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The relationship between inflammation markers, positron emission tomography/ /computed tomography parameters and disease prognosis in advanced non-small-cell lung cancer patients

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ABSTRACT

Introduction. Inflammation is known to be related to the development, spread, prognosis, and treatment response in cancer patients. Our study aimed to evaluate the correlation between inflammation indices and positron emission tomography-computed tomography (PET/CT) parameters and investigate their relationship with progression-free survival (PFS) and overall survival (OS) in patients diagnosed with stage-IV non-small cell lung cancer (NSCLC).

Material and methods. Demographic, clinicopathological, laboratory, and PET/CT data of 179 patients diagnosed with stage-IV NSCLC who presented to the Oncology Department of Dicle University, Faculty of Medicine between 2010–2020 were retrieved from patient files and the hospital database system.

Results. The median age at diagnosis was 64 (27–87) years. All patients included in the study had NSCLC: 72.6% had adenocarcinoma, 21.2% had squamous cell carcinoma, and 6.1% had other histological types. Of the 78 patients who were subjected to molecular analysis, 26 (33.3%) were *EGFR*-mutation positive. During the 10-month median follow-up, median first-line PFS was 6 months (95% CI 5.00–6.99), and median OS was 10 months (95% CI 7.8–12.1). The multivariate analysis performed for first-line PFS determined hemoglobin (HR = 1.01; 95% CI 1.003–1.02; p = 0.005) and PET total lesion glycolysis (TLG) (HR = 1.002; 95% CI 1.001–1.003; p = 0.003) values as independent prognostic factors. The multivariate analysis for OS determined positive *EGFR* mutation status (HR = 0.385; 95% CI 0.213–0.696; p = 0,014) and performance status (HR = 1.88; 95% CI 1.092–3.238; p = 0,008) as independent prognostic factors.

Conclusions. Our study determined the hemoglobin level and PET TLG from PET/CT parameters to be independent prognostic factors for PFS, and performance status and *EGFR* mutation positivity to be independent prognostic factors for OS.

Keywords: inflammation, non-small-cell lung cancer, PET/CT
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Introduction

Non-small-cell lung cancer (NSCLC) is among the cancers with the highest rates of mortality despite the treatment advances in recent years [1]. Although several prognostic factors have been identified in advanced NSCLC patients, the search for more precise prognostic factors to determine the course of the disease, optimize treatment choices, and avoid unnecessary treatment continues [2, 3]. Systemic inflammation has been shown to be involved in the development and progression of lung cancer. Elevated systemic inflammation indices indicate a poor prognosis in all cancer patients [4]. Another area that is being explored in relation to cancer-related inflammation concerns parameters obtained from positron emission tomography-computed tomography (PET/CT) imaging. The relationship between fluorodeoxyglucose-PET/CT (FDG-PET/CT) tumor metabolism markers and systemic inflammation has been demonstrated in a variety of cancers [5]. However, studies on the relationship between inflammation and PET/CT parameters in NSCLC are scarce.

Positron emission tomography-computed tomography is used in diagnosis, staging, and evaluation of treatment response in lung cancer. The standardized uptake value ($SUV_{max-mean}$) indicates tumor FDG uptake, which is prognostic in many cancers including lung cancer [3]. To date, a wide variety of inflammation parameters have been used to evaluate the inflammatory state in cancer [6]. The neutrophil-lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), and c-reactive protein (CRP) are widely used markers of systemic inflammation. Laboratory parameters are easily evaluated, repeatable, and inexpensive tests that are easy to use in daily practice. This study aimed to evaluate the correlation between inflammation indices and PET/CT parameters and investigate their relationship with progression-free survival (PFS) and overall survival (OS) in patients diagnosed with disseminated (stage IV) NSCLC.

Material and methods

For this study, patients who presented to the Oncology Clinic of Dicle University, Faculty of Medicine between 2010–2020, were followed up for a diagnosis of NSCLC. Their diagnostic PET/CT imaging was performed in the Nuclear Medicine Department of Dicle University, Faculty of Medicine or the Nuclear Medicine Department of Gazi Yaşargil Training and Research Hospital and was retrospectively screened. Files, examination results, and PET/CT scans of a total of 179 patients with NSCLC diagnosis confirmed by histopathological exams as stage IV according to the American Joint Committee on Cancer (AJCC) 8th edition tumor/node/metastasis (TNM) staging, who met the study criteria, were examined. Patients with acute and/or chronic inflammatory diseases [acute/chronic infection, collagen vascular diseases (e.g. rheumatoid arthritis, systemic lupus erythematosus (SLE)] were excluded from the study.

Patient sex, age, history of smoking, Eastern Cooperative Oncology Group (ECOG) performance status, presence of comorbid diseases, histopathological type, metastasis sites, diameter and localization of the primary tumor, date of pathological diagnosis, complete blood count parameters (neutrophil, lymphocyte, platelet, hemoglobin), NLR, PLR levels, PET/CT parameters [Lung SUV_{max}, Lung SUV_{mean}, Lung Bn_{max}, Lung Bn_{mean}, Lung total lesion glycolysis (TLG), Lung metabolic tumor volume (MTV), PET highest SUV_{max}, PET highest SUV_{mean}, PET highest Bn_{max}, PET highest Bn_{mean}, PET TLG, PET MTV], molecular analysis and immunohistochemistry (IHC) results (*EGFR* mutations and *ALK* or *ROS1* fusions, PDL-1 status), treatment options, treatment outcomes, and final status were recorded.

Hematological parameters were obtained from routine blood tests. Blood tests performed within 28 days before the initial treatment were taken into consideration. The indices (NLR, PLR) used in the study were calculated according to the formulae from previously published studies. The PLR was obtained by division of the absolute platelet count by the absolute lymphocyte count. NLR was obtained by division of the absolute neutrophil count by the absolute lymphocyte count.

Progression-free survival was defined as the length of time from the diagnosis to progression or the date of death, while OS was defined as the length of time from the diagnosis to death from any cause. In the evaluation of the patients in terms of progression, imaging performed after 3–4 cycles of systemic chemotherapy or after 3 months in patients receiving tyrosine kinase inhibitor (TKI) was taken as the basis.

Ethical approval was obtained for this study from Dicle University Faculty of Medicine Ethics Committee (Date/number: 06.05.2021/357).

Analysis of imaging

All patients were asked to stop food intake at least 6 hours before the scan. If they received intravenous (i.v.) glucose, it was stopped. Blood sugar was confirmed as 140 mg/dL in all patients before ^{18}F-FDG injection. One hour from ^{18}F-FDG injection (3.5–5.5 MBq/kg), computed tomography (CT) images [120 kV,80 mAs/slice, 700 mm transaxial field of view (FOV), no gap, 64 × 0.625 mm collimation, 1.4 pitch, 0.5 s rotation time, 3.3 mm slice thickness, and 512 × 512 matrix] from vertex to mid-femur were

obtained in the supine position using a 4-ring, 20-cm axial FOV Discovery IQ PET/CT device (GE Healthcare, Milwaukee, WI, US). PET [20 cm 3D FOV, ordered subset expectation maximization algorithm (OSEM), 5 iterations/12 subsets, full width at half maximum (FWHM) 3 mm] images were obtained starting from 2.5 minutes per bed position. All patients without contraindication were given 1.5 mL/kg i.v. contrast before CT imaging. Attenuation was obtained by corrected emission images and contrast or non-contrast CT data.

All ^{18}F-FDG PET/CT images were evaluated by a nuclear medicine specialist with 10 years of experience using PET Volume Computer-Assisted Reading (PET-VCAR; GE Healthcare) and Advantage Workstation software (version 4.7; GE Healthcare). Volumes of interest (VOI) were drawn manually to include the primary lung lesion, regional lymph nodes, and distant metastases (liver, lung, bone, etc.) on three planes. MTV and TLG (MTV × SUV_{mean}) values were obtained for each lesion using a 40% SUV threshold. MTV and TLG levels were obtained from all lesions, and whole-body MTV (WBMTV) and whole-body TLG (WBTLG) were calculated.

Statistical analysis

Statistical analyses were performed with the Statistical Package for Social Sciences (SPSS) version 25 software (IBM Corp. Armonk, NY, US). In the comparison of two independent groups, the Mann-Whitney U test was used for quantitative data. Spearman's rho was preferred for analysis of correlations between the variables. Categorical variables were compared using Pearson chi-square and/or Fisher's exact tests. The effects of PFS and OS parameters were analyzed using the Kaplan-Meier or Mantel-Coxlog-rank tests. Cox regression analysis was used on significant independent variables to measure the effects of prognostic variables on survival. Variables were analyzed at a 95% confidence interval, and $p < 0.05$ was considered statistically significant.

Results

This study included a total of 179 patients: 151 (84.4%) males and 28 (15.6%) females. The median age of the included patients was 64 (27–87) years at diagnosis. Of the 173 patients whose ECOG performance score at diagnosis could be retrieved, 69.9% (n = 121) had performance status (PS) of 0–1. All patients included in this study had a pathological diagnosis of NSCLC — 130 (72.6%) had adenocarcinoma, 38 (21.2%) had squamous cell carcinoma, and 11 (6.1%) had other histological subtypes. Of the 78 patients who were subjected to molecular analysis, 26 (33.3%) were *EGFR*-mutation positive. Of the 29 patients who were also examined for other driver mutations, four (13.8%) were *ALK*-fusion positive.

When the patients were evaluated with regard to comorbidities, 53 (29.6%) had a history of comorbid diseases — 14 (23.7%) had diabetes mellitus, 23 (38.9%) had hypertension, and 16 (27.1%) had coronary artery disease.

All of the 179 patients had stage IV disease. When the primary tumor localizations were examined, 101 (58.7%) had the primary tumor in the right lung. The history of previous operations was positive in three patients. Evaluation of metastatic disease sites revealed 86 (48%) patients with multiple metastases, 26 (14.5%) patients with bone metastasis, 21 (11.7%) with lung metastasis, 9 (5.1%) patients with adrenal metastasis, 8 (4.5%) patients with brain metastasis, 6 (3.4%) patients with liver metastasis, and 23 (12.8%) patients with involvement of other organs.

The majority of patients — 127 (84.6%) — had received combination and/or single-agent cytotoxic chemotherapy as first-line therapy. A total of 23 patients received tyrosine kinase inhibitors (TKI) as targeted therapy, with 21 (14%) receiving erlotinib, and 2 (1.4%) receiving alectinib (ALK inhibitor). Twenty-nine patients (16.2%) had not received therapy due to refusal or poor performance status. Of the 60 patients who could advance to second-line treatment, 46 (76.7%) received chemotherapy, 4 (6.7%) received erlotinib, 2 (3.3%) patients received osimertinib, 1 (1.7%) patient received alectinib, and 7 (11.7%) patients received immune checkpoint inhibitors. The treatments received by the 10 patients who could advance to third-line treatment included chemotherapy in 7 (70%) patients and immunotherapy in 3 (30%) patients. Detailed baseline demographic and clinicopathological data of the patients are presented in Table 1.

During the 10-month median follow-up duration, 16 (89.9%) patients died and 18 (10.1%) survived. Median OS was 10 months (95% CI 7.8–12.1), and median PFS after first-line therapy was 6 months (95% CI 5.00–6.99). In these patients, those with *EGFR* mutations had median OS of 14 months and median PFS of 9 months. Patients without driver mutations had median OS of 8 months and median first-line PFS of 5 months.

In the univariate survival analysis that evaluated the effects of general patient characteristics, laboratory parameters, PET/CT parameters on first-line PFS, hemoglobin ($p = 0.012$) from hemogram parameters, PET TLG ($p = 0.001$) and PET lung TLG ($p = 0.046$) from imaging parameters were determined to be associated with first-line PFS. Meanwhile, the p-values determined for variables such as NLR ($p = 0.09$), PET MTV ($p = 0.079$), PET lung MTV ($p = 0.094$), and positive *EGFR* mutation status ($p = 0.060$)

Table 1. General patient characteristics

Parameters	n = 179	[%]
Age (median, range)	64 (27–87)	
Smoking (n = 151)		
Yes	119	78.8
No	32	21.2
Sex		
Female	28	15.6
Male	151	84.4
ECOG performance status (n = 173)		
0–1	121	69.9
≥ 2	52	30.1
Comorbidity	53	29.6
Diabetes mellitus	14	7.8
Hypertension	23	12.8
Ischemic heart disease	16	8.9
Histopathology		
Adenocarcinoma	130	72.6
Squamous cell carcinoma	38	21.2
Others	11	6.1
Primary tumor localization (n = 172)		
Right hemithorax	101	58.7
Left hemithorax	71	41.3
Metastasis area		
Bone	26	14.5
Lung	21	11.7
Surrenal	9	5.1
Brain	8	4.5
Liver	6	3.4
Multiple	86	48
Others	23	12.8
EGFR mutation (n = 78)		
Negative	52	66.7
Positive	26	33.3
ALK fusion (n = 29)		
Negative	25	86.2
Positive	4	13.8
First-line Treatment (n = 150)		
Chemotherapy	127	84.6
Erlotinib	21	14
Alectinib	2	1.4
Second-line Treatment (n = 60)		
Chemotherapy	46	76.7
Erlotinib	4	6.7
Alectinib	1	1.7
Osimertinib	2	3.3
Immunotherapy	7	11.6
Third-line Treatment (n = 10)		
Chemotherapy	7	70
Immunotherapy	3	30

ALK — anaplastic lymphoma kinase, ECOG — Eastern Cooperative Oncology Group, EGFR — epidermal growth factor receptor

were found to approach statistical significance. When evaluated in multivariate analysis, the hemoglobin level (HR = 1.01; 95% CI 1.003–1.02; p = 0.005) and PET TLG (HR = 1.002; 95% CI 1.001–1.003; p = 0.003) were found to be independent prognostic factors predicting first-line PFS (Tab. 2).

In the univariate survival analysis that evaluated the effects of the general characteristics, laboratory parameters, and PET/CT parameters of the patients on overall survival, performance status (p = 0.013), neutrophil level at diagnosis (p = 0.026), NLR (p = 0.008), PET MTV (p = 0.016), PET TLG (p = 0.018), and positive *EGFR* mutation status (p = 0.011) were found to be associated with OS. The p-values determined for variables such as sex (p = 0.088) and hemoglobin (p = 0.081) approached statistical significance. When evaluated in multivariate analysis, positive *EGFR* mutation status (HR = 0.38; 95% CI 0.21–0.69; p = 0.02) and performance status (HR =1.88; 95%CI 1.09–3.23; p = 0.023) were found to be independent prognostic factors predicting OS. Positive *EGFR* mutation status was associated with good overall survival while ECOG performance status ≥ 2 was associated with poor overall survival (Tab. 3). Significant cut-off values could not be determined for PET/CT parameters.

In our study, the hemoglobin level showed a negative correlation with almost all PET/CT parameters while lymphocyte at diagnosis did not have significant correlations with all PET/CT parameters. The results concerning the correlations between inflammation markers and PET/CT metabolic parameters are presented in Table 4.

Discussion

In recent years, systemic inflammation has been shown to play a significant role in the development and progression of lung cancer. Elevated systemic inflammation markers indicate a poor prognosis in all cancer patients [4].

The identification of prognostic factors in advanced cancer patients is important when choosing a treatment method. To date, a multitude of prognostic factors including age, sex, performance status, smoking history, histopathological type, sites and numbers of metastases, previous treatments, SUV values on PET/CT, presence of mutations that affect the treatment choice (*EGFR*, *ALK*, and *ROS1* genes), and tumor PDL-1 expression have been identified [7, 8]. Moreover, weight loss and systemic inflammation (CRP, albumin) were also shown to predict survival in advanced lung cancer patients [9]. NSCLC patients are assiduously studied to determine more sensitive prognostic factors to help optimize treatment approaches in these patients [10].

Table 2. Univariate and multivariate analysis results in terms of progression-free survival

	Univariate analysis			Multivariate analysis		
Parameters	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
Age	1.006	0.992–1.021	0.337			
Sex (male*/female)	0.772	0.468–1.274	0.311			
Smoking (no*/yes)	1.273	0.765–2.118	0.353			
ECOG performance status (0–1*/≥2)	0.75	0.451–1.255	0.276			
Comorbidity (no*/yes)	1.804	0.629–5.172	0.272			
Primary tumor localization	0.833	0.551–1.260	0.387			
Primary tumor diameters	1.00	0.998–1.002	0.872			
Metastasis area	1.010	0.916–1.114	0.844			
Neutrophil count	1.017	0.954–1.085	0.606			
Lymphocyte count	0.88	0.706–1.098	0.257			
Platelet count	1.00	0.90–1.001	0.513			
Hemoglobin level	1.009	1.002–1.017	**0.012**	**1.01**	**1.003–1.02**	**0.005**
PLR	1.00	0.998–1.001	0.947			
NLR	1.06	0.991–1.135	0.09			
PET lung SUV_{max}	1.012	0.986–1.039	0.367			
PET lung SUV_{mean}	1.033	0.981–1.088	0.218			
PET lung Bn_{max}	1.017	0.976–1.059	0.427			
PET lung Bn_{mean}	0.039	0.958–1.128	0.354			
PET lung MTV	1.002	1.00–1.003	0.094			
PET lung TLG	1.002	1.00–1.003	**0.046**	1.001	1.00–1.005	0.101
PET Highest SUV_{max}	0.995	0.98–1.011	0.557			
PET Highest SUV_{mean}	1.002	0.974–1.031	0.896			
PET Highest Bn_{max}	1.018	0.982–1.056	0.325			
PET Highest Bn_{mean}	0.996	0.97–1.023	0.779			
PET MTV	1.001	1.00–1.002	0.079			
PET TLG	1.002	1.001–1.003	**0.001**	**1.002**	**1.001–1.003**	**0.003**
EGFR mutation (no*/yes)	0.547	0.292–1.025	0.06			

*Reference category; CI — confidence interval; ECOG — Eastern Cooperative Oncology Group; EGFR — epidermal growth factor receptor; HR — hazard ratio; MTV — metabolic tumor volume; NLR — neutrophil lymphocyte ratio; PET — positron emission tomography; PLR — platelet lymphocyte ratio; SUV — standardized uptake value; TLG — total lesion glycolysis

Performance status is an important factor in assessment of quality of life, treatment choice, and prognosis evaluation in cancer patients. It is the most widely used prognostic factor for cancer patients in daily practice. The only disadvantage of performance status evaluation is that it is a subjective method. In a study that included 404 NSCLC patients with a performance status of 0–2, it was found to be the strongest prognostic factor [11]. Likewise, our study performance status was an independent prognostic factor for OS (p = 0.023). Thus, the results of our study confirm that performance status remains the gold standard prognostic measure.

Testing newly diagnosed NSCLC patients for driver mutations is now accepted as a standard method in treatment management [12]. The presence of driver mutations in NSCLC patients is among strong prognostic factors. Studies have shown that patients with *EGFR* mutations who receive targeted therapy achieve a significant survival advantage compared to those without *EGFR* mutations in advanced lung cancers [12]. Accordingly, our study determined positive *EGFR* mutation status as a statistically significant prognostic factor for overall survival (p = 0.014). In an analysis conducted by Luis Paz-Ares et al. [13] that evaluated the treatment modalities in NSCLC patients, NSCLC patients with *EGFR* mutations were found to achieve longer PFS with erlotinib (13.2 months) or gefitinib (9.8 months) therapies compared to cytotoxic chemotherapy (5.9 months).

Table 3. Univariate and multivariate analysis results in terms of overall survival

	Univariate analysis			Multivariate analysis		
Parameters	**HR**	**95% CI**	**p**	**HR**	**95% CI**	**p**
Age	1.01	0.996–1.023	0.155			
Sex (male*/female)	0.683	0.44–1.05	0.088			
Smoking (no*/yes)	1.406	0.920–2.149	0.115			
Performance status (0–1*/≥ 2)	1.54	1.096–2.162	0.013	**1.88**	**1.092–3.238**	**0.023**
Comorbidity (no*/yes)	1.20	0.606–2.374	0.601			
Primary Tumor Localization	1.066	0.773–1.471	0.696			
Primary Tumor diameters	1.00	0.998–1.002	0.69			
Metastasis area	1.01	0.916–1.114	0.844	1.119	0.945–1.325	0.194
Neutrophil count	1.063	1.007–1.122	0.026	1.056	0.935–1.193	0.378
Lymphocyte count	0.89	0.738–1.095	0.291			
Platelet count	1.00	0.90–1.001	0.449			
Hemoglobin level	1.006	0.99–1.013	0.081			
PLR	1.00	0.90–1.001	0.985			
NLR	1.071	1.018–1.127	0.008	1.034	0.911–1.174	0.603
PET lung SUV_{max}	1.013	0.989–1.037	0.287			
PET lung SUV_{mean}	1.032	0.986–1.080	0.174			
PET lung Bn_{max}	1.022	0.986–1.059	0.23			
PET lung Bn_{mean}	0.054	0.981–1.132	0.151			
PET lung MTV	1.001	1.00–1.003	0.150			
PET lung TLG	1.001	1.00–1.002	0.122			
PET highest SUV_{max}	0.997	0.982–1.011	0.661			
PET highest SUV_{mean}	0.998	0.971–1.025	0.862			
PET highest Bn_{max}	1.016	0.985–1.047	0.324			
PET highest Bn_{mean}	0.995	0.97–1.021	0.725			
PET MTV	1.001	1.00–1.002	0.016	1.001	1.00–1.003	0.171
PET TLG	1.002	1.01–1.003	0.018	1.01	1.00–1.03	0.203
EGFR mutation (no*/yes)	0.484	0.277–0.845	0.011	**0.385**	**0.213–0.696**	**0.02**

*Reference category; CI — confidence interval; ECOG — Eastern Cooperative Oncology Group; EGFR — epidermal growth factor receptor; HR — hazard ratio; NLR — neutrophil lymphocyte ratio; MTV — metabolic tumor volume; PET; positron emission tomography; PLR — platelet lymphocyte ratio; SUV — standardized uptake value; TLG — total lesion glycolysis

In our study, median first-line PFS was 9 months, and median OS was 14 months in the 26 patients with *EGFR* mutations compared to median OS of 8 months and median first-line PFS of 5 months in patients without mutations. This result was confirmed to be longer when compared with patients without driver mutations.

In a study by Yue-Hua Zhang et al. [14] that included 416 patients with NSCLC and 206 patients with stage IV disease, the hemoglobin level was determined to be an independent prognostic factor for overall survival. On the other hand, our study determined it to be an independent prognostic factor for first-line PFS ($p = 0.005$), while, for OS ($p = 0.088$), it approached significance in the univariate analysis.

To date, multiple studies have examined inflammatory indices (GPS, ALI, NLR, PLR, etc.) in patients with stage IV lung cancer. Two that are the most recognized are the NLR [15] and PLR [16]. The NLR and PLR were shown to have a prognostic role in many types of cancer including lung cancer [17]. However, although the role of the NLR in NSCLC is relatively clear, the role of the PLR in NSCLC remains uncertain [18].

The increase in NLR is a result of an elevated neutrophil count or a reduced lymphocyte count. A higher NLR is associated with a poor prognosis in patients with NSCLC [19]. In a study by Yildirim et al. [20] that evaluated inflammation markers in patients with advanced NSCLC, the NLR was shown to be an

Table 4. Correlation between positron emission tomography (PET) parameters and inflammation indices

	Neutrophil	Lymphocyte	PLT	HB	PLR	NLR
PET lung SUV_{max}						
r	0.169*	–0.022	0.071	–0.190*	0.073	0.147
p	**0.025**	0.773	0.35	**0.012**	0.333	0.051
PET lung SUV_{mean}						
r	0.146	–0.039	0.037	–0.143	0.057	0.138
p	0.053	0.612	0.63	0.059	0.452	0.069
PET lung Bn_{max}						
r	0.166*	–0.014	0.159*	–0.168*	0.174*	0.152*
p	**0.029**	0.855	**0.035**	**0.026**	**0.021**	**0.044**
PET lung Bn_{mean}						
r	0.121	–0.041	0.106	–0.125	0.148	0.14
p	0.11	0.59	0.163	0.1	0.05	0.064
PET lung MTV						
r	0.1	–0.001	0.191*	–0.207**	0.139	0.079
p	0.187	0.994	0.011	**0.006**	0.066	0.297
PET lung TLG						
r	0.152*	–0.038	0.189*	–0.221**	0.167*	0.144
p	**0.045**	0.62	**0.012**	**0.003**	**0.027**	0.057
PET Highest SUV_{max}						
r	0.191*	–0.043	0.051	–0.197**	0.1	0.155*
p	**0.01**	0.565	0.498	0.008	0.184	0.038
PET Highest SUV_{mean}						
r	0.180*	–0.123	0.04	–0.189*	0.142	0.217**
p	**0.016**	0.101	0.594	**0.011**	0.058	**0.004**
PET Highest Bn_{max}						
r	0.180*	–0.032	0.13	–0.189*	0.184*	0.159*
p	**0.016**	0.669	0.084	**0.011**	**0.014**	**0.033**
PET Highest Bn_{mean}						
r	0.149*	–0.091	0.119	–0.161*	0.216**	0.191*
p	**0.046**	0.225	0.114	**0.031**	**0.004**	**0.011**
PET MTV						
r	0.143	–0.096	0.122	–0.230**	0.169*	0.192**
p	0.057	0.202	0.103	**0.002**	**0.024**	**0.01**
PET TLG						
r	0.183*	–0.057	0.105	–0.229**	0.128	0.172*
p	**0.014**	0.45	0.162	**0.002**	0.087	0.022

*Correlation is significant at the 0.05 level; **Correlation is significant at the 0.01 level; EGFR — epidermal growth factor receptor; MTV — metabolic tumor volume; SUV — standardized uptake value; TLG — total lesion glycolysis

independent prognostic factor. However, the PLR was not found to have a relationship with the prognosis [20]. Meanwhile, various studies have reported conflicting results. In a large meta-analysis that included 214 studies and 1514 patients, a high PLR was revealed to have a significant relationship with poor OS and PFS in NSCLC patients [18].

In a retrospective analysis including 325 NSCLC patients treated with platinum-based chemotherapy, a high NLR was found to be correlated with low OS and PFS. Moreover, in a meta-analysis including 14 different studies with NSCLC patients, a high NLR was found to be associated with poor prognosis and low overall survival when a cut-off value of 5 was used for the NLR [21].

Meanwhile, in our study, neutrophil ($p = 0.026$) and NLR inflammation markers were not found to be independent prognostic factors. Similarly, the PLR did not have a statistically significant relationship with OS or PFS.

The problem with confirming NLR and PLR values as prognostic factors is that there is no certain threshold value. In the literature, various values for the NLR (3.0, 4.0, 5.0) were adopted. The subjective and inconsistent cut-off values for these inflammation markers may lead to errors in interpretation and hamper the routine use of these parameters in clinical practice. Another problem with inflammation markers is that these markers can also be affected by comorbid conditions and factors that are commonly encountered in cancer patients such as infection and coronary disease. It is also known that these conditions are encountered at higher rates depending on the age of NSCLC patients [21]. Further prospective and large-scale studies are needed to confirm the prognostic importance of the NLR and PLR.

Mechanisms that might explain the relationship between inflammation markers and a poor prognosis are quite complicated. However, certain hypotheses have been proposed. Inflammation and inflammation markers (neutrophil, platelet) alter the tumor microenvironment, contributing to angiogenesis, tumor development, and metastatic processes while lymphocyte releases inflammatory factors that prevent proliferation and metastatic processes [22].

Another area that is investigated in relation to cancer-related inflammation concerns the parameters obtained from PET/CT imaging and their correlations with inflammation markers. FDG-PET/CT tumor metabolism markers were shown to possess prognostic importance and have a relationship with systemic inflammation in many types of cancer [23]. Although the basis of the relationship between tumor glucose uptake and systematic inflammatory response markers is not clear, it is proposed that it is associated with stromal tumor activity and inflammatory cell activity in cancer.

Although PET/CT is widely used in NSCLC patients, data on whether semi-quantitative PET/CT parameters predict patient outcomes is currently limited [24]. Various semi-quantitative PET/CT parameters such as SUV_{max}, MTV, and TLG have been evaluated [25]. Some studies have shown these parameters to have prognostic value in NSCLC patients [26, 27].

In our study, PET TLG ($p = 0.003$) from prognostic factors predicting first-line PFS was shown to be an independent prognostic factor. When analyzed with regard to OS, the prognostic factors from PET/CT parameters that predicted OS in univariate analysis were PET MTV ($p = 0.016$) and PET TLG ($p = 0.018$). However, these were not determined as prognostic factors in multivariate analysis.

In line with our study, PET MTV and TLG were determined as prognostic factors associated with overall survival in a study by Sharma et al. [28] that included stage III or IV NSCLC patients and evaluated prognostic factors. This result was confirmed by multiple studies [27].

In a study by Polverari et al. [24] that was conducted with 57 candidates for immunotherapy who had NSCLC, patients with higher MTV and TLG values showed a higher probability of disease progression. In contrast, SUV_{max} did not show a significant relationship with either PFS or OS. These results indicate a superior correlation with volumetric ^{18}F-FDG PET/CT parameters rather than SUV_{max} alone [24]. In a meta-analysis including 1474 patients, univariate analyses determined SUV_{max} as a strong prognostic factor. However, it was stated that this needed to be supported by studies that could conduct multivariate analyses [29]. In a study with a similar design by Mirilli et al. [33], SUV_{max} and SUV mean were found to possess lower prognostic importance than PET TLG and PET MTV, in line with our study. However, the majority of these studies are small single-center retrospective studies that involve heterogeneous patient populations in terms of disease stage and treatment. MTV and TLG are usually calculated by using a fixed SUV_{max} threshold. The calculation of lower or higher values for these parameters may be an issue in certain situations. Various cut-off values were proposed for PET/CT parameters in different studies. However, these values need to be validated. Determining optimal cut-off values would promote the use of these imaging parameters in routine daily practice.

Both PET/CT metabolic parameters and hematological parameters can be useful in evaluation of NSCLC prognosis. However, it is not clear whether these two types of parameters are correlated. If correlated, PET/CT and hematological parameters can be used in combination in the evaluation of the prognosis, providing complementary information. The correlation between PET/CT parameters and inflammatory parameters has been inspected in many cancers in various studies in the literature. However, our knowledge on this matter is limited to metastatic lung cancer patients.

This study determined a weak to moderate correlation between inflammation markers and PET/CT parameters (Tab. 4).

In a study conducted by Komek et al. [31], biomarkers such as the NLR and the PLR were investigated with regard to their correlations with the PET/CT parameters of the patients, and no significant difference was found between the subgroups in terms of the NLR or PLR. Although the cited study and our study differed in terms of the parameters that were compared and the patient populations, it is remarkable that a correlation between

inflammatory parameters and PET/CT parameters was found.

The limitations of this study are its retrospective design that involved a limited number of centers and the small patient population it included. In addition, heterogeneities in patient treatments that may have resulted in differences in clinical outcomes and the combined evaluation of patients with and without driver mutations are also among the study limitations. Studies with large patient populations are needed to confirm the results of this study.

Conclusions

Positron emission tomography-computed tomography parameters and inflammation markers are easily obtained, non-invasive markers and may provide complementary information in metastatic NSCLC patients. In our study, PET TLG and the hemoglobin level at diagnosis were shown to be independent prognostic factors for PFS, and performance status and EGFR status were shown to be independent prognostic factors for overall survival.

Article Information and Declarations

Data availability statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Ethics statement

This study was approved by the Institutional Ethics Committee and conducted in compliance with the ethical principles defined in the Declaration of Helsinki (permit no-date: 357- 06.05.2021).

Author contributions

E.P., Z.O., S.E.: conception and design of the study, data analysis and interpretation and writing of the article; Y.G., H.K., M.K., Z.U., M.A.K.: acquisition of clinical data and data analysis and interpretation; B.T., A.I.: data analysis and interpretation.

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Conflict of interest

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Supplementary material

None.

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