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Research Article

The Significance of Hemogram Parameters for Diagnosis, Prognosis and Treatment of Lung Cancer

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Abstract

Objectives: We aimed to investigate the relation between neutrophil/lymphocyte ratio (NLR), lymphocyte/monocyte ratio (LMR) and platelet/lymphocyte ratio (PLR) with survival and mortality in lung cancer.

Methods: 309 patients diagnosed of lung cancer were evaluated in our study. NLR, LMR, PLR were calculated by recording of absolute neutrophil, absolute lymphocyte, absolute monocyte and platelet values from the complete blood count at the time of diagnosis. The cut-off values were determined as 5.28 for NLR, 2.07 for LMR and 150 for PLR by investigating previous studies.

Results: The median survival was 13 months, survival was high in adeno carcinoma patients with17 months(median), and low in patients with carcinoid tumors and the tumors whose pathology could not be categorized with 5 months (median), ($p<0.05$). Overall survival is shorter in patients with high NLR levels and longer high LMR levels ($p<0.05$ for both). No statistically significant relation was found between survival and PLR level.

Conclusion: High NLR and low LMR values were associated with short overall survival but there is no association between PLR level and overall survival. The cut off values specified for NLR and LMR may be beneficial to predict prognosis in patients with lung cancer.

Keywords: Lung cancer, neutrophil/lymphocyte ratio, lymphocyte/monocyte ratio, platelet/lymphocyte ratio

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Lung cancer is the most common cause of death due to cancer in men and after breast cancer second common cause in women. Smoking is a major risk factor of lung cancer, the first way to prevent development of lung cancer is smoking cessation.[1]

Lung cancer, also known as bronchogenic carcinoma, refers to cancers originating from lower respiratory tract or pulmonary parenchyma. Small cell cancer (SCLC) and non-small cell cancer (NSCLC) form %95 of all lung cancer cases. Cancers originating from other cell types of the lung make the remaining 5 percent.[2] Distinction of cell types are important in staging, treatment and prognosis.

Inflammation constitutes the basis of cancer development and progression. Previous studies have shown the role of inflammatory markers in determining cancer progression and survival. Complete blood count is one of the most common tests performed in clinical admission. Neutrophil, lymphocyte and monocyte counts change during inflammatory processes. Association between neutrophil/lymphocyte ratio (NLR), lymphocyte/monocyte ratio (LMR)

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and platelet/lymphocyte ratio (PLR) with prognosis of the disease and response to treatment have shown certain studies.[3] Increased systemic inflammation can associated with fatigue, cancer cachexia, and cancer progression. The effects of systemic inflammation has shown in studies that reduce response to anti-cancer drugs, increase tumor cell proliferation, cause angiogenesis and metastasis, and associated with poor prognosis.[4]

The aim of this retrospective study was investigate the relationship between serum neutrophil/lymphocyte ratio, thrombocyte/lymphocyte ratio, lymphocyte/monocyte ratio, with lung cancer's pathological type and stage of the disease, reveale the effectiveness in determining response to treatment and overall survival (OS).

Methods

All patients diagnosed of lung cancer and were followed up between January 2016 and June 2019 by Sakarya University Hospital Oncology Clinic were evaluated. Patients with previous lung cancer and presenting with recurrence, having malignancy in another organ and diagnosed as second primary lung cancer, diagnosed at an external center and biochemical tests deficinetly performed at the time of diagnosis were excluded from the study. PET/CT, cranial CT and cranial MR, abdominal USG, bone scintigraphy and other images were evaluated retrospectively and the cases were staged according to TNM 8. Absolute neutrophil, absolute lymphocyte, absolute monocyte and thrombocyte values were recorded from the hemograms of the pathological diagnosis confirmed cases. Neutrophil/lymphocyte ratio (NLR), lymphocyte/monocyte ratio (LMR), platelet/neutrophil ratio (PLR) were calculated. The cut-off value determined by investigating the previous studies and taken as 5.28 for NLR, 2.07 for LMR and 150 for PLR.

Statistical Analysis

Analyzes were performed using SPSS version 22 (IBM Corp., Armonk, NY, USA). Clinical and general characteristics of the patients were analyzed using descriptive statistics. Normal distribution conformity assessment of numerical variables tested with visual and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests used). Correlation coefficients and statistical significance for minimum one non-normallay distributed variables calculated with Spearman test. According to reference studies obtained by literature review, predetermined optimal threshold (cut-off) values for NLR, LMR and PLR were used to predict the prognosis of lung cancer. Later, the hemogram parameters of all lung cancer cases included in the study were dichotomized according to the optimal threshold values in accordance with the study design. Categorical variables were compared using the Chi-square test. Survival analyzes were performed using the Kaplan-Meier test. Survival comparisons were made using the Log-Rank test. In multivariate analysis, by use of possible factors identified in previous analyzes, independent factors predicting survival were examined using Cox proportional hazards regression analysis by selecting the enter method. All statistical evaluations were interpreted as 2-sided and $p<0.05$ was used for statistical significance of the results.

Results

Our study included 309 patients with lung cancer [male: 279 (90.3%), female: 30 (9.7%)]who were followed in our clinic between 2016-2019. The mean age was 63.9±9.6 years (age range: 30-89) and the rate of smoking history was 93.2% (n=288). At the time of diagnosis, 7.8% of the cases were stage-1 (n=24), 12.6% stage-2 (n=39), 36.9% stage-3 (n=114) and 42,7% of them were determined as stage-4 (n=132) (Table 1).

All cases in our study divided into risk groups based on previous studies, pre-treatment values for NLR<5.28 and ≥5.28, LMR<2.07 and ≥2.07, PLR<150 and ≥150. In two cases, all data were not available for analysis and not included in the assessment. Survival analysis and comparison were made according to inflammatory hemogram parameter and survival was shorter in cases with NLR levels above the threshold, while it was longer in cases with LMR levels above the threshold and these two situations were statistically significant ($p<0.05$). The analysis according to PLR level, survival was shorter above the threshold value, but this was not statistically significant ($p=0.09$) (Table 2, Fig. 1). In addition, the effect of inflammatory hemogram parameters on mortality risk for the period followed (3 years) was evaluated using the "Cox proportional hazards regression" method. The evaluations for NLR and PLR, results above the threshold value before treatment were found to be associated with increased mortality risk, although it was not statistically significant (HR [Hazard Ratio]: 1.32 and 1.07, 95%

Table 1. General and clinical features

	Frequency (n)	%
Men	279	90.3
Women	30	9.7
Smoking (+)	288	93.2
Smoking (-)	21	6.8
Stage-1	24	7.8
Stage-2	39	12.6
Stage-3	114	36.9
Stage-4	132	42.7
Toplam	309	100

Table 2. Survival analysis and comparison according to inflammatory hemogram parameters

Hemogram parameters	Number of patients	Median survival (Month)	95% Confidence Interval		p
			Lower limit	Upper limit	
NLR					
High (NLR≥5.28)	68	8	5.2	10.7	0.006
Low (NLR<5.28)	239	13	10.3	15.6	
LMR					
High (LMR≥2.07)	220	17	11	16.9	0.006
Low (LMR<2.07)	87	9	6.3	11.7	
PLR					
High (PLR≥150)	161	10	6	13.9	0.09
Low (PLR<150)	146	13	9.9	16.1	
Total	307	13	10.4	15.5	<0.05

NLR: Neutrophil/lymphocyte ratio; LMR: Lymphocyte/monocyte ratio; PLR: Platelet/lymphocyte ratio.

Table 3. Effects of inflammatory hemogram parameters on mortality

Hemogram parameters	Hazard ratio	95% Confidence Interval		p
		Upper limit	Lower limit	
NLR	1.32	0.88	1.98	0.17
LMR	0.75	0.52	1.07	0.11
PLR	1.07	0.75	1.49	0.68

NLR: Neutrophil/lymphocyte ratio; LMR: Lymphocyte/monocyte ratio; PLR: Platelet/lymphocyte ratio.

Table 4. Correlation analysis of hemogram parameters

Correlation coefficient (r) p	NLR	LMR	PLR
NLR	1	-0.629	0.682
	-	<0.001	<0.001
LMR	-0.629	1	-0.460
	<0.001	-	<0.001
PLR	0.682	-0.460	1
	<0.001	<0.001	-

NLR: Neutrophil/lymphocyte ratio; LMR: Lymphocyte/monocyte ratio; PLR: Platelet/lymphocyte ratio.

Confidence Interval: 0.88-1.98 and 0.76-1.49, p=0.17 and 0.68, respectively). Results that were above the threshold value before treatment were found to be associated with decreased mortality risk, although it was not statistically significant in the evaluation made for LMR (HR: 0.75, 95% Confidence Interval: 0.52-1.07, p=0.11) (Table 3).

Hemogram parameters were investigated in terms of correlation with each other. When the correlation matrix was examined, a significant positive correlation was detected between NLR and PLR (r=0.682, p<0.05), while a significant negative correlation was observed with LMR (r=-0.629, p<0.05). A significant negative correlation was found between LMR and PLR (r=-0.460, p<0.05) (Table 4).

Discussion

İnflammatory response can an important role in different stages of tumor development by preventing apoptosis and accelerating angiogenesis. The association of inflammatory microenvironment with immune surveillance and treatment response of tumor were shown in previous studies.[4]

Neutrophil/lymphocyte ratio, lymphocyte/monocyte ratio, and platelet/lymphocyte ratio are based on the values obtained with complete blood count. These parameters are easy acquirable and cheap also show systematic inflammatory response and their prognostic value in colon, stomach and lung cancer has been shown by studies.[5]

Neutrophils play a key role in tumor progression as they trigger genetic instability, increase tumor growth, angiogenesis, and support the invasive behavior of cancer cells.[6] Lymphocytes provide cell-mediated immune regulation, detect and destroy residual malignant cells and micro metastases. Some studies showed a positive relation between preoperative lymphocyte count and disease-free survival.[7]

Macrophages stimulate tumor proliferation, activate angiogenesis, and increase the tendency to invasion and metastasis by producing growth factors, angiogenic factors and secreting the protease enzymes, like neutrophils.[8] The relationship between platelets and solid tumor prognosis has been discussed in many studies, but the underlying mechanism is not clearly resolved. Their capability to adhere to the vascular wall and secretions as vascular endothelial growth factor (VEGF) and platetlet-produced endothelial growth factor (PDEGF) are held responsible for tumor progression.[9]

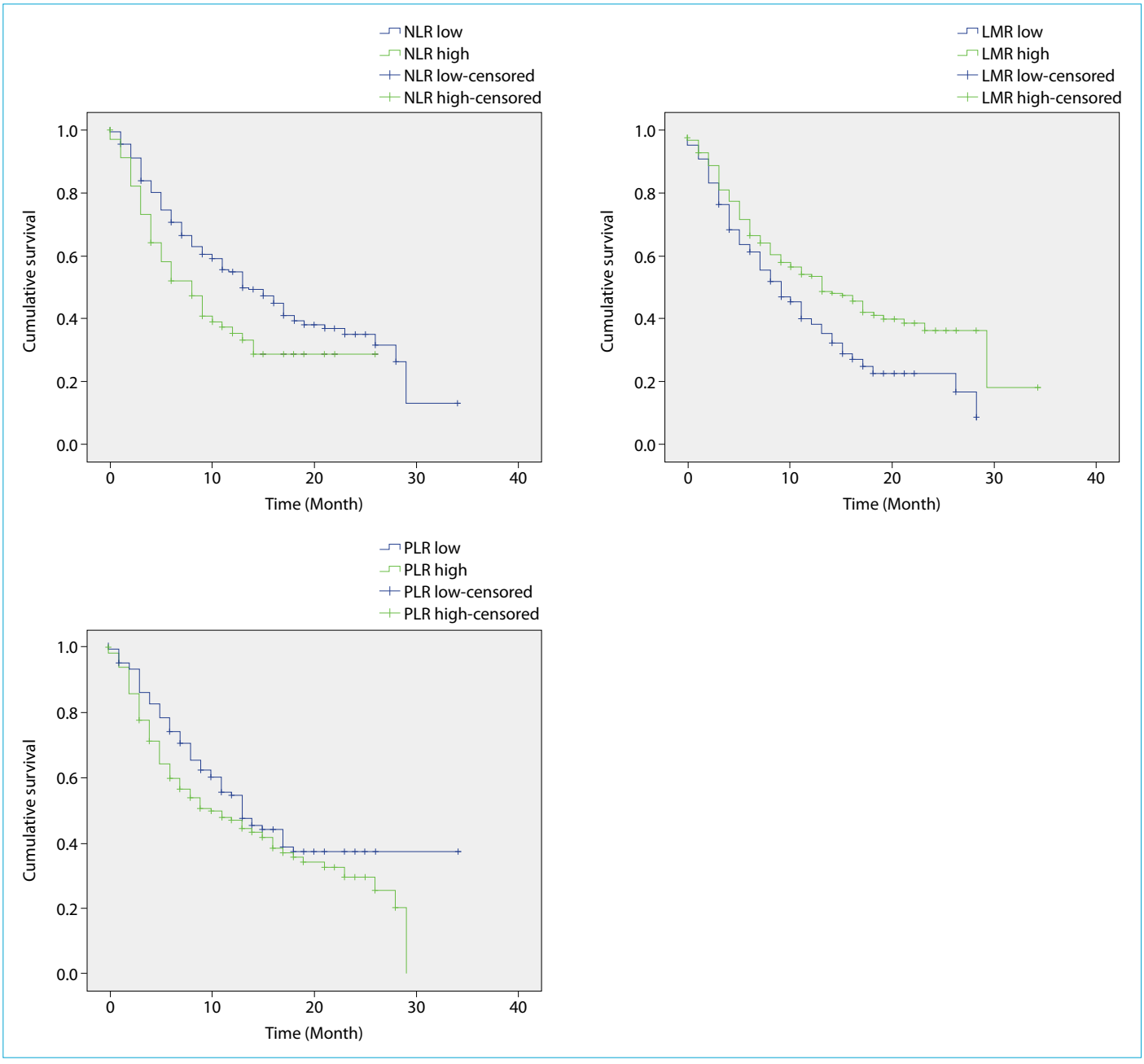

Figure 1. Graphical interpretation of survival analysis and comparison according to inflammatory hemogram parameters; low NLR (NLR<5.28), high NLR (NLR≥5.28), low LMR (LMR <2.07), high LMR (LMR≥2.07) and low PLR (PLR<150), high PLR (PLR≥150), Time (month), cumulative survival.
NLR: Neutrophil/lymphocyte ratio; LMR: Lymphocyte/monocyte ratio; PLR: Platelet/lymphocyte ratio.

In the study by Liu et al. consist of 139 patients diagnosed with SCLC, the cut-off value for NLR was determined as 4.55. Values greater than 4.55 were defined as high NLR, and values 4.55 and below as low NLR, so the patients were divided into 2 groups. The incidence of advanced stages has been increased and the hepatic metastasis rate has been higher in cases with high NLR compared to low NLR patients. In the same study, the cut-off value for PLR was determined as 148 and divided into two groups. Above 148 defined as high PLR, 148 and below as defined low PLR. Advanced stages of disease were higher in the high PLR group and increased rate of bone and liver metastasis were found. The cases were divided into two groups as limited disease and advanced stage disease, high NLR was found to be associated with short survival in both groups.[10]

The prognostic significance of combination of LMR and platelet count (COP-LMR) was investigated in the study of Lim et al., that consisted 217 NSCLC patients diagnosed at stage four. The LMR threshold value was determined as 2.47 and platelet threshold value was calculated as $30.05x10^4$

mm^3 by ROC analysis. COP-LMR has been identified as an important predictor of survival. The study has shown, survival and progression-free follow-up were reduced when COP-LMR score was increased.[11]

Sakin et al. was investigated the relationship between survival with NLR and PLR and their study was consisted of 113 advance stage SCLC patients. ROC analysis was performed for each ratio and threshold values were determined as 3 for NLR and 150 for PLR. In patients with NLR≥3, survival was found significantly shorter and mortality increased 2.2 times. Survival was significantly shorter in patients with PLR≥150, while mortality increased 1.6 times.[12]

The prognostic significance of NLR was examined in the study of Suziki et al., consisted of 252 advanced stage SCLC cases. The NLR threshold was determined as 4. Cases with high NLR (NLR>4) have associated with lower survival.[13]

In our study, survival was significantly shorter in cases with NLR levels above the threshold value. High NLR (NLR≥5.28) levels were found an independent risk factor leading to short survival. However, when analyzing the relationship between increased NLR and mortality, mortality rates were increase in cases with high NLR even though it was not statistically significant.

In many studies shown that lymphocytes have an important role in anti-tumoral immunity. High NLR reflects increasing neutrophil count or decreasing lymphocyte count, so there is an impaired balance in inflammatory pathways. This explains the increase in recurrence and metastasis rate and decrease in survival times in cases with high NLR.[14]

PLR is another systemic inflammatory indicator. Certain studies have shown activated platelets and coagulation system are critical in tumor metastasis although its exact mechanism has not been explained yet. The mechanism might be associated with cytokines and growth factors secreted from platelets. High PLR means increased platelet count or decreased lymphocyte count. Impaired inflammatory balance may be associated with recurrence and metastases.[15,16]

In this study, when the cases with high PLR (PLR>150) and low PLR (PLR≤150) were compared, no statistically significant difference was found between the two groups in terms of survival. High PLR was not demonstrated as an independent risk factor for short survival. When the relation with mortality is analyzed, mortality rates were found to be increased in cases with high PLR but it was not found statistically significant.

In another study with pre-treatment SCLC patients, high NLR level was found to be associated with poor prognosis and no relation was found between high PLR and prognosis.[14] In the study of Kasmann et al. including 65 SCLC cases, relation was found between high NLR and short survival, but no relation was shown with PLR.[17] Similar results were found in the study of Kang et al.[18] The results in our study were also similar to the literature.

The different results between studies may be derived from the differences in the number of lung cancer cases examined in the studies or due to histological types, stages, the type of surgical or medical treatment preferred, and the changes on PLR threshold value.

Certain hematological malignancies have a relation between high LMR level and prognosis.[19,20] Also relation with non-hematological malignancies and LMR were shown in previous studies. The prognocytic importance of LMR has been revealed for cancers such as colorectal, pancreatic, urothelial carcinoma. Prognocytic importance for lung cancer was also shown in certain studies and the studies was found low LMR levels were associated with poor prognosis and short survival.[21,22]

The relations between LMR and prognosis was examined in a study involving 1453 patients with lung cancer who underwent surgery by Hu et al. In that study, LMR threshold value was determined as 3.68 by ROC analysis. A significant relation was shown between low LMR and low survival, and mortality was found 1.5 times higher in cases with low LMR. In addition, advanced age and high TNM stage were associated with lower survival were found as an outcome of that study.[23]

The effect of circulating monocyte count, lymphocyte count and LMR on prognosis was compared in 370 metastatic lung cancer patients in a study by Lin et al. High LMR, low monocyte count, and high lymphocyte counts were associated with increased survival and improved progression-free survival in that study. In addition, decreased mortality was observed in cases with performance score below 2 and cases with histological type NSCLC.[24]

A meta-analysis was performed to investigate the prognocytic importance of LMR in Asian lung cancer patients by Li et al. In that meta-analysis, 63 articles were found from the database and after elimination according to criterias as a result 8 articles were examined. The LMR threshold value ranges 2.62 to 4.56 between studies. Low LMR levels were associated with short progression-free survival has found. Low LMR level has been associated with a significantly worse prognosis compared to a high LMR level.[5]

In our study, the cases with LMR level above the threshold were compared with cases with LMR level below the threshold and survival was significantly longer in high LMR group.

Our results about LMR and its effect on survival are similar to the results obtained in other studies performed with patients diagnosed as lung cancer. And in our study no relation was found between LMR and mortality.

In this study, high LMR and low NLR levels were related with long survival. High NLR and low LMR levels were associated with poor prognosis and short survival. PLR has no effect on survival.

The limitations of this study was conducted in a single center, analysis consist of the hemogram parameters only at the time of diagnosis and different threshold values of NLR, PLR and LMR used in literatüre from the threshold values we used. The design of our study is retrospective.

Conclusion

The results in our study show that high NLR and low LMR values are associated with short survival, and PLR value has no effect on survival. Many studies involving various stages and therapies on this issue take place in literature, some studies have resulted the same as ours, some are different, because of this contrast more comprehensive, prospective studies are needed to clarify the effects of NLR, PLR and LMR on survival and mortality.

Disclosures

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Sakarya University Faculty of Medicine and was conducted in accordance with the principles of the Declaration of Helsinki (714522473/050.01.04/19).

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