Research Article

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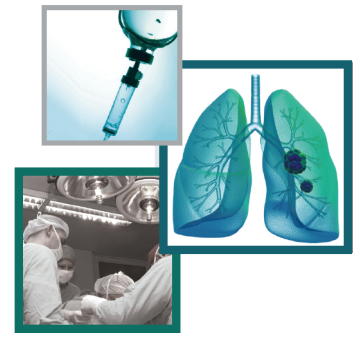
Lung Cancer Management



Inflammatory parameters in NSCLC with driver mutation

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Aim: The tumor microenvironment of NSCLC with driver mutations, such as *EGFR*, *ALK* and *ROS*, is less inflammatory. **Materials & methods:** This retrospective study included 38 patients with NSCLC driver mutations. The relationship between clinical and inflammatory markers concerning progression-free survival and overall survival was analyzed based on Kaplan-Meier curves. **Results:** The mean age of the patients was 59.8 ± 11.9. Progression-free survival and overall survival were significantly longer in patients under 65 years of age and with low neutrophil–lymphocyte ratio, low systemic immune-inflammation index and high lymphocyte count ($p < 0.05$). **Conclusion:** Unlike tumor biology, peripheral inflammatory parameters, such as neutrophil–lymphocyte ratio, systemic immune-inflammation index and lymphocyte count may be associated with survival in NSCLC patients with driver mutations.

Plain language summary: Lung cancer is the most common cancer worldwide and has a high mortality rate. Overall survival expectancy in metastatic NSCLC has increased from 11 months to 18 months. The detection of targeting mutations and the introduction of targeted treatments are the factors that increase overall survival. The contribution of immunotherapy to NSCLC is indisputable. The contribution of immunotherapy is low in NSCLC with driver mutation. We found that survival was associated with peripheral parameter indicators of inflammation despite the less inflamed tumor microenvironment. For immunotherapy to be effective in NSCLC, where there are not many treatment options, investigating different immune checkpoints or escape mechanisms and treatment planning for these will further improve survival.

Tweetable abstract: Peripheral inflammatory parameters may be associated with survival in driver mutation NSCLC, in contrast to a less inflammatory tumor microenvironment.

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Keywords: driver mutation • inflammatory markers • non-small-cell lung cancer • survival

Lung cancer stands as the prevailing neoplastic condition on a global scale, exhibiting a steady rise in both morbidity and mortality rates. Approximately 80% of afflicted individuals present with NSCLC [1]. Noteworthy advancements in molecular and genetic testing of tumor cells over the past decade have identified pivotal driver mutations in advanced and metastatic NSCLC. This, in turn, has paved the way for targeted therapeutic interventions directed toward the *EGFR*, *ALK* and *ROS*, resulting in an appreciable enhancement in overall survival (OS) rates [2–4].

Recent studies have demonstrated a significant correlation between systemic inflammation and the process of carcinogenesis. Cytokines released within the tumor microenvironment have been found to potentiate angiogenesis, tumor proliferation and the metastatic potential of the tumor. Research indicates that tumors exhibiting heightened levels of inflammation tend to manifest a less favorable prognosis [5].

Neutrophils are the first responding cells of the immune system. Neutrophils synthesize certain cytokines that initiate systemic inflammation. Lymphocytes are potent predictors of the inflammatory response. Neutrophils interact with lymphocytes to regulate the immune response. Across a spectrum of malignancies, systemic inflammatory

parameters, including the prognostic nutritional index (PNI), neutrophil–lymphocyte ratio (NLR) and systemic immune-inflammation index (SII), have been demonstrated to exert a notable influence on tumor recurrence and OS [6,7].

The NLR is an easily accessible and simple test that provides valuable information about systemic inflammation [8]. It effectively serves as a peripheral indicator of the systemic inflammatory reaction in the tumor microenvironment. As the NLR escalates, the heightened inflammation surrounding the tumor tends to foster tumor growth. Concurrently, a diminished count of lymphocytes may render patients more susceptible to malignancies, as well as certain bacterial and viral infections, potentially impacting the patient's prognosis. Significantly, the prognostic value of NLR has been established in various malignancies [9].

The SII is a simple, affordable and accessible test. As it indicates the degree and clinical course of inflammation in many inflammatory diseases, it has also been found to affect prognosis in some studies with cancer patients [10,11].

The PNI, an indicator of patients' nutritional status, is prognostic in many cancer types, such as lung, stomach and colorectal cancer. PNI is important in perioperative immunological status and risk stratification of postoperative complications. The relationship between cancer immunotherapy and PNI has not yet been clarified [12].

In light of the resistance mechanisms that develop after first-line targeted treatments, different studies have been conducted for second-line and subsequent treatments. One of these is immunotherapy targeting PD-1 or PD-L1 [13]. NSCLC immunotherapy has a positive effect of approximately 20%, which increases according to the PDL-1 positivity rate [14–17]. PDL-1 positivity is lower in patients with driver mutations than in patients without driver mutations, and the benefit of immunotherapy is less [18].

One of the important markers in tumor immunotherapy is the CD8 lymphocyte ratio. In many cancer types, a low CD8 lymphocyte ratio is associated with poor prognosis [19,20]. The tumor-infiltrating lymphocyte rate, PDL-1 positivity and tumor mutation burden were significant indicators of immunotherapy response in studies of patients who progressed after treatment targeting driver mutations [21]. Studies have been conducted on the efficacy of immunotherapy in patients with driver mutations, both alone in the second line and conjunction with radiotherapy (RT) and chemotherapy (CT) [22,23].

Several studies have demonstrated that patients with driver mutations have a lower-inflammatory tumor microenvironment [21,24]. Nevertheless, whether peripheral inflammatory parameters play an important role in patients with driver mutations is unknown. This study aimed to investigate the relationship between systemic inflammatory response parameters and survival in patients with driver mutations.

Materials & methods

The study included patients with stage 4 lung adenocarcinoma who presented to our oncology clinic between April 2010 and September 2021 with positive driver mutations by next-generation sequencing, such as *EGFR*, *ALK* and *ROS*. Study participants with missing data, no driver mutation, other malignancies, chronic inflammatory diseases and hematological malignancies were excluded.

Demographic data, sex, Eastern Cooperative Oncology Group (ECOG) performance scores of 0, 1, 2, 3 and 4, smoking status as smokers and nonsmokers, and lung, brain, bone, adrenal and multiple metastasis areas information were obtained from patient files. Since the number of patients aged 74 years and over is low, age groups were grouped as <65 and ≥ 65 years by reviewing the literature [25].

The patients' leukocyte, neutrophil, lymphocyte, monocyte, hemoglobin, red blood cell distribution width (RDW), red blood cell (RBC), platelet, lactate dehydrogenase (LDH), alkaline phosphatase (ALP), albumin and C-reactive protein (CRP) values were obtained from the hospital's information system. Blood samples of our patients were taken before starting the treatment.

The SII formula was platelet (P) $\times$ neutrophil (N)/lymphocyte (L), and the ratio of NLR neutrophil count to lymphocyte count was calculated with the PNI formula (10 $\times$ albumin (g/l) + (0.005 $\times$ total lymphocyte count). The patients' neutrophil, lymphocyte, SII, NLR, and PNI cutoff values were calculated with an ROC curve. Approval was obtained from the ethics committee of Atatürk University Faculty of Medicine (2023/110). The Declaration of Helsinki was followed during all procedures.

Statistics

Categorical data are shown as numbers and percentages. The Pearson chi-square and Fisher's exact tests analyzed relationships between clinicopathological parameters and PNI, SII, and NLR. *Post hoc* analysis was performed for data with multiple groups.

Using the date of diagnosis of NSCLC, the OS of patients undergoing first- or second-line tyrosine kinase inhibitor (TKI) therapy was calculated based on the date of death or the last control date. Based on the date of progression, death, or the last time the patient was seen during the use of a TKI, progression-free survival (PFS) was calculated. Kaplan-Meier analysis was used to estimate the mean and median PFS and OS times, and the long rank test was used to compare the survival times between the clinical and pathological data of the patients. SPSS Statistics 21.0 was used for all statistical analyses. Statistical significance was defined as $p < 0.05$. Bonferroni adjustment was performed at p values for multiple group comparisons.

Results

Sociodemographic and clinical variables are given in Table 1. Of the 38 patients in our study, 17 (44.7%) were female, and 21 (55.3%) were male. The mean age was 59.8 ± 11.9. The number of patients with an ECOG performance score of 0, 1, 2 and 3 was 3, 23, 10 and 2, respectively. Nonsmokers were more common, and the rate was 63.2%. Our study patients mostly had *EGFR* driver mutations (23, 60.5%), *ALK* driver mutations (12, 31.6%), *ROS* driver mutations (2, 5.3%), and other mutations (1, 2.6%). During the follow-up of patients, 32 (84.2%) progressed, and 30 (78.9%) died.

Receiver operating characteristic curve analysis was used to determine the most sensitive and specific cutoff values for the NLR, PNI and SII. The area under the curve of NLR was 0.58 (sensitivity 73% and specificity 63%), PNI was 0.59 (sensitivity 63% and specificity 60%), SII was 0.54 (sensitivity 70% and specificity 63%), neutrophil count was 0.58 (sensitivity 63% and specificity 67%), and lymphocyte count was 0.60 (sensitivity 63% and specificity 60). Based on the cut-off values obtained for NLR, PNI, SII, neutrophils and lymphocytes, the corresponding sensitivity and specificity were 2.57, 37.7, 779.5, 5.2 and 2.03, respectively.

The relationships between inflammatory indices and other variables are given in Table 2. A significant relationship was found between the NLR and age (higher rate of age ≥65 at NLR ≥2.57 group, p = 0.012), sex (higher rate of men at NLR ≥2.57 group, p = 0.009), mutation type (p = 0.005), and site of metastasis at diagnosis (p = 0.002). According to *post hoc* analysis, the *EGFR* mutation rate was higher in the NLR ≥2.57 group than in the NLR <2.57 group. In the NLR ≥2.57 group, lung metastasis was significantly higher than that in the NLR <2.57 group.

PNI had a significant relationship with the site of metastasis at diagnosis (p = 0.002). According to *post hoc* analysis, lung metastasis in the PNI ≥37.7 group was significantly higher than in the PNI <37.7 group and bone metastasis was significantly higher in the PNI <37.7 group.

There was a significant relationship between the SII and sex (higher rate of men in the SII ≥799.5 group, p = 0.027), mutation type (p = 0.015), site of metastasis at diagnosis (p = 0.006) and presence of progression (higher rate of presence of progression in the SII ≥799.5 group, p = 0.018). According to *post hoc* analysis, the *EGFR* mutation rate was higher in the SII ≥799.5 group than in the SII <799.5 group. In the SII ≥799.5 group, lung metastasis was significantly higher than that in the SII <799.5 group.

PFS and OS relationships with categorical data are given in Table 3. The median PFS and OS times were 17.7 and 23.4 months for the whole cohort, respectively. The median PFS (21 vs 13 months, p = 0.006) and OS (58 vs 14 months, p = 0.002) times were longer at <65 years than at ≥65 years and were statistically significant (Figures 1A & 2A). The group with an NLR <2.57 had a significantly longer median PFS (48 vs 13 months, p = 0.002) and median OS (59 vs 19 months, p = 0.012) than the group with an NLR ≥2.57 (Figures 1B & 2B). The median PFS (48 vs 13 months, p = 0.003) and median OS (59 vs 19 months, p = 0.042) were significantly longer in the group with SII values <799.5 than in the group with SII values ≥799.5 (Figures 1C & 2C). The median PFS (17 vs 43 months, p = 0.001) and median OS (18 vs 49 months, p = 0.025) were significantly shorter in the group with lymphocyte values <2.03 than in the group with lymphocyte values ≥2.03 (Figures 1D & 2D).

Discussion

Among all malignancies, lung cancer is the most common cause of death. Treatment of lung cancer is, therefore, of utmost importance. Due to the detection of mutations, such as *EGFR*, *ALK* and *ROS*, are drivers of NSCLC, personalized targeting therapy agents have advanced in recent years, improving patient survival. Studies continue to show that some mutation types of *BRAF* may also be driver mutations [26,27].

EGFR is a transmembrane protein that regulates tumor growth, invasion, metastasis and angiogenesis. *EGFR* inhibitors act by blocking signaling pathways and causing apoptosis in tumor cells [28]. The *ALK* fusion gene and

Table 1. Presents the sociodemographic and clinic characteristics.

	n	%
Age		
– <65 years	24	(63.2)
– ≥65 years	14	(36.8)
Sex		
– Women	17	(44.7)
– Men	21	(55.3)
ECOG		
– 0	3	(7.9)
– 1	23	(60.5)
– 2	10	(26.3)
– 3	2	(5.3)
Smoking status		
– No	24	(63.2
– Yes	13	(34.2)
Comorbidity		
– No	26	(68.4)
– Yes	10	(26.3)
Mutation		
– *EGFR*	23	(60.5)
– *ALK*	12	(31.6)
– *ROS*	2	(5.3)
– *BRAF*	1	(2.6)
Which series		
– First line	19	(50.0)
– Second line and after	19	(50.0)
Metastasis site in diagnosis		
– Lung	13	(34.2)
– Brain	7	(18.4)
– Bone	12	(31.6)
– Surrenal	3	(7.9)
– Multiple	2	(5.3)
Brain metastases on follow-up		
– No	8	(21.1)
– Yes	29	(76.3)
Progression		
– No	6	(15.8)
– Yes	32	(84.2)
Latest status		
– Live	8	(21.1)
– Exitus	30	(78.9)
NLR		
– <2.57	13	(34.2)
– ≥2.57	25	(65.8)
PNI		
– <37.7	21	(55.3)
– ≥37.7	17	(44.7)
SII		
– <799.5	14	(36.8)
– ≥799.5	24	(63.2)
Neutrophil		
– <5.2	15	(39.5)
– ≥5.2	23	(60.5)
Lymphocyte		
– <2.03	21	(55.3)
– ≥2.03	17	(44.7)

ECOG: Eastern Cooperative Oncology Group; NLR: Neutrophil–lymphocyte ratio; PNI: Prognostic nutritional index; SII: Systemic immune-inflammation index.

proto-oncogene *ROS* were rearranged after *EGFR*. *ALK* inhibition could be more effective with crizotinib treatment in the targeted treatments of driver mutations in lung cancer [29].

The role of inflammation in the tumor microenvironment in increasing tumorigenesis and metastasis has been well documented in recent studies [5]. In addition to inflammation in the tumor microenvironment, peripheral

Table 2. The relationship between inflammatory indices and other variables.

	NLR			PNI			SII		
	<2.57	≥2.57	p-value	<37.7	≥37.7	p-value	<799.5	≥799.5	p-value
Age									
– <65 years	12 (92.3)	12 (48.0)	**0.012**	13 (61.9)	11 (64.7)	0.859	11 (78.6)	13 (54.2)	0.132
– ≥65 years	1 (7.7)	13 (52.0)		8 (38.1)	6 (35.3)		3 (21.4)	11 (45.8)	
Sex									
– Women	11 (84.6)	10 (40.0)	**0.009**	14 (66.7)	7 (41.2)	0.116	11 (78.6)	10 (41.7)	**0.027**
– Men	2 (15.4)	15 (60.0)		7 (33.3)	10 (58.8)		3 (21.4)	14 (58.3)	
ECOG									
– 0	1 (7.7)	2 (8.0)	0.935	1 (4.8)	2 (11.8)	0.387	1 (7.1)	2 (8.3)	0.875
– 1	8 (61.5)	15 (60.0)		11 (52.4)	12 (70.6)		9 (64.3)	14 (58.3)	
– 2	4 (30.8)	6 (24.0)		7 (33.3)	3 (17.6)		4 (28.6)	6 (25.0)	
– 3	0 (0.0)	2 (8.0)		2 (9.5)	0 (0.0)		0 (0.0)	2 (8.3)	
Smoking									
– No	11 (84.6)	13 (54.2)	0.083	14 (70.0)	10 (58.8)	0.478	12 (85.7)	12 (52.2)	0.074
– Yes	2 (15.4)	11 (45.8)		6 (30.0)	7 (41.2)		2 (14.3)	11 (47.8)	
Comorbidity									
– No	9 (69.2)	17 (73.9)	1.000	14 (70.0)	12 (75.0)	>0.999	10 (76.9)	16 (69.6)	0.716
– Yes	4 (30.8)	6 (26.1)		6 (30.0)	4 (25.0)		3 (23.1)	7 (30.4)	
Mutation									
– *EGFR*	4 (30.8)	19 (76.0)	**0.005**	11 (52.4)	12 (70.6)	0.099	5 (35.7)	18 (75.0)	**0.015**
– *ALK*	7 (53.8)	5 (20.0)		9 (42.9)	3 (17.6)		7 (50.0)	5 (20.8)	
– *ROS*	2 (15.4)	0 (0.0)		0 (0.0)	2 (11.8)		2 (14.3)	0 (0.0)	
– *BRAF*	0 (0.0)	1 (4.0)		1 (4.8)	0 (0.0)		0 (0.0)	1 (4.2)	
Which series									
– First line	8 (61.5)	11 (44.0)	0.305	12 (57.1)	7 (41.2)	0.328	9 (64.3)	10 (41.7)	0.179
– Seond line and after	5 (38.5)	14 (56.0)		9 (42.9)	10 (58.8)		5 (35.7)	14 (58.3)	
Metastasis site in diagnosis									
– Lung	10 (76.9)	3 (12.5)	**0.002**	8 (40.0)	5 (29.4)	**0.011**	10 (71.4)	3 (13.0)	**0.006**
– Brain	1 (7.7)	6 (25.0)		5 (25.0)	2 (11.8)		1 (7.1)	6 (26.1)	
– Bone	2 (15.4)	10 (41.7)		2 (10.0)	10 (58.8)		3 (21.4)	9 (39.1)	
– Surrenal	0 (0.0)	3 (12.5)		3 (15.0)	0 (0.0)		0 (0.0)	3 (13.0)	
– Multiple	0 (0.0)	2 (8.3)		2 (10.0)	0 (0.0)		0 (0.0)	2 (8.7)	
Brain metastases on follow-up									
– No	11 (84.6)	18 (75.0)	0.685	17 (81.0)	12 (75.0)	0.705	11 (78.6)	18 (78.3)	1.000
– Yes	2 (15.4)	6 (25.0)		4 (19.0)	4 (25.0)		3 (21.4)	5 (21.7)	
Progression									
– No	4 (30.8)	2 (8.0)	0.154	2 (9.5)	4 (23.5)	0.378	5 (35.7)	1 (4.2)	**0.018**
– Yes	9 (69.2)	23 (92.0)		19 (90.5)	13 (76.5)		9 (64.3)	23 (95.8)	
Latest status									
– Live	5 (38.5)	3 (12.0)	0.094	3 (14.3)	5 (29.4)	0.426	5 (35.7)	3 (12.5)	0.117
– Exitus	8 (61.5)	22 (88.0)		18 (85.7)	12 (70.6)		9 (64.3)	21 (87.5)	

Bold p-values indicate they are statistically significant.
ECOG: Eastern Cooperative Oncology Group; NLR: Neutrophil–lymphocyte ratio; PNI: Prognostic nutritional index; SII: Systemic immune-inflammation index.

inflammatory parameters, such as NLR, SII, PNI, neutrophil count and lymphocyte count, have also been investigated in many tumor types [30,31]. In our study, age, smoking, NLR, SII, neutrophil and lymphocyte count were associated with PFS among prognostic inflammatory and clinical markers. Age, NLR, SII and lymphocyte count were found to be associated with OS.

In the chemotherapy treatment of age-based lung cancer patients, it was found that the patient group aged ≥65 years was more fragile and had a higher rate of hospitalization, and patients aged <65 years had better compliance with the treatment. Factors, such as age, presence of additional comorbidities and differences in tumor biology, are important in the management of lung cancer. The role of age in influencing inflammatory parameters and survival was investigated in our study in the ≥65 and <65 age groups. PFS and OS at <65 years of age were longer than those at ≥65, similar to the literature [25].

Ramagopalan *et al.* found that patients with *ALK* driver mutations survived better than those with *EGFR* driver mutations [32]. Similarly, in our study, patients with *ALK* driver mutations had better OS times than those with *EGFR* driver mutations.

According to Berardi *et al.*, increased neutrophil count and low lymphocyte count in NSCLC patients with mutant or wild-type *EGFR* were associated with poor prognosis for both PFS and OS but were not independent

Table 3. Progression-free survival and overall survival relationships with categorical data.

	PFS			OS		
	Mean	Median	p-value	Mean	Median	p-value
Age						
– <65 years	36.2	21.7	**0.006**	46.4	58.3	**0.002**
– ≥65 years	15.8	13.3		22.5	14.4	
Sex						
– Women	31.6	18.0	0.332	39.1	31.7	0.540
– Men	25.7	16.6		33.5	21.7	
ECOG						
– 1	31.3	17.9	0.763	35.3	21.7	0.592
– 2	25.5	17.6		37.7	23.4	
Smoking						
– No	34.9	22.4	**0.036**	40.0	31.7	0.463
– Yes	20.4	14.0		31.5	21.7	
Comorbidity						
– No	29.6	17.9	0.707	38.6	27.1	0.563
– Yes	27.9	12.1		31.5	21.6	
Mutation						
– *EGFR*	21.1	13.3	0.371	27.4	18.0	0.211
– *ALK*	39.0	25.9		48.5	46.4	
Which series						
– First line	32.3	18.0	0.478	40.1	46.4	0.580
– Second line and after	24.4	17.5		33.1	23.0	
Metastasis site in diagnosis						
– Lung	44.2	48.8	0.083	51.4	59.6	0.136
– Brain	19.1	17.5		33.2	27.1	
– Bone	25.3	13.4		27.9	19.3	
Brain metastases on follow-up						
– No	31.8	21.7	0.117	37.8	27.1	0.688
– Yes	21.6	13.4		33.8	19.4	
NLR						
– <2.57	46.2	48.8	**0.002**	51.8	59.5	**0.013**
– ≥2.57	19.9	13.4		28.5	19.3	
PNI						
– <37.7	23.3	17.5	0.216	33.2	21.7	0.500
– ≥37.7	34.5	31.4		40.2	40.1	
SII						
– <799.5	45.6	48.8	**0.003**	48.3	59.5	**0.042**
– ≥799.5	20.1	13.4		29.5	19.4	
Neutrophil						
– <5.2	40.7	23.0	**0.024**	46.4	37.5	0.078
– ≥5.2	21.3	14.5		30.1	21.6	
Lymphocyte						
– <2.03	17.6	13.3	**0.001**	27.0	18	**0.025**
– ≥2.03	43.1	48.8		47.8	49.9	

Bold p-values indicate they are statistically significant.
ECOG: Eastern Cooperative Oncology Group; NLR: Neutrophil–lymphocyte ratio; OS: Overall survival; PFS: Progression-free survival; PNI: Prognostic nutritional index; SII: Systemic immune-inflammation index.

prognostic factors [33]. Similarly, in our study, those with neutrophil counts above 5.02 and lymphocyte counts below 2.03 had shorter PFS and OS times.

The study by Zhang *et al.* demonstrated that only *EGFR* mutation-positive patients had an NLR cutoff of 2.9 and that PFS and OS were significantly longer in those with low NLR values [34]. In another study, the NLR cutoff value was taken as 5.0 in the study by Ding *et al.* in patients with favorable *EGFR* mutations, and the NLR value was revealed to be a prognostic factor for both PFS and OS [35]. The NLR cutoff value in our study was 2.57, and both PFS and OS times were longer in patients with low NLR values, similar to the studies of Zhang *et al.* and Ding *et al.*, but the prognostic importance cannot be tested because the number of patients was low.

An analysis of 12 studies of patients with stage-independent NSCLC with or without driver mutations by Hu *et al.* found that different PNI cutoff values and low PNI were poor prognostic factors for PFS and OS [36]. The PNI cutoff value in our study was 37.7, and although patients with low PNI had shorter PFS and OS times, the

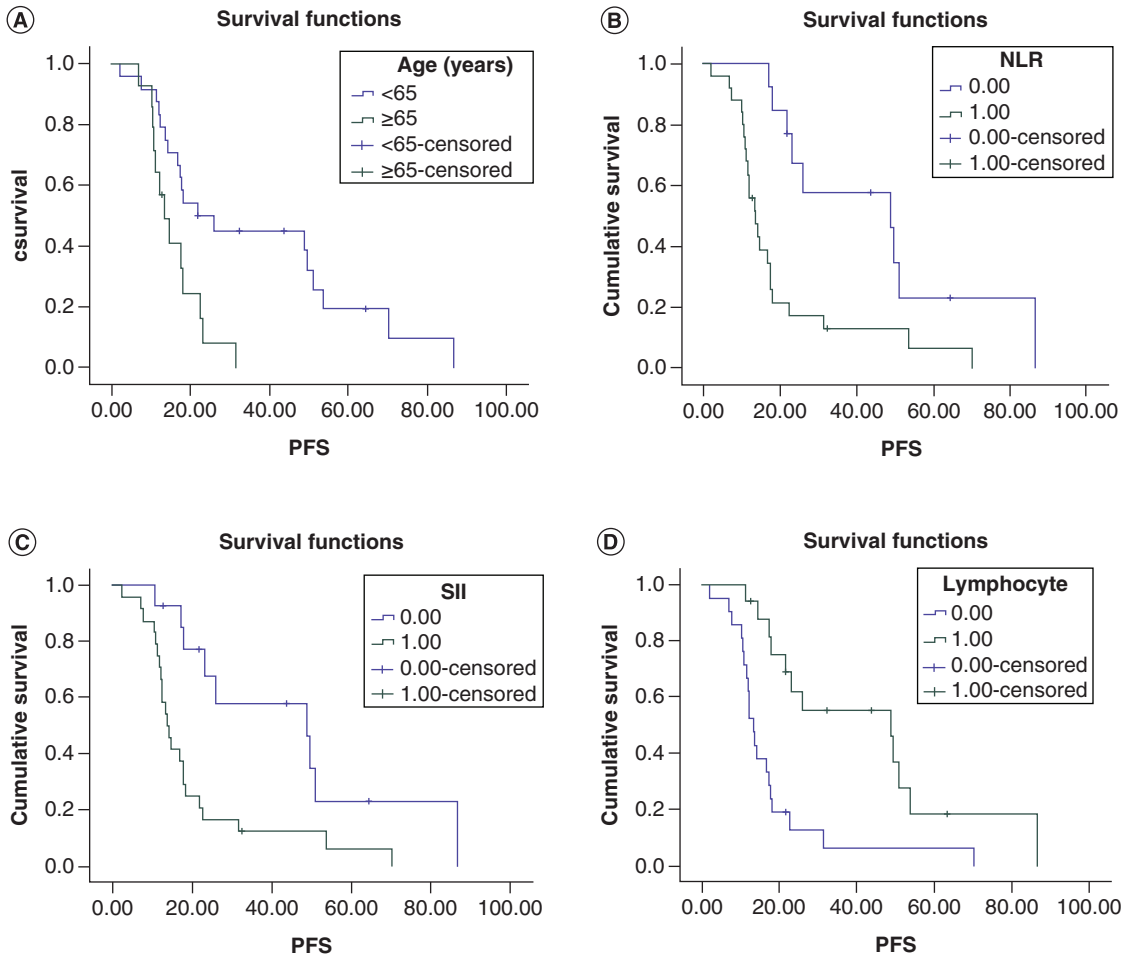

Figure 1. Progression-free survival relationship of age and inflammatory parameters, Kaplan-Meier graphics. (A) Age, **(B)** NLR, **(C)** SII and **(D)** lymphocyte. NLR: Neutrophil–lymphocyte ratio; PFS: Progression-free survival; SII: Systemic immune inflammation index.

difference was not statistically significant. This may be due to the small number of patients in our study or the group size difference between patients with stage 4, adenocarcinoma histology, and driver mutations.

In the study by Ju *et al.*, the mean SII cutoff value was 855.3 in patients with *EGFR* mutations, and both PFS and OS were prolonged in patients with low SII values, which were shown to be independent prognostic markers [37]. In our study, the SII cutoff value was found to be 799.5. Similar to the study of Ju *et al.*, both PFS and OS times were longer for low SII. However, as in NLR, prognostic significance could not be calculated due to the small number of patients.

Some studies have reported that the tumor microenvironment of patients with NSCLC driver mutations is less inflamed. A study by Gainor *et al.* demonstrated that 12 patients with *EGFR*-positive tumors lacked CD8 lymphocyte infiltration in their tumor microenvironment [27]. The low PD-L1 positivity rate among patients with driver mutations and the low tumor mutation burden among nonsmokers were considered to be reasons for the poor response to immunotherapy. Therefore, Dong *et al.* described immune escape and tolerance in their study [21]. Retmeyer *et al.* investigated ways to break immune resistance by combining different checkpoint inhibitors in patients with driver mutations [26]. Additionally, Reits *et al.* and Franceschini *et al.* investigated breaking the immune resistance of the tumor by sensitizing the tumor with radiotherapy [22,23].

Anti-PD-1 and anti-PD-L1 agents used for immunotherapy in patients with driver mutations are ineffective, and their efficacy in treatment is controversial. Therefore, the relationship between driver mutation-positive lung cancer and inflammatory parameters is important. Currently, the efficacy of immunotherapy does not exactly match PD-L1 scores.

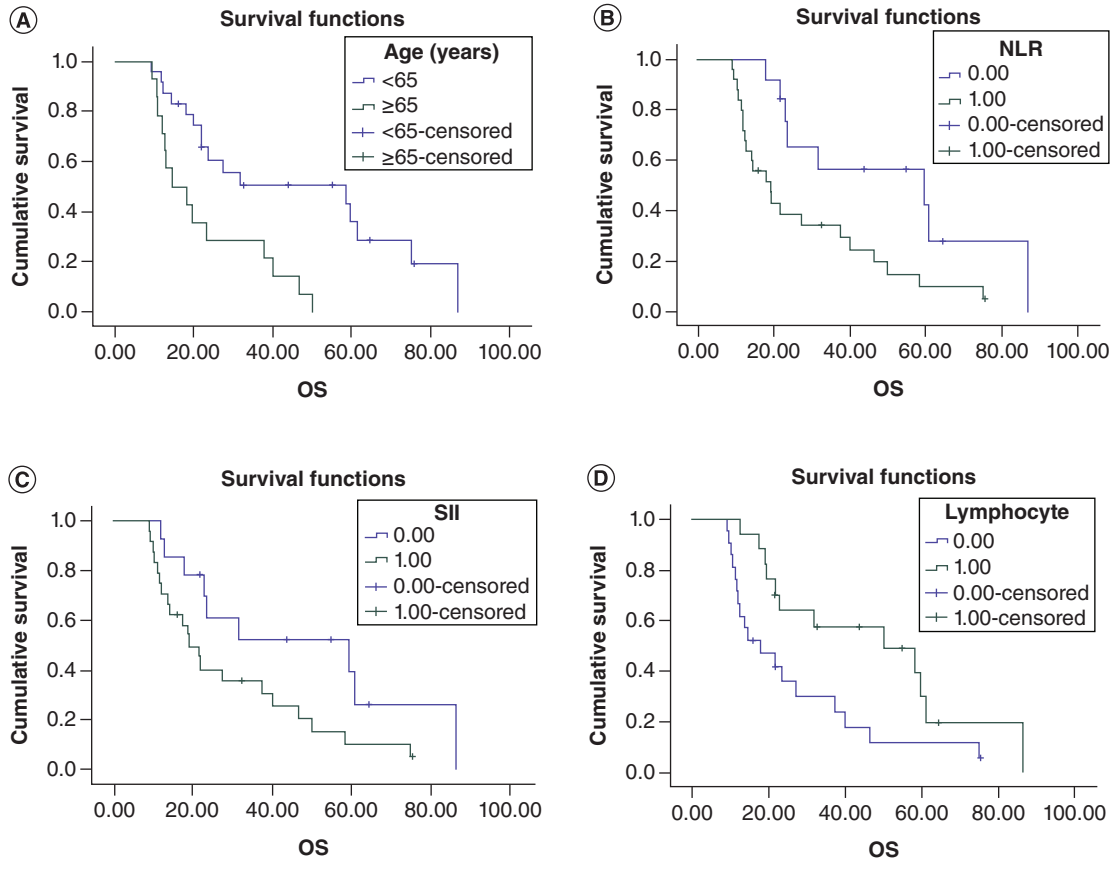

Figure 2. Overall survival relationship of age and inflammatory parameters, Kaplan-Meier graphics. (A) Age, **(B)** NLR, **(C)** SII and **(D)** lymphocyte. NLR: Neutrophil–lymphocyte ratio; OS: Overall survival; SII: Systemic immune inflammation index.

To our knowledge, no study in the literature investigates the relationship between inflammatory parameters and survival in NSCLC patients with driver mutations. The study we conducted is the first to address this topic. Our study showed the relationship between driver mutation-positive lung cancer survival and peripheral inflammatory parameters. It seems contradictory that lung cancer with driver mutations has lower inflammation and is also associated with peripheral inflammatory parameters.

However, rather than the relationship between the state of the tumor microenvironment and the effectiveness of immunotherapy, it is possible to find situations that provide immune escape in the future or to discover other immune checkpoints. In addition to the fact that the tumor maintains the microenvironment by presenting antigens and escapes the immune system by secreting some substances, it is also necessary to identify new checkpoints that can show the response to immunotherapy. Further studies are needed to elucidate the interaction between tumor and host immunity. Finally, due to the small number of patients in this study, supporting it with different studies will make the results more meaningful.

The study's limitations include the small sample size, which may alter the CI of the test results, the absence of a control group, and the fact that it was retrospective and restricted to a single center. Driver mutations in NSCLC are less common in our region compared with Far East data, and in our retrospective study, 38 patients were identified by scanning the archives of NSCLC patients who applied to our center between 2010 and 2021 and were found to be mutation positive as a result of genetic analysis.

Conclusion

In patients with driver mutation NSCLC, the tumor microenvironment is less inflamed. However, the fact that PFS and OS are correlated with parameters, such as peripheral inflammatory status indicators, such as NLR, SII, and lymphocyte count, suggests that the relationship between the tumor microenvironment and peripheral

inflammatory parameters in this patient group is not sufficiently clarified. The results are similar to those without driver mutations and suggest that there may be different pathways, especially regarding the immune response. There is a need for further research on this subject, particularly regarding the effectiveness of immunotherapy. The findings of this study are expected to guide future studies and contribute to the literature on this topic.

Summary points

- NSCLC is a tumor with high morbidity and mortality.
- New drugs are coming into use for driver mutations and targetable mutations.
- The tumor microenvironment is less inflamed, and the immune response–tumor relationship is unclear.
- The effectiveness of immunotherapy is poor in patients with driver mutations.
- After targetable therapy, chemotherapy and other treatment options are limited.
- PD-L1 score is not sufficient to predict the effectiveness of immunotherapy.
- The reflection of inflammation in the tumor microenvironment on peripheral parameters may be seen in many tumor types.
- The relationship was found between less inflammatory NSCLC and peripheral inflammatory parameters.
- Some are unknown about the tumor–immune response or immune escape and microenvironment relationship.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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