Original Article

Prognostic impact of the ^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography metabolic parameters and correlation with hematological inflammatory markers in lung cancer

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ABSTRACT

Introduction: Hematological inflammatory markers and metabolic parameters in positron-emission tomography/computed tomography (PET/CT) are important indicators predicting the prognosis of the disease in lung cancer as in many cancers. This study aimed to evaluate the correlation between pretreatment hematological inflammatory markers and PET/CT metabolic parameters in nonsmall cell lung cancer (NSCLC) patients and to predict the prognostic value of these parameters.

Materials and Methods: A total of 132 patients with diagnosed NSCLC who underwent PET/CT at staging were retrospectively evaluated. Hematological parameters were obtained from the hemogram taken no more than 2 weeks prior to PET/CT. Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and mean platelet volume (MPV) were recorded. Maximum standard uptake value, SUVmean, metabolic tumor volume (MTV), and total lesion glycolysis (TLG) were calculated. Clinical stage, tumor pathology, and overall survival were analyzed with these parameters.

Results: NLR and PLR were significantly positively correlated with MTV and TLG (all $P < 0.001$), MPV was negatively correlated with TLG ($P = 0.021$). While TLG, MTV, NLR, and PLR were increased in advanced stage disease, MPV was decreased. Univariate Cox-regression analysis demonstrated that greater age ($P = 0.015$), advanced stage ($P < 0.001$), low MPV ($P = 0.017$), high NLR ($P < 0.001$), PLR ($P < 0.001$), MTV ($P = 0.004$), TLG ($P = 0.001$) values, multivariate Cox-regression analysis revealed that NLR ($P < 0.001$) and advanced stage ($P < 0.001$) were significant predictors of poor prognosis in patients with NSCLC.

Conclusions: There were significant associations between hematological inflammatory markers and PET/CT metabolic parameters in the patients with NSCLC at the time of diagnosis. These indicators can contribute to predicting prognosis in patients with NSCLC.

KEY WORDS: Hematological parameter, metabolic tumor volume, nonsmall cell lung cancer, prognosis, total lesion glycolysis

INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths in both sexes, and the incidence of lung cancer is increasing with time.[1] The stage of the disease is still the most important prognostic factor.[2-5]

^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography (^{18}F-FDG PET/CT) is useful for staging in patients with nonsmall cell lung cancer (NSCLC) and contributes to predicting prognosis by providing information about the metabolic activity of the tumors. Many studies have suggested that metabolic parameters, such as maximum standard uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG), are important

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factors in determining the clinical course and prognosis in several types of cancers such as NSCLC.[6-12]

Systemic inflammation is known to be important in carcinogenesis.[13,14] Studies have shown that mean platelet volume (MPV), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) are indicators of systemic inflammation and were recently recognized as the indicators of prognosis in patients with various cancers.[15-17] Although the relationship between systemic inflammation and cancer importance is increasing in recent years, MPV, NLR, and PLR have been used as predictive parameters in cancer prognosis and survival in many cancer types.[17-25]

Although many studies show that both metabolic PET/CT parameters and hematological parameters predict the prognosis in many cancers, there are limited studies evaluating their relationship with each other.

This study aimed to evaluate the prognostic impact of NLR, PLR, MPV, SUVmax, MTV, and TLG of primary tumor during initial PET/CT and to investigate the correlation between systemic hematological inflammatory markers with the PET/CT metabolic parameters of a primary tumor in patients with NSCLC.

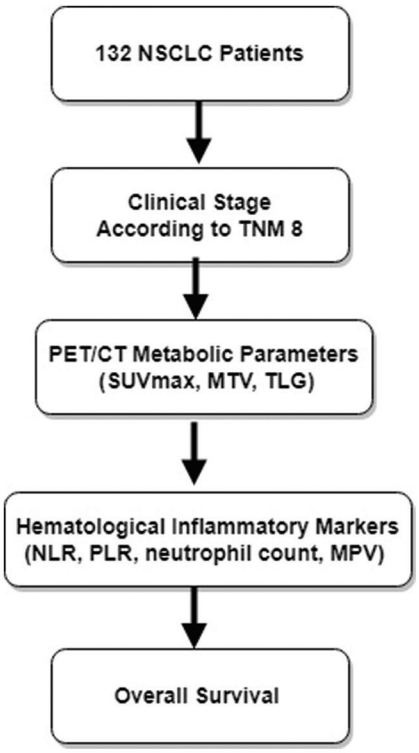

Figure 1: Flowchart of the study design

MATERIALS AND METHODS

Patient selection

A total of 204 patients diagnosed with NSCLC between March 2013 and December 2017 who underwent PET/CT for initial staging were retrospectively evaluated and 132 patients (10 females and 122 males) were included in this study. Exclusion criteria from the study were received neoadjuvant or adjuvant therapy, underwent surgery, had any sign of inflammatory or infectious disease or leukocytosis (≥10,000/μL), recently received blood transfusion, or those with the presence of hematological or autoimmune disease or a secondary malignancy.

Data collection

Patients' clinical data were retrieved from the hospital's electronic medical records. Tumor stage was classified according to the eighth edition of the tumor-node-metastasis 8 classification system. Hematological markers including absolute neutrophil count, absolute lymphocyte count, absolute platelet count, and MPV value were obtained from the complete blood count, which were obtained within 2 weeks of the baseline PET/CT scan. NLR, PLR, and MPV were recorded for all the patients. Overall survival (OS) was calculated as the time between the initial PET/CT scan and death or the last follow-up. The flowchart of the study design is shown in Figure 1.

The study was started after obtaining local ethical committee of Adnan Menderes University permission dated December 20, 2018, with numbers 2018/1546.

^{18}F-fluorodeoxyglucose positron-emission tomography/computed tomography and measurement (maximum standard uptake value, metabolic tumor volume, and total lesion glycolysis)

All the patients fasted for at least 6 h before PET/CT. The fasting blood glucose levels of all the patients were <200 mg/dL prior to scanning. Approximately 220–370 MBq ^{18}F-FDG was PET/CT. Oral contrast agent was given to all patients. The patients were subjected to the PET/CT (Siemens Biograph mCT, 16 slices) with 3D mode and TOF features, following a resting period of 50–60 min in the waiting room. Images were acquired from the head to the upper thigh region. Low-dose CT data were collected at an average of 120 kV and 50 mAs. The PET acquisition was obtained at a rate of 2 min per bed position.

All PET/CT images were visually and semi-quantitatively evaluated by two nuclear medicine physicians. SUVmax, SUVmean, and MTV values were calculated for only primary tumor. Lymph node and distant organ metastasis lesions were not included in the calculation. MTV was calculated by total tumor volume of 40% SUVmax or greater, and TLG was calculated by the following formula: TLG = MTV × SUVmean.

Statistical analysis

Statistical analysis was performed using the statistical package SPSS 22.0. Kolmogorov–Smirnov test was conducted to determine whether the quantitative variables were normally distributed in the groups. The dependence between the qualitative variables was determined by the Chi-square analysis. Mann–Whitney U-test was used for independent two-group

comparisons. Kruskal–Wallis H-test was used for more than two independent group comparisons. Descriptive statistics on quantitative variables were given as median (25^{th}–75^{th} percentile), and qualitative variables were given as number (*n*) and percentage (%). The correlation between continuous variables was analyzed by the Spearman correlation test. Linear regression analysis was used to determine the correlation between hematological inflammatory markers and SUVmax, MTV, and TLG values of the primary tumor.

The predictors of survival were analyzed by the Kaplan–Meier method. The prognostic significance of the variables for OS was assessed by univariate and multivariate analyses, using the Cox proportional-hazard regression model (Forward procedure, Wald method). $P < 0.05$ was considered statistically significant.

RESULTS

Clinical–demographic characteristics and laboratory and PET/CT metabolic parameters of all the patients are given in Table 1. The median age was 69 years (range 32–91 years). The majority of patients (67.4%) had squamous cell carcinoma diagnosis. Most patients had an advanced disease. The stage distribution of the patients is given in Table 1.

Based on the study conducted by Jeong *et al.*,[26] the 75^{th} percentile of cutoff value was applied to these parameters, and high-low PET/CT metabolic parameters and hematological inflammatory markers were detected. The cutoff values were 19.5 for SUVmax, 79.3 cm^3 for MTV, 674.6 g for TLG, 6.3 for NLR, 291.6 for PLR, and 10.5 fL for MPV.

Median OS was 9.8 months (range 0.5–68 month), and 117 (88.6%) patients died during the follow-up period. Mean OS was found to be 15.26 ± 15.14 months. Relationship of OS with the PET/CT metabolic parameters and hematological inflammatory markers of patients is shown in Table 2. OS was found to be shorter in patients with higher MTV ($P = 0.003$), TLG ($P = 0.001$), NLR ($P < 0.001$), PLR ($P < 0.001$), and lower MPV ($P = 0.014$) according to these high and low cutoff values. However, SUVmax had no prognostic significance in OS. Kaplan–Meier survival analyses of MTV and TLG are shown in Figures 2 and 3.

Prognostic factors of the disease were analyzed using univariate and multivariate Cox-regression analyses. Locally advanced and advanced stage; age (each 1-year increase); high MTV (≥79.3 cm^3), TLG (≥674.6 g), NLR (≥6.34), and PLR (≥291.6) values; and lower MPV (<10.5 fL) values were associated with poor prognosis in univariate Cox-regression analysis [Table 3]. Multivariate Cox-regression analysis revealed that only NLR level ($P < 0.001$, hazard ratio [HR] = 2.672, 95% confidence interval [CI] = 1.746–4.088) and locally advanced/advanced stage disease ($P < 0.001$, HR = 7.770, 95% CI = 2.617–23.073) were significant independent risk factors for poor prognosis.

When the association between the stage of disease and PET/CT metabolic parameters – hematological inflammatory markers – was analyzed, statistically significant differences were found between these parameters. While NLR ($P < 0.001$), PLR ($P < 0.001$), MTV ($P = 0.009$), and TLG ($P = 0.024$) levels were found to be increased in advanced-stage disease, MPV ($P = 0.029$) was found to be decreased. Moreover, there was no significant relationship between the SUVmax and the stage of the disease.

Table 1: Clinical and demographic characteristics of all patients

Patient's characteristics	Total subjects (*n*=132), *n* (%)
Age, median	69.0 (61.0-76.0)
Gender	
Male	122 (92.4)
Female	10 (7.6)
Neutrophil (×10^3/μL), mean	6.72±1.35
MPV (fL), mean	9.7±1.16
NLR, median	3.8 (2.8-6.3)
PLR, median	184.9 (128.2-291.6)
SUVmax, median	14.7 (10.7-19.5)
MTV (cm^3), median	37.4 (17.9-79.3)
TLG (g), median	286.2 (152.7-674.6)
Histopathology	
SCC	89 (67.4)
Adenocarcinoma	43 (32.6)
Stage	
I–II	14 (10.6)
III	45 (34.1)
IV	73 (55.3)
Median OS, months	9.8 (0.5-68)

MPV=Mean platelet volume, NLR=Neutrophil-to-lymphocyte ratio, PLR=Platelet-to-lymphocyte ratio, SUVmax=Maximum standardized uptake value, MTV=Metabolic tumor volume, TLG=Total lesion glycolysis, SCC=Squamous cell carcinoma, OS=Overall survival

Table 2: Relationship of overall survival with high/low cutoff values of positron-emission tomography/computed tomography metabolic parameters and hematological inflammatory markers

Variables	*n* (%)	OS (month)		*P*
		Mean	Median	
MPV (fL)				
<10.5	95 (72)	14.3	8	0.014
≥10.5	37 (28)	23.1	16	
NLR				
<6.34	99 (75)	21.1	14	<0.001
≥6.34	33 (25)	5.5	3	
PLR				
<291.6	99 (75)	20.6	13	<0.001
≥291.6	33 (25)	6.8	3	
MTV (cm^3)				
<79.3	99 (75)	19.6	12	0.003
≥79.3	33 (25)	9.5	5.5	
TLG (g)				
<674.6	99 (75)	19	13	0.001
≥674.6	33 (25)	9.8	3.5	
SUVmax				
<19.5	99 (75)	16.9	8	0.726
≥19.5	33 (25)	16.5	10	

MPV=Mean platelet volume, NLR=Neutrophil-to-lymphocyte ratio, PLR=Platelet-to-lymphocyte ratio, SUVmax=Maximum standardized uptake value, MTV=Metabolic tumor volume, TLG=Total lesion glycolysis, OS=Overall survival

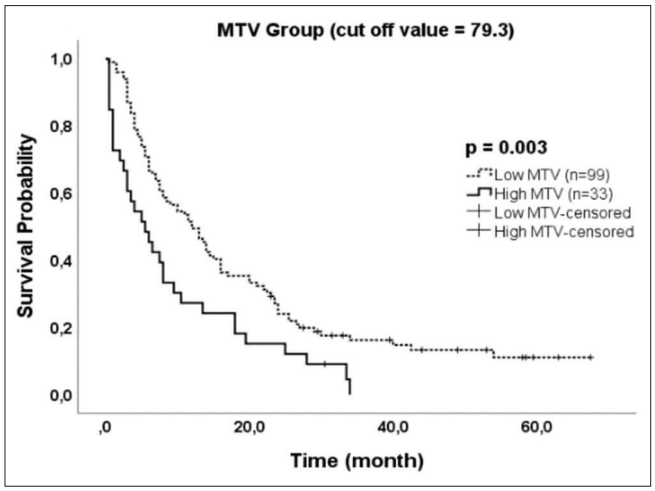

Figure 2: Kaplan–Meier overall survival curve of metabolic tumor volume

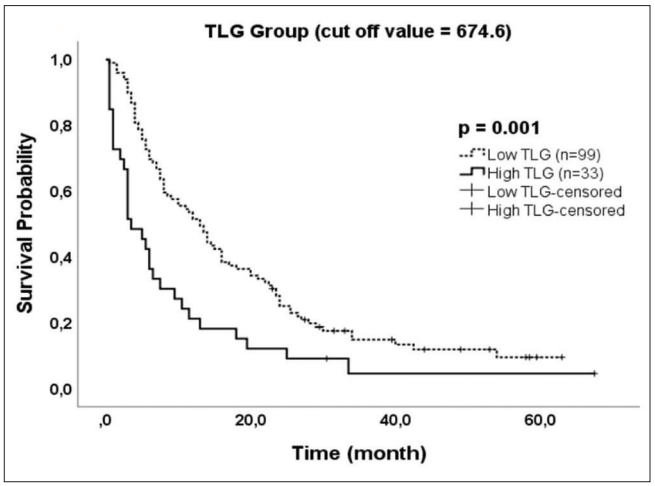

Figure 3: Kaplan–Meier overall survival curve of total lesion glycolysis

Table 3: Univariate Cox-regression analysis of overall survival

Variables	Categories	HR	95% CI	*P*
Age	Each 1 year increase	1.022	1.004-1040	0.015
Gender	Male/female	1.077	0.545-2.129	0.831
MPV (fL)	≤10.5 versus>10.5	0.596	0.390-0.910	0.017
NLR	≤6.3 versus>6.3	3.662	2.402-5.582	<0.001
PLR	≤291.6 versus>291.6	2.831	1.871-4.284	<0.001
SUVmax	≤19.5 versus>19.5	0.929	0.610-1.414	0.730
MTV (cm^3)	≤79.3 versus>79.3	1.830	1.214-2.759	0.004
TLG (g)	≤674.6 versus>674.6	2.018	1.334-3.053	0.001
Histopathology	SCC Adenocarcinoma	1.129	0.766-1663	0.540
Stage	Stage I–II Stage III–IV	11.985	4.162-34.516	<0.001

MPV=Mean platelet volume, NLR=Neutrophil-to-lymphocyte ratio, PLR=Platelet-to-lymphocyte ratio, SUVmax=Maximum standardized uptake value, MTV=Metabolic tumor volume, TLG=Total lesion glycolysis, SCC=Squamous cell carcinoma, CI=Confidence interval, HR=Hazard ratio

In the correlation analysis, it was found that the MTV and TLG were positively correlated with the hematological inflammatory markers. However, SUVmax had no correlation with these markers. The MTV and TLG showed positive correlation with NLR (for MTV, $r = 0.524$, $P < 0.001$; for TLG, $r = 0.540$, $P < 0.001$) and PLR (for MTV, $r = 0.445$, $P < 0.001$; for TLG, $r = 0.460$, $P < 0.001$). Moreover, there was a negative correlation between the MPV and TLG ($r = -0.201$, $P = 0.021$). Linear regression analyses are shown in Figures 4 and 5.

DISCUSSION

NSCLC is one of the most aggressive malignant tumors. Although the most important prognostic factor is still the stage of the disease, it has many prognostic indicators. Identification of the indicators that contribute to predict prognosis is clinically important in patients with NSCLC. The importance of PET/CT metabolic parameters and hematological inflammatory markers is increasing to predict prognosis in NSCLC, as in other malignancies.

Our study demonstrated that MTV and TLG at initial PET/CT are associated with systemic inflammatory markers and are significant prognostic factors in patients with NSCLC. According to recent literature, there are rare reports about the relationship between hematological inflammatory markers and PET/CT metabolic parameters in patients with NSCLC.

In many studies, PET/CT metabolic parameters were investigated as additional prognostic parameters.[6,7,27] Similar to our study, Davison *et al*.[28] showed that MTV and TLG were significantly greater in patients who died than in those who survived, and there was no relationship between SUVmax and OS. Similar to these results, recent studies showed that the volume-based PET/CT metabolic parameters such as the MTV and TLG are better prognostic indicators than SUVmax, in NSCLC patients.[29,30]

The relationship between high NLR and PLR values with a poor prognosis has been demonstrated in many cancers including NSCLC.[20,22,24] In accordance with the literature, our study showed that NLR and PLR correlated with the stage of the disease in patients with NSCLC. In addition, we demonstrated in this study that low MPV value is a poor prognostic factor in NSCLC patients. Similar to our study, Kumagai *et al*.[31] concluded that low MPV was associated with poor prognosis in patients with NSCLC. In addition, another study showed that MPV was decreased in patients with advanced stage NSCLC, similar to our study.

However, contrary to these results, Omar *et al*.[32] showed that increased MPV was an important prognostic factor, indicative of poor prognosis in patients with NSCLC. The difference in the results in the literature may be due to the low number of patients, different stages of patients, and the inclusion of different histopathological subtypes in these studies. Studies have shown that the relationship between MPV and prognosis is not clear yet in patients with NSCLC. These clinical results should be evaluated with a larger number of patients and in homogeneous patient groups.

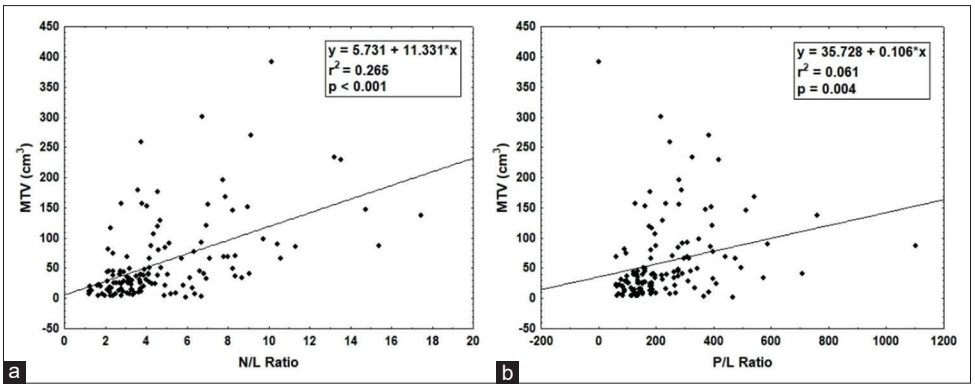

Figure 4: Linear regression analyses between metabolic tumor volume with neutrophil-to-lymphocyte ratio (a) and platelet-to-lymphocyte ratio (b)

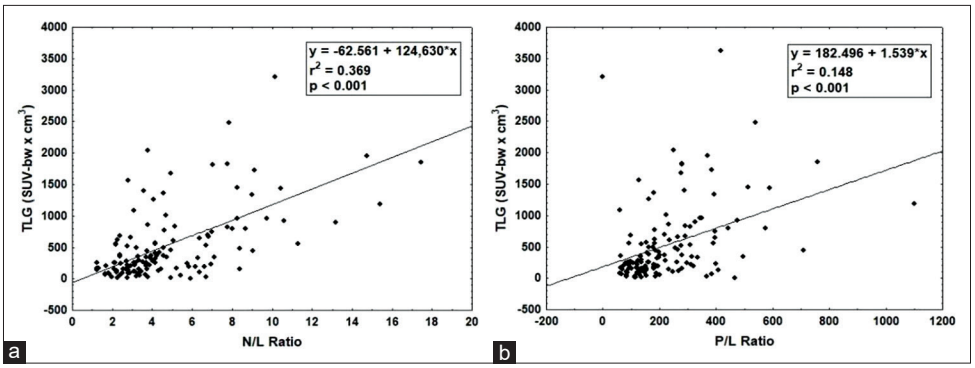

Figure 5: Linear regression analyses between total lesion glycolysis with neutrophil-to-lymphocyte ratio (a) and platelet-to-lymphocyte ratio (b)

There are a limited number of studies investigating the relation between PET/CT metabolic parameters and hematological inflammatory markers in malignancies. Tatsumi *et al.*[33] showed that there was a positive correlation between TLG and neutrophil count in esophageal cancer, at the time of diagnosis. In another study, the authors reported that there was a significant positive correlation between NLR and MTV in patients with esophageal cancer.[34] Mirili *et al.*[25] investigated the relationship between PET/CT metabolic parameters and hematological inflammatory markers in small cell lung cancer. Although MTV and TLG were significantly correlated with NLR, there was no correlation between MPV and PET/CT metabolic parameters in this study. Another study reported that there were significant positive correlations between NLR with MTV-SUVmax-TLG values, and PLR with MTV-TLG values in patients with colorectal cancer.[35]

Jeong *et al.*[26] investigated the relationship between SUVmax and hematological inflammatory markers in lung cancer. There was a significant positive correlation between SUVmax and neutrophil count in this study. On the contrary, there was no relationship between SUVmax and hematological inflammatory markers, in our study. The difference in the results may be justified by the differences between the distribution of the histopathological subtypes and stages of the disease. Jeong *et al.* included only stage 1 lung cancers in their study; but in our study, patients irrespective of the stage were included. In our study, the patient population had stage 4 disease predominantly. This is one of the limitations of our study.

In addition, SUVmax cannot represent glucose metabolism, tumor growth, and progression potential of the whole tumor. Metabolic volumetric parameters such as MTV and TLG are more reliable in the glucose metabolism of primary tumor and progression potential of disease than the SUVmax.[10]

CONCLUSIONS

MTV and TLG of the primary tumor provide metabolic and volumetric information. Systemic hematological inflammation markers such as NLR and PLR are prognostic factors in various malignancies. High hematological inflammatory markers and high MTV and TLG values at initial staging may be useful to predict advanced stage and poor prognosis in patients with NSCLC. The relation between PET/CT metabolic parameters and hematological inflammatory markers suggests that the evaluation of pretreatment metabolic tumor parameters, with hematological markers, together is more useful to detect clinical course, prognosis, and survival. Studies with a larger number of homogeneous patient groups are needed to understand the relation between these parameters and prognosis.

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Nil.

Conflict of Interest

The authors declare no conflict of interest.

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