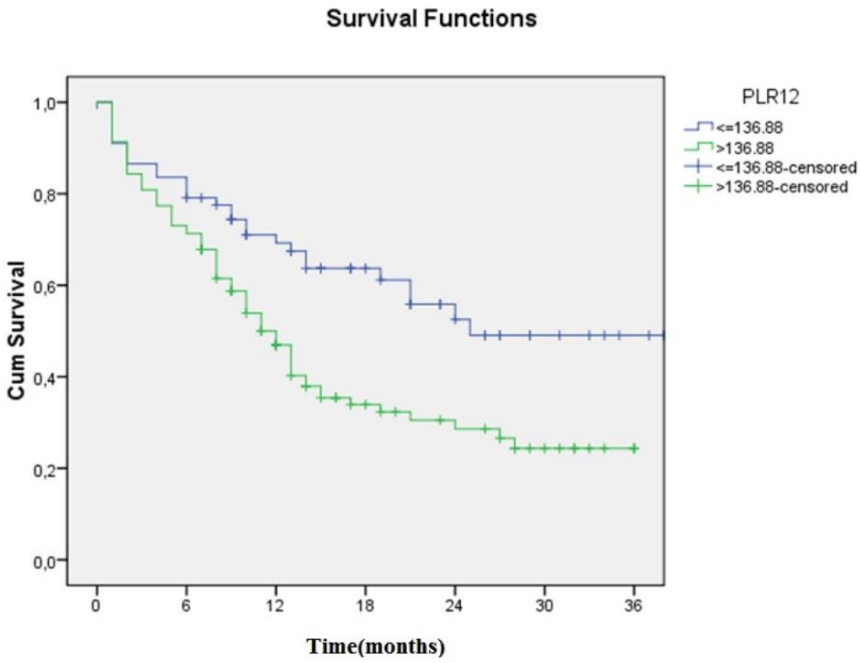

Figure 2: The mean survival time of the groups with PLR>136.9 and PLR≤ 36.9.

In our study, when we take all patients with lung cancer into consideration, there was a statistically significant difference between the groups consisting of survivors and non-survivors in respect of neutrophil and lymphocyte count, CRP, NLR, and PLR values. There was a statistically significant difference between the survivors and non-survivors of the NSCLC group regarding the neutrophil and lymphocyte count, CRP, NLR, and PLR values. There was a statistically significant difference between the early and advanced stage patients of the NSCLC group considering CRP, NLR, and PLR values.

The correlation between inflammation and cancer demonstrated in several studies. The contribution of the inflammation to the tumor development and angiogenesis is well known (Coussens and Werb, 2002). Studies had shown that inflammation increased the risk in several cancer types like colorectal and pancreatic carcinoma (Shim et al., 2005).

Some systemic inflammatory markers are related to the clinical and pathological characteristics of the tumor. Neutrophils, T- and B-lymphocytes have a prominent role in tumor inflammation (Lin et al., 2012; Schreiber et al., 2011). It was determined in several studies, that the increased NLR value measured from the peripheral blood was an independent prognostic factor in esophagus, colon, stomach and lung cancers (Noh et al., 2013; Sharaiha et al., 2011).

In a study, 386 patients with lung cancer evaluated and it was determined that the median survival time was shorter in patients with NLR≥3 than in patients with NLR <3 (Akinci Ozyurek et al., 2017). In our study, we found out that the mean survival time was shorter in patients with NLR>3.43 than those with NLR ≤3.43. In a study conducted with stage 3B and four lung cancer patients, the pretreatment values of neutrophil count and NLR correlated with poor prognosis (Teramukai et al., 2009). In our study, the comparison of survivors and non-survivors of the NSCLC group showed that there was a statistically significant difference between these groups in respect of neutrophil and lymphocyte count and NLR value. It suggested that these parameters were related to the poor prognosis in lung cancer patients. In

a study, a correlation was determined between the increased NLR value and poor prognosis (Cedres et al., 2012).

In NSCLC patients with a resectable tumor, a correlation was demonstrated between the short survival time and NLR and CRP levels at the time of diagnosis (Tomita et al., 2011). In a study conducted by Ünal et al., 94 patients were investigated, and it was found out that there was a significant correlation between the increased pre-treatment NLR values and the survival rates (Unal et al., 2013).

In another study, similar to our research, NLR was associated with short survival time in patients with advanced stage NSCLC (Yao et al., 2013). The meta-analysis of 14 studies had shown that increased NLR value is correlated with the short survival time (Yin et al., 2015). Another study revealed that an NLR of < 3 at 2 and four weeks after nivolumab treatment may be an independent prognostic biomarker in patients with advanced NSCLC (Nakaya et al., 2018).

In our study, we were not able to evaluate the correlation between NLR and survival time in SCLC due to the limited number of subjects. Studies did not show any correlation between NLR and mean survival time in SCLC patients (Akinci Ozyurek et al., 2017). In another study focused on SCLC patients, it was shown that the high NLR value was an independent risk factor for survival (Deng et al., 2017). In a study conducted in 65 patients with limited-stage SCLC, it was found out that the NLR value was an independent risk factor for survival (Kasmann et al., 2017). In our study, there was no significant difference between survivors and non-survivors in the SCLC group regarding the mean NLR values.

In the previous studies, it was determined that the platelet count was positively correlated with the lymph node metastasis and negatively correlated with the survival (H. B. Liu et al., 2013). PLR, which considered as an indicator of the systemic inflammation in recent years, was investigated in several centers for the determination of its relationship with the survival of lung cancer patients. In a study with NSCLC patients, similar to our study, the increased PLR value was correlated with the poor prognosis (H. Liu et al., 2013). In our study, we found out that the survival time was shorter in the group with PLR >136.9 than the group with PLR≤136.9. PLR is another indicator of the systemic inflammation, and some studies demonstrated that the activation of the platelets and the coagulation system is critical for the tumor metastasis. However, its mechanism has not fully elucidated (Bambace and Holmes, 2011; Gay and Felding-Habermann, 2011). In the subgroup of the metastatic NSCLC group consisting of the patients with high PLR value at diagnosis, the median survival time was shorter than the group with low PLR value at diagnosis (Diem et al., 2017). The study with operable NSCLC patients did not show a correlation between the PLR and survival time (Pinato et al., 2014). A meta-analysis of 3720 patients showed that high PLR values were associated with poor prognosis (Zhao et al., 2016). In our study, in the NSCLC group, PLR value was significantly higher among the survivors compared to the non-survivors.

In a study with SCLC patients, the high PLR values were correlated to the poor prognosis (Deng et al., 2017). In our study, there was a significant difference between the survivors and non-survivors of the SCLC group.

The retrospective study design, the different numbers of NSCLC and SCLC patients, the limited number of SCLC patients were the limitations of our study.

When examined in conjunction with the literature, NLR and PLR have an important role in the inflammation of lung cancer as well as in other cancers. It is an easily accessible, simple, and inexpensive blood parameter, and it will shed some light on the prognosis when carefully interpreted.

CONCLUSION

Subgroups consisting of survivors and non-survivors in the NSCLC group showed a statistically significant difference considering neutrophil and lymphocyte count, CRP, NLR, and PLR values ($p<0.05$).

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