RESEARCH ARTICLE

Are Neutrophil/Lymphocyte and Platelet/Lymphocyte Rates in Patients with Non-Small Cell Lung Cancer Associated with Treatment Response and Prognosis?

Dilek Unal[1]*, Celalettin Eroglu[2], Neslihan Kurtul[2], Arzu Oguz[3], Arzu Tasdemir[4]

Abstract

Background: Inflammation is a critical component of tumor progression. Many cancers arise from sites of infection, chronic irritation, and inflammation. It is now becoming clear that the tumour microenvironment, which is largely orchestrated by inflammatory cells, is an essential participant in the neoplastic process, promoting proliferation, survival and migration. Platelets can release some growth factors such as platelet-derived growth factor, platelet factor 4, and thrombospondin. Such factors have been shown to promote hematogenous tumour spread, tumor cell adhesion and invasion, and angiogenesis and to play an important role in tumor progression. In this study, we aimed to investigate effects of the pretreatment neutrophil to lymphocyte ratio (NLR) and the platelet to lymphocyte ratio (PLR) on survival and response to chemoradiotherapy in patients with non-small-cell lung cancer (NSCLC). Materials and Methods: Ninety-four patients with non-metastatic NSCLC were included and separated into two groups according to median valuse of NLR and PLR (low:<3.44 or high:≥3.44 and low:<194 or high≥194, respectively). Results: Pretreatment high NLR and PLR were associated with significantly shorter disease-free and overall survival rates. Multivariate analysis revealed that the overall survival rates were significantly linked with PLR (OR: 1.87, CI: 1.20-2.91, p: 0.006) and response to chemoradiotherapy (OR: 1.80, CI: 1.14-2.81, p: 0.012) and the disease-free survival rates were significantly associated with NLR (OR: 1.81, CI: 1.16-2.82, p: 0.009) and response to chemoradiotherapy (OR: 2.30, CI: 1.45-3.66, p: 0.001). There was no significant difference between patients with high and low NLR in terms of response to chemoradiotherapy. Similarly, there was no significant influence of the PLR. Conclusions: Pretreatment NLR and PLR measurements can provide important prognostic results in patients with NSCLC and assessment of the two parameters together appears to better predict the prognosis in patients with NSCLC. The effect of inflammation, indicators of NLR and PLR, on survival seems independent of the response to chemoradiotherapy.

Keywords: Neutrophil to lymphocyte ratio - non-small-cell lung cancer - platelet to lymphocyte ratio - prognosis

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Introduction

Inflammation is a critical component of tumor progression. Many cancers arise from sites of infection, chronic irritation, and inflammation. It is now becoming clear that the tumour microenvironment, which is largely orchestrated by inflammatory cells, is an essential participant in the neoplastic process, promoting proliferation, survival and migration (Coussens and Werb, 2002). Cytokine and chemokine balances regulate neoplastic outcome. The balance of cytokines in any given tumour is critical for regulating the type and extent of inflammatory infiltrate that forms. Tumors that produce little or no cytokines or an overabundance of anti-inflammatory cytokines induce limited inflammatory and vascular responses, resulting in constrained tumour growth. In contrast, production of an abundance of pro-inflammatory cytokines can lead to a level of inflammation that potentiates angiogenesis, thus favoring neoplastic growth. Alternatively, high levels of monocytes and/or neutrophil infiltration, in response to an altered balance of pro-versus anti-inflammatory cytokines, can be associated with cytotoxicity, angiostasis and tumour regression (Coussens and Werb, 2002).

Pretreatment high neutrophil count has been reported as a poor prognostic factor for survival in patients with renal cell carcinoma (Négrier et al., 2002), metastatic melanoma (Schmidt et al., 2005), and advanced non-small-cell lung cancer (NSCLC) (Teramukai et al., 2009). Neutrophil to lymphocyte ratio (NLR), an index of systemic inflammation, has been associated with worse survival for many types of cancer including NSCLC

*[1]Department of Radiation Oncology, [3]Department of Medical Oncology, [4]Department of Pathology, Kayseri Education and Research Hospital, [2]Department of Radiation Oncology, Erciyes University Medical School, Kayseri, Turkey *For correspondence: dilekunaldr@gmail.com*

(Cedrés et al., 2012).

Platelets can release some growth factors such as platelet-derived growth factor (PDGF), platelet factor 4 (PF4), and thrombospondin (Kaplan et al., 1979; Dubernard et al., 1997). The factors have been shown to promote hematogenous tumor spread, tumor cell adhesion and invasion, and angiogenesis and to play an important role in tumor progression (Qian et al., 1996).

Pretreatment platelet to lymphocyte ratio (PLR) has been found to relate with poor prognosis in patients with epithelial ovarian cancer (Raungkaewmanee et al., 2012). To the best of our knowledge, there is no study investigating relationship between PLR and survival and response to chemoradiotherapy in patients with lung cancer.

The aim of this study was to investigate effects of the blood NLR and PLR on survival and response to chemoradiotherapy in patients with NSCLC.

Materials and Methods

Ninety-four patients with non-metastatic NSCLC were included in the study. Patients were excluded if they were <18 years old, had severe disease such as heart failure and hepatic failure, had a history of any other cancer, or had a metastatic disease.

We recorded responses to chemoradiotherapy including complete remission, regression, stable disease, and disease progression, and overall and disease-free survival. Survival time was measured from the date of chemoradiotherapy until death or last clinical evaluation.

Complete blood counts with automated differential counts, which included total white blood cells, neutrophils, lymphocytes, and platelets, were obtained before chemoradiotherapy. NLR and PLR were calculated as the ratio of the neutrophils and platelets to lymphocytes. Median value was used for NLR and PLR because normal distribution was absent. The patients were separated into two groups according to median value of NLR and PLR (low:<3.44 or high:≥3.44 and low:<194 or high≥194, respectively).

Histopathology of NSCLC was squamous cell carcinoma in 66 (70.2%), adenocarcinoma in 15 (16.0%), large cell neuroendocrine carcinoma in 1 (1.1%), adenosquamous carcinoma in 1 (1.1%), and unclassified non-small cell lung cancer in 11 (11.7%) patients. The stage of the lung cancer was IIA in 1 (1.1%), IIB in 8 (8.5%), IIIA in 40 (42.6%), and IIIB in 45 (47.9%) patients.

Radiotherapy and chemotherapy

Two-dimensional treatment planning system was used by conventional X-ray simulator and RT was delivered by a linear accelerator device including 6-18 Million Volts photons. Total dose of 66 Gy in 2.0 Gy fractions was given. During radiotherapy concomitantly weekly docetaxel 20 mg/m^2 and cisplatin 20 mg/m^2 infusion were administered at the 1st day of the for 6,5 weeks. The initial planning target volume consisted of the primary tumor, the ipsilateral hilum and mediastinum with a margin of 2 cm. Special blocks were employed in order to prevent the exposure of normal tissues to radiation. This initial field was treated by parallel-opposed anterior and posterior fields to 46 Gy in 23 fractions. Boost dose of radiotherapy was administered after 46 Gy to the primary tumors and the involved nodes were included with a margin of 0.5-1.5 cm from oblique parallel-opposed fields with protecting spinal cord.

After chemoradiotherapy, complete remission developed in 13 (13.8%), regression in 44 (46.8%), stable disease in 14 (14.9%), and disease progression in 23 (24.5%) patients. Stable disease or disease progression after chemoradiotherapy was defined as lack of response to chemoradiotherapy. In contrast, complete response or disease regression after chemoradiotherapy was defined as response to chemoradiotherapy. The response to chemoradiotherapy was observed in 57 (60.6%) patients whereas 37 (39.4) patients did not respond to chemoradiotherapy.

Statistical analysis

SPSS 15.0 software was used for the statistical analysis. Continuous variables with normal distribution were presented as mean±SD. Median value was used where normal distribution is absent. Statistical analysis for the parametric variables was performed using the Student's t-test between two groups. The Mann-Whitney U test was used to compare nonparametric variables between two groups. Qualitative variables are given as percent and the correlation between categorical variables was investigated using the chi-square test and Fisher's exact tests. Disease-free survival and overall survival was estimated using the Kaplan-Meier method and the log-rank test was used for comparison of outcomes. Mortality risks were analyzed using the multivariate Cox regression model in which we included (in a backward-wald manner) all the significant variables from the univariate analysis. A p value of <0.05 was considered significant.

Results

Mean age of 94 patients was 58.1±8.6 (30-78) years; 88 (93.6%) of 94 patients were male whereas the rest were female. Eighty-one (86.2%) patients died.

Overall and disease-free survival was 12 and 8 months, respectively (Figure 1). The overall survival rates according to characteristics of patients are shown in Table 1. NLR and PLR and response to chemoradiotherapy were the characteristics that significantly influenced the overall survival (p: 0.006, p: 0.006, and p: 0.015, respectively). The patients with higher NLR and PLR had decreased

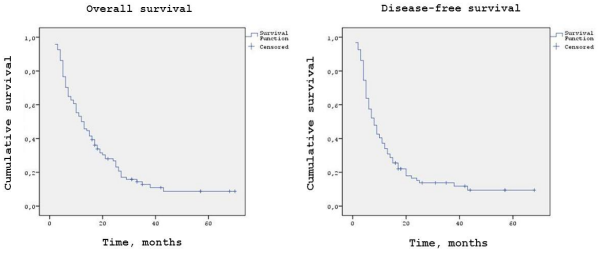

Figure 1. Predicted Probability of Overall and Disease-Free Survival

survival ratios (Figure 2).

Univariate and multivariate analyses were performed to identify the risk factor(s) related to overall survival. Table 2 shows the results regarding nine variables examined in univariate analysis as potential risk factors for overall survival. Three of the nine factors differed significantly between these groups (p<0.05). The multivariate Cox regression analysis identified that the overall survival rates were significantly associated with PLR (low or high; OR: 1.87, CI: 1.20-2.91, p: 0.006) and response to chemoradiotherapy (presence or absence; OR: 1.80, CI: 1.14-2.81, p: 0.012).

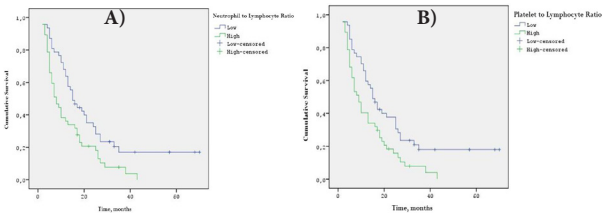

Figure 2. The Overall Survival According to A) Neutrophil to Lymphocyte Ratio and B) Platelet to Lymphocyte Ratio

Table 1. Overall Survival and p value According to Characteristics of Patients

		No. of Patients (%)	Survival Month (95% Confidence Interval)	p value
Age	≥60 years	42 (44.7)	10 (4.71-15.29)	0.606
	<60 years	52 (55.3)	12 (7.29-16.71)	
Gender	Female	6 (6.4)	17 (11.00-23.00)	0.762
	Male	88 (93.6)	12 (8.94-15.06)	
Histopathology				
Adenocarcinoma		15 (16.0)	18 (7.90-28.10)	0.527
Epidermoid carcinoma		66 (70.2)	12 (8.46-15.54)	
Unclassified		13 (13.8)	11 (3.95-18.05)	
Neutrophil/lymphocyte ratio				
	Low	47 (50.0)	15 (11.01-18.99)	0.006
	High	47 (50.0)	8 (5.13-10.87)	
Platelet/lymphocyte ratio				
	Low	47 (50.0)	15 (11.69-18.31)	0.006
	High	47 (50.0)	9 (6.32-11.68)	
Stage	II	9 (9.6)	10 (4.16-15.84)	0.686
	IIIA	40 (42.6)	12 (7.35-16.65)	
	IIIB	45 (47.9)	13 (7.53-18.47)	
Response to treatment*				
	Presence	57 (60.6)	15 (1.34-18.67)	0.015
	Absence	37 (39.4)	6 (3.62-8.38)	
T status	T0-2	23 (24.5)	15 (5.61-24.39)	0.450
	T3-4	71 (75.5)	12 (9.00-15.00)	
Lymph node metastasis				
	N0	43 (45.7)	11 (6.99-15.02)	0.552
	N1-3	51 (54.3)	15 (8.06-21.94)	

*Presence: complete response or disease regression /Absence: stable disease or progression after chemoradiotherapy

Univariate and multivariate analyses were performed to identify the risk factor(s) related to disease-free survival. Table 2 shows the results regarding nine variables examined in univariate analysis as potential risk factors for overall survival. Three of the nine factors differed significantly between these groups (p<0.05). The multivariate Cox regression analysis identified that the disease-free survival rates were significantly associated with NLR (low or high; OR: 1.81, CI: 1.16-2.82, p: 0.009) and response to chemoradiotherapy (presence or absence; OR: 2.30, CI: 1.45-3.66, p: 0.001).

Table 3 shows comparison of data of patients with and patients without response to chemoradiotherapy. There was no significant difference between two groups in terms of age, NLR value and NLR groups, PLR value and PLR groups, histopathology, T status, and lymph node metastasis (p>0.05).

Table 4 shows comparison of demographic and clinical parameters and response to treatment of patients classified according to NLR and PLR. There is no significant difference between patients with high NLR and those with low NLR. Similarly, there is no difference between patients with high PLR and those with low PLR.

Table 3. Comparison of Data of Patients With and Patients Without Response to CRT

	Patients with response to CRT n: 57	Patients without response to CRT n: 37	p value
Age (year)	59±11	58±7	0.788
Neutrophil/lymphocyte ratio	3.40 (1.16-18.64)	3.47 (1.11-14.05)	0.932
Low	30 (52.6)	17 (45.9%)	0.337
High	27 (47.4%)	20 (54.1%)	
Platelet/lymphocyte ratio	199 (54-883)	189 (68-641)	0.801
Low	27 (47.4%)	20 (54.1%)	0.337
High	30 (52.6)	17 (45.9%)	
Histopathology			
Adenocarcinoma	9 (15.8%)	6 (16.2%)	0.997
Epidermoid carcinoma	40 (70.2%)	26 (70.3%)	
Unclassified	8 (14.0%)	5 (13.5%)	
T status			
T0-2	15 (26.3%)	8 (21.6%)	0.396
T3-4	42 (73.7%)	29 (78.4%)	
Lymph node metastasis			
N0	24 (42.1%)	19 (51.4%)	0.252
N1-3	33 (57.9%)	18 (48.6%)	

CRT: chemoradiotherapy

Table 2. Univariate and Multivariate Analysis of Risk Factors for the Overall Survival and Disease-Free Survival

Risk factor	Overall Survival				Disease-free Survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Age (≥60 years or <60 years)	1.12 (0.72-1.74)	0.616	-	-	1.06 (0.69-1.65)	0.772	-	-
Gender (female or male)	1.13 (0.49-2.61)	0.768	-	-	0.87 (0.46-2.48)	0.872	-	-
Histopathology (epidermoid or others)	1.13 (0.71-1.81)	0.609	-	-	1.01 (0.63-1.61)	0.969	-	-
Neutrophil/lymphocyte ratio (low or high)	1.81 (1.16-2.81)	0.008	-	-	1.80 (1.15-2.80)	0.010	1.81 (1.16-2.82)	0.009
Platelet/lymphocyte ratio (low or high)	1.80 (1.16-2.81)	0.009	1.87 (1.20-2.91)	0.006	1.60 (1.03-2.49)	0.037	-	-
Stage (II or III)	1.20 (0.55-2.62)	0.646	-	-	1.34 (0.62-2.92)	0.460	-	-
Response to chemoradiotherapy (presence or absence)*	1.72 (1.09-2.70)	0.019	1.80 (1.14-2.81)	0.012	2.29 (1.45-3.63)	<0.001	2.30 (1.45-3.66)	<0.001
T status (T0-2 or T3-4)*	1.21 (0.73-1.99)	0.464	-	-	1.05 (0.64-1.73)	0.853	-	-
Lymph node metastasis (N0 or N1-3)*	1.14 (0.73-1.77)	0.563	-	-	1.08 (0.70-1.68)	0.723	-	-

*Presence: complete response or disease regression/Absence: stable disease or progression, OR: odds ratio, CI: confidence interval

Table 4. Parameters of Patients Classified According to Neutrophil/Lymphocyte and Platelet/Lymphocyte Ratios

Parameters		Neutrophil/Lymphocyte ratio			Platelet/Lymphocyte ratio		
		Low	High	p value	Low	High	p value
Age	<60 (%)	29 (61.7)	23 (48.9)	0.150	29 (61.7)	23 (48.9)	0.150
	≥60 (%)	18 (38.3)	24 (51.1)		18 (38.3)	24 (51.1)	
Gender	Male (%)	46 (97.9)	42 (89.4)	0.102	46 (97.9)	42 (89.4)	0.102
	Female (%)	1 (2.1)	5 (10.6)		1 (2.1)	5 (10.6)	
Tumor type	Adenocarcinoma (%)	8 (17.0)	7 (14.9)	0.328	7 (14.9)	8 (17.0)	0.903
	Epidermoid carcinoma (%)	35 (74.5)	31 (66.0)		34 (72.3)	32 (68.1)	
	Unclassified (%)	4 (8.5)	9 (19.1)		6 (12.8)	7 (14.9)	
T status	T0 (%)	1 (2.1)	3 (6.4)	0.897	1 (2.1)	3 (6.4)	0.377
	T1 (%)	1 (2.1)	1 (2.1)		2 (4.3)	-	
	T2 (%)	9 (19.1)	8 (17.0)		10 (21.3)	7 (14.9)	
	T3 (%)	12 (25.5)	12 (25.5)		10 (21.3)	14 (29.8)	
	T4 (%)	24 (51.1)	23 (48.9)		24 (51.1)	23 (48.9)	
N status	N0 (%)	24 (51.1)	19 (40.4)	0.389	23 (48.9)	20 (42.6)	0.468
	N1 (%)	2 (4.3)	1 (2.1)		2 (4.3)	1 (2.1)	
	N2 (%)	19 (40.4)	21 (44.7)		20 (42.6)	20 (42.6)	
	N3 (%)	2 (4.3)	6 (12.8)		2 (4.3)	6 (12.8)	
Response to treatment	Yes (%)	30 (63.8)	27 (57.4)	0.337	27 (57.4)	30 (63.8)	0.337
	No (%)	17 (36.2)	20 (42.6)		20 (42.6)	17 (36.2	
Total (%)		47 (100)	47 (100)		47 (100)	47 (100)	

Discussion

It is well known that there is the relationship between inflammation and cancer. Inflammation is important for tumor proliferation and survival in patients with malignancy (Schmidt et al., 2005). Unfortunately, the mechanism(s) of this association is not been elucidated completely. Understanding a cause-effect relationship between inflammation and cancer may lead to important results in terms of the diagnosis and the treatment.

Tumour cells produce various cytokines and chemokines that attract leukocytes. The inflammatory component of a neoplasm may include a different leukocyte subtypes such as neutrophils, macrophages, and dendritic cells. All these cells produce cytokines, cytotoxic mediators such as reactive oxygen species, and soluble mediators such as tumor necrosis factor-alpha (TNF-α) and interleukins. Inflammatory cells have powerful effects on tumour development. Early in the neoplastic process, these cells are powerful tumour promoters, producing an attractive environment for tumour growth, facilitating genomic instability and promoting angiogenesis. On the other hand, inflammatory responses should also be anti-tumour, but cancer patients are often defective in their inflammatory responses (Coussens and Werb, 2002).

Neutrophils are the most common leukocyte subset in the bloodstream. Recent evidences suggest that neutrophils play a role in cancer-related inflammation and have prognostic significance in human cancers (Donskov, 2013). Paesmans et al reported that high neutrophil count had an independent relation with poor survival in patients with advanced NSCLC (Paesmans et al., 1995). In a study by Teramukai et al. (2009) it has been shown that pretreatment elevated neutrophil count associated with poor survival rates in patients advanced NSCLC receiving chemotherapy.

Kobayashi et al. (2012) have been found that preoperative lymphocyte count was an independent prognostic factor in node-negative NSCLC. When the cut-off value of lymphocyte count was 1900 mm^{-3} with a maximum log-rank statistical value, overall 5-year survival rates were 67.9% for the low lymphocyte group and 87.7% for the high lymphocyte group. Also low lymphocyte count was correlated with vascular invasion and recurrence of NSCLC (Kobayashi et al., 2012). Similarly Zhang et al. (2013) reported that low-lymphocyte count was an independent unfavorable prognostic factor of disease-free survival in patients with NSCLC. Also, low lymphocyte count was related with lymphatic invasion and recurrence of NSCLC. In contrast, peripheral neutrophil count had no impact on survival (Zhang et al., 2013).

In cancer patients, recent studies evaluated prognostic significance of NLR and PLR, as well as neutrophil, lymphocyte, platelet count. NLR and PLR can be an indicator of tissue damage, which is not associated with treatment.

NLR is a simple, readily available and robust laboratory marker. NLR has also been previously found to independently predict outcomes in non-malignant disease such as chronic kidney disease (Kocyigit et al., 2013) and ST-elevated myocardial infarction (Kaya et al., 2013), in which the systemic inflammation response has been accused as a major contributing factor. These findings emphasize the use of NLR as a potential biomarker of the systemic inflammatory response.

A number of studies investigated the relationship between NLR and survival and response to chemotherapy in patients with cancer. Cendes et al. have found that higher NLR associated with poor prognosis in patients with stage IV NSCLC (Cedrés et al., 2012). Wang and colleagues have observed that high NLR was an independent prognostic factor in patients with bone metastasis (Wang et al. 2011). Also it has been reported that higher preoperative inflammatory markers including NLR and C-reactive protein predict poor survival in resected NSCLC (Tomita et al., 2012).

NLR may predict chemotherapy outcomes in patients with cancer. Chua et al. have evaluated the relationship between NLR and outcomes of first-line palliative chemotherapy in 349 patients with metastatic colorectal cancer and found that lower NLR was significantly

associated with improved clinical benefit. Furthermore, normalization of NLR after one cycle of chemotherapy resulted in improved progression-free survival (Chua et al., 2011). Yao et al. (2013) have investigated the association between NLR and therapy response and survival in 182 advanced NSCLC patients receiving first-line platinum-based chemotherapy and found that high pretreatment NLR was associated with worse response to first-line platinum-based chemotherapy and shorter survival (Yao et al., 2013).

When tissue injury occurs, white blood cells and platelets move the damaged area through the venous system. Platelets secrete some growth factors including platelet-derived growth factor (PDGF), PF4, TGF-β, vascular endothelial growth factor (VEGF), and thrombospondin-1 (Kaplan et al., 1979; Assoian and Sporn, 1986; Qian et al., 1996; Raungkaewmanee et al., 2012). These growth factors can stimulate tumour cells proliferation and adhesion to other cells leading to tumour growth and metastases, respectively (Qian et al., 1996; Raungkaewmanee et al., 2012; Stone et al., 2012). It has been shown that VEGF is an important mediator of tumor angiogenesis in malignant lesions in a genetically engineered mouse model of lung adenocarcinoma (Majeti et al., 2013). Divella et al. (2013) have found that high levels of TGF-β were associated with a poor prognosis in metastatic breast cancer.

Recent new evidences suggest that PLR is closely related to clinical outcomes in cancer patients. Raungkaewmanee et al. (2012) evaluated whether PLR and NLR could predict outcomes in patients with epithelial ovarian cancer. They observed that pretreatment higher PLR had significantly shorter progression-free and overall survival rates and PLR was a better prognostic predictor for survival compared to NLR (Raungkaewmanee et al., 2012). Wang et al. (2013) reported that preoperative NLR and PLR were significantly associated with cervical stromal involvement in patient with surgical treated endometrium carcinoma. Similarly, Asher et al. (2011) observed that high preoperative PLR was significantly associated with poor survival in patients with ovarian cancer.

Evidence for the use of these inflammatory markers (i.e. NLR and PLR) as direct predictors of outcome in patients with NSCLC receiving chemoradiotherapy is lacking. To the best of our knowledge, several studies evaluated the relationship between NLR and the survival, but there is no study evaluating the association of PLR with survival in patients with NSCLC. Furthermore, the effects NLR and PLR on response to radiotherapy have not been investigated in the patient population.

In the study, we found that the overall and disease-free survival rates were significantly associated with NLR and PLR in the univariate analysis. In multivariate analysis, however, there was significant association between PLR and overall survival whereas NLR was significantly associated with disease-free survival. Also response to chemoradiotherapy significantly associated with the overall and disease-free survival in multivariate analysis. On the other hand, there was no significant relationship between chemoradiotherapy and inflammatory indicators (i.e. NLR and PLR). So, the effect of inflammation, indicators of where are NLR and PLR, on survival seems independent from response to chemoradiotherapy.

In conclusion, NLR and PLR are simple, readily available and robust laboratory parameters. Pretreatment NLR and PLR measurements can provide important prognostic results in patients with NSCLC and assessment of two parameters together appears to better to predict the prognosis in patients with NSCLC. Our results need further study in a larger population to validate the prognostic role of these inflammatory biomarkers, especially PLR.

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