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OPEN ARAŞTIRMA MAKALESİ / RESEARCH ARTICLE

Prognostic Risk Factors Affecting Survival in Patients with Metastatic Non-Small Cell Lung Cancer Receiving Nivolumab As Second-Line Therapy

Nivolumab Kullanan Metastatik Küçük Hücreli Dışı Akciğer Kanserli Hastalarda Sağkalımı Öngören Prognostik Risk Faktörleri

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ÖZET

Amaç: Küçük hücreli dışı akciğer kanseri (KHDAK), sık görülen ve ölümcül seyreden bir kanser türüdür. Bu çalışmanın amacı, platin bazlı tedavi sonrası ikinci basamak tedavi olarak nivolumab kullanılan metastatik KHDAK tanılı hastalarda, klinik, laboratuvar ve sistemik inflamatuar yanıt verilerinin hastalıksız sağkalım (PFS) ve genel sağkalım (OS) üzerindeki etkilerini incelemektir.

Gereçler ve Yöntemler: Çalışma retrospektif ve tek merkezli olarak yürütüldü. İkinci basamak tedavi olarak nivolumab kullanan 84 metastatik KHDAK tanılı hastaların demografik verileri, kanser tanısıyla ilişkili özellikleri ve nivolumab başlanmadan hemen öncesine ait hastaların laboratuvar parametreleri kaydedildi. C-reaktif protein/albumin oranı (CAR), aspartat aminotransaminaz/alanin aminotransaminaz (De Ritis) oranı, Glasgow prognostik skoru (GPS), nötrofil/lenfosit oranı (NLR), platelet/lenfosit oranı (PLR), prognostik nütrisyonel indeks (PNI) ve sistemik immün-inflamasyon indeksi (SII) parametreleri her hasta için ayrı ayrı hesaplandı.

Bulgular: Tüm katılımcılar için ortalama yaş 62.08±8.43 yıl idi. Medyan PFS ve OS süreleri sırasıyla 6.4 ve 13 ay olarak belirlendi. PFS açısından yapılan tek değişkenli risk analizinde, Doğu Kooperatif Onkoloji Grubu Performans Durumu (ECOG PS) (p=0.05) ve CAR (p=0.046) PFS açısından önemli birer prognostik risk faktörü olarak belirlendi. Ancak, çok değişkenli analiz bu iki parametrenin PFS ile ilişkisini desteklemedi. OS açısından yapılan analizde ise, tek değişkenli analizde ECOG PS (p=0.01), kemik metastazı (p=0.047), CAR (p=0.019) ve De Ritis oranı (p=0.051) prognostik risk faktörleri olarak belirlendi. Çok değişkenli analizde ise, ECOG PS (HR=0.45, %95 GA 0.22-0.94, P=0.035), kemik metastazı (HR=0.38, %95 GA 0.19-0.78, P=0.008) ve De Ritis oranı (HR=0.47, %95 GA 0.23-0.96, P=0.037) bağımsız risk faktörleri olarak tespit edildi.

Sonuç: Bu çalışmada, ikinci basamak tedavi olarak nivolumab kullanan metastatik KHDAK tanılı hastalarda, kötü ECOG performans durumu, kemik metastazı ve yüksek De Ritis oranı daha kısa OS süresiyle ilişkilendirilen birer bağımsız prognostik faktör olarak belirlendi. Bu faktörler, klinik pratikte hastaların prognozlarını değerlendirmede yardımcı olabilir.

Anahtar Kelimeler: Akciğer kanseri, nivolumab, prognostik faktörler, CAR, De ritis oranı

ABSTRACT

Aim: Non-small cell lung cancer (NSCLC) is a commonly occurring and potentially fatal type of cancer. The aim of this study is to investigate the effects of clinical, laboratory, and systemic inflammatory response data on progression-free survival (PFS) and overall survival (OS) in metastatic NSCLC patients who were treated with nivolumab as a second-line treatment following platinum-based therapy.

Materials and Methods: The sample of this retrospective single-center study consisted of 84 adult patients with metastatic NSCLC receiving nivolumab as second-line treatment. Demographic data, cancer diagnosis-related characteristics and laboratory parameters of the patients just before nivolumab was started were recorded. The C-reactive protein/albumin ratio (CAR), aspartate aminotransferase/alanine aminotransferase (De Ritis) ratio, Glasgow prognostic score (GPS), neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), prognostic nutritional index (PNI), and systemic immune-inflammation index (SII) parameters were calculated for each patient.

Results: The mean age for all participants was 62.08 ± 8.43 years. The median PFS and OS were 6.4 and 13 months, respectively. In the univariate risk analysis for PFS, Eastern Cooperative Oncology Group Performance Status (ECOG PS) (p=0.05), and CAR (p=0.046) were identified as significant prognostic risk factors for PFS. However, the multivariate analysis did not confirm these two parameters as prognostic factors for PFS. In the multivariate analysis, ECOG PS (HR=0.45, 95% CI 0.22–0.94, p=0.035), bone metastasis (HR=0.38, 95% CI 0.19–0.78, p=0.008), and the De Ritis ratio (HR=0.47, 95% CI 0.23–0.96, p=0.037) remained independent prognostic risk factors of OS.

Conclusion: In this study, in patients with metastatic NSCLC receiving nivolumab as second-line treatment, poor ECOG performance status, bone metastasis, and a high De Ritis ratio were identified as independent prognostic factors associated with shorter overall survival OS. These factors may help in evaluating patients' prognosis in clinical practice.

Keywords: Lung cancer, nivolumab, prognostic factors, CAR, Deritis ratio

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INTRODUCTION

Lung cancer is an important cause of morbidity and mortality worldwide and is the second most common cancer in both men and women (1). According to the Surveillance, Epidemiology, and End Results (SEER), an estimated 238,340 new lung cancer cases will occur in the USA in 2023 and 127,070 people will die from this disease (2). Non-small cell lung cancer (NSCLC), which includes lung adenocarcinoma, squamous cell carcinoma, and large cell carcinoma, accounts for 80~85% of all primary lung cancer (3). In metastatic or inoperable patients, treatment is based on targeted agents or immune checkpoint inhibitors (ICIs) in combination with cytotoxic chemotherapy (4,5).

Nivolumab is a human recombinant monoclonal IgG4 antibody targeting programmed cell death protein-1 (PD-1), a key checkpoint molecule in T-cell regulation. Inhibition of PD-1 receptors on the surface of activated T cells by nivolumab increases T cell activation and proliferation, continuing T cell-mediated cytotoxic reactivity against cancer cells (6,7).

As second-line treatment, nivolumab monotherapy had better response rates and overall survival than docetaxel chemotherapy in patients with metastatic lung cancer with both squamous and non-squamous histology in randomized phase 3 clinical trials (8,9). Nivolumab efficacy was correlated with the tumor PD-1 level in patients with non-squamous lung cancer (8-10). Although some patients with lung cancer respond to ICI treatment, others develop resistance to treatment from the outset or via mechanisms acquired during treatment (11). Therefore, this study investigated the factors affecting progression-free (PFS) and overall (OS) survival in patients with metastatic NSCLC given nivolumab as second-line treatment after platinum-based therapy.

MATERIALS AND METHODS

Informed consent

The protocol for sample collection was approved by our Hospital Ethics Committee and was carried out according to the requirements of the Declaration of Helsinki.

Study population

This retrospective single-center study enrolled patients with de novo or recurrent metastatic NSCLC admitted to the Medical Oncology outpatient clinic between November 2021 and June 2023. All patients received platinum-based chemotherapy as first-line treatment, and all patients were started on nivolumab as second-line treatment. Patients were followed until disease progression or death while receiving nivolumab. The patients' demographic data at the time of diagnosis and characteristics related to cancer diagnosis (presence of metastasis, metastasis localization, palliative radiotherapy, chemotherapy regimen, and bisphosphonate use) were recorded.

Evaluated parameters

The patients' laboratory parameters just before nivolumab was started were recorded. The dates on which nivolumab was started, when progression under nivolumab occurred, and death or last follow-up were recorded. The C-reactive protein/albumin ratio (CAR), aspartate transaminase/alanine transaminase (De Ritis) ratio, Glasgow prognostic score (GPS), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), prognostic nutritional index (PNI), and systemic immune-inflammation index (SII) were calculated for each patient. Cytopenia ratios and immune-related side effects (pneumonitis, nephritis, thyroiditis, and hypophysitis) developing during nivolumab treatment were recorded.

The selection method of these patients and inclusion criteria were given as follows:

1. having de novo or recurrent metastatic disease,
2. being over 18,
3. agreeing to receive platinum-based therapy as first line treatment,
4. agreeing to receive nivolumab as part of the informed consent process,
5. having received nivolumab treatment for at least three months,
6. not having had surgery

On the other hand, the exclusion criteria of the study were determined as follows:

1. having a history of autoimmune disease,
2. having a history of active infection,
3. using an ICI other than nivolumab,
4. having been diagnosed with a second primary cancer,
5. lack of laboratory tests,
6. Lost to follow-up,
7. having high-grade anemia (Hemoglobin<8 g/dL), thrombocytopenia (Platelets<75,000x109 /L) or neutropenia (Neutrophils<1,000x109 /L),
8. having an Eastern Cooperative Oncology Group (ECOG) performance status of 3-4,
9. having any of epidermal growth factor receptor (EGFR) mutation, or anaplastic lymphoma kinase (ALK) or receptor tyrosine kinase 1 (ROS 1) rearrangement

In the end, a total of 84 non-small cell lung cancer patients, 76 males and 8 females, were included in the sample (Figure 1).

Statistical Analysis

Statistical analyses were performed using SPSS Statistics 27 (ver. 20.2.1.15749). Categorical variables are presented as

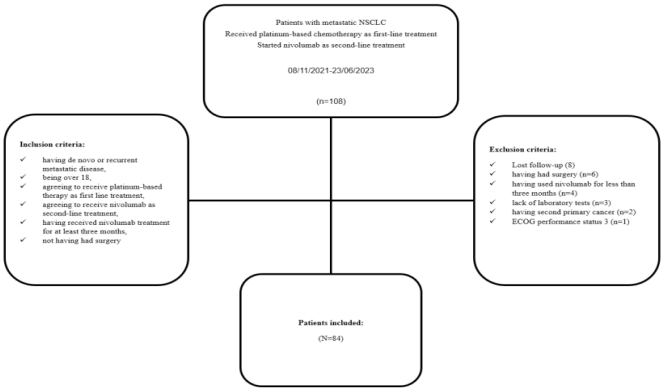

Figure 1. Patient selection flow diagram.

numbers and percentages and continuous measures as the mean and standard deviation. Median-based cutoff values for CAR, De Ritis ratio, GPS, NLR, PLR, PNI, SII, and other laboratory parameters were determined based on the median values and used to separate the 'low' and 'high' groups. Survival was analyzed using the Kaplan–Meier method and the log-rank test was used for group comparison. Univariate and multivariate analyses of factors affecting survival used Cox proportional hazards models. For multivariate analysis, the "Forward: LR" method was used. The hazard ratio (HR) was reported with the corresponding 95% confidence intervals (95% CI). The endpoint for PFS was defined as clinical or radiological disease progression after starting nivolumab, and the endpoint for OS was defined as death after starting nivolumab or the date of last follow-up. Statistical significance was accepted as $p < 0.05$.

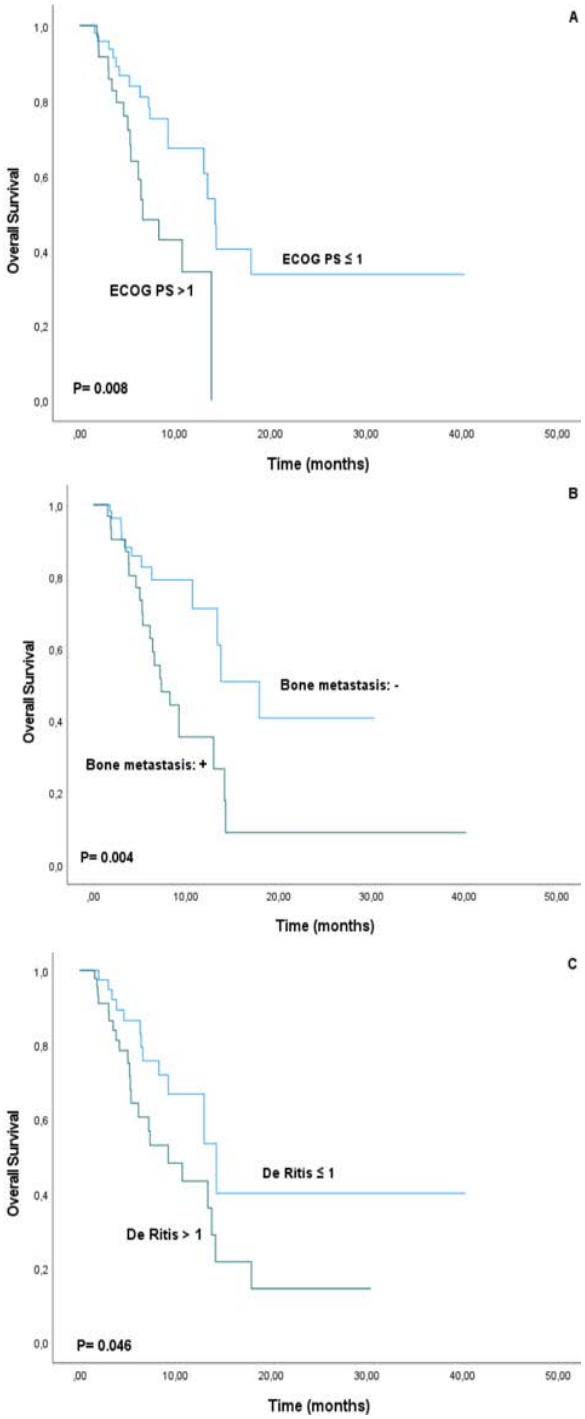

Figure 2. Kaplan Meier survival curves for Overall Survival according to ECOG PS (A), Bone metastasis (B) and De Ritis (C).

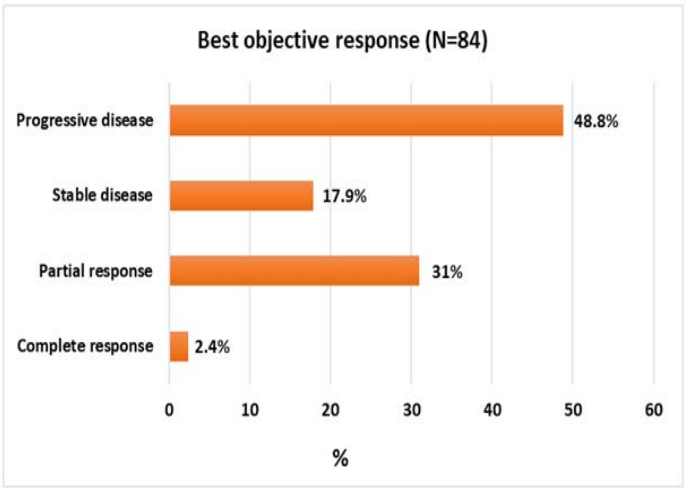

Figure 3. Best objective response.

RESULTS

Clinicopathological and laboratory parameters

The mean age of the 84 patients was 62.08 ± 8.43 years, and 90.5% of them were male. At the time of diagnosis, 57.1% of the patients had an Eastern cooperative oncology group performance status (ECOG PS) of 0 or 1. Programmed cell death ligand 1 (PD-L1) was positive in 58.3% of the patients and kirsten rat sarcoma viral oncogene (KRAS) was positive in 25%. In terms of cancer subtype, 64.3% of the patients were diagnosed with adenocarcinoma and 35.7% with squamous cell cancer. Of the patients, 30.9% had received palliative radiotherapy.

Using the median values, the optimum cutoff values were 5.73 for CAR, 1 for the De Ritis ratio, 1 for GPS, 3.74 for NLR, 223.5 for PLR, 46 for PNI, and 970.2 for SII. Table 1 gives details of the clinicopathological and laboratory parameters.

Risk Factors For Progression Free Survival

The median PFS of our patients was 6.4 months. In the univariate analysis risk assessments of the patients, age, gender, PD-L1, surgery history, metastasis status, brain metastasis, alcohol history, smoking history, BMI, bone metastasis, blood group, the De Ritis ratio, GPS, NLR, PLR, PNI, and SII were not associated with PFS. In the univariate risk analysis for PFS, ECOG PS (p=0.050), and CAR (p=0.046) were identified as

Table 1. Clinicopathological and laboratory parameters of the patients.

Clinical parameters	**N=84**	**%**
Age (years)	62.08*	8.43**
Gender (male)	76	90.5
Weight (kg)	71.60*	13.35**
Height (cm)	167.74*	18.14**
BMI (kg/m^2)	24.86*	3.96**
ECOG PS (≥2)	36	42.9
Smoker (yes)	55	65.5
Alcohol (yes)	16	19
PD-L1 (positive)	49	58.3
BRAF (positive)	0	0
KRAS (positive)	12	25
Cancer Subtypes (adenocarcinoma/squamous cell ca)	54/30	64.3/35.7
Metastasis site (CL lung/brain/liver/adrenal/bone/ENLM)	12/12/9/19/36/16	14.3/14.3/10.7/22.6/42.8/19
Blood group (0/A/B/AB//Rh+/Rh-)	32/30/13/9//75/9	38/35.7/15.5/10.7//89.3/10.7
First-line chemotherapy (yes)	84	100
Palliative radiotherapy (yes)	26	30.95
Bisphosphonate use (yes)	34	40.5
Laboratory Parameters	**Mean**	**SD**
Bun (mg/dl)	38.11	15.26
Kreatinin (mg/dl)	1.11	3.08
Sodium (MeQ/L)	138.71	2.77
Potassium (MeQ/L)	4.54	0.58
CRP (mg/dL)	34.05	38.53
Glucose (mg/dL)	115.62	44.06
Lactate dehydrogenase (U/L)	229.05	112.25
AST (IU/L)	17.74	10.21
ALT (IU/L)	21.85	26.12
Total bilirubin (mg/dL)	0.41	0.25
Total protein (g/dL)	68.06	11.95
Albumin (g/dL)	38.98	5.59
Hemoglobin (g/dL)	12.14	2.01
Platelets (109 /L)	309.23	108.55
Leukocyte (109 /L)	8.17	4.54
Neutrophil (109 /L)	5.42	3.61
Lymphocyte (109 /L)	1.43	0.87
Monocytes (109 /L)	0.7	0.41
Basophil (109 /L)	0.04	0.02
Eosinophils (109 /L)	0.13	0.13
Laboratory Indexes	**Median**	**Min-Max**
CAR	5.73	0.20-59.33
De-ritis	1.00	0.31-3.17
GPS	1.00	0.00-2.00
NLR	3.74	0.19-235.50
PLR	223.50	58.00-11250.00
PNI	46.00	23.00-66.00
SII	970.20	34.98-59223.08

*Mean** SD, Standard deviation. ALT, Alanine aminotransferase; AST, Aspartic transaminase; BRAF, V-raf murine sarcoma viral oncogene homolog B; BUN, Blood urea nitrogen; BMI, Body mass index; CAR, C-reactive protein/albumin ratio; CL, Contralateral; CRP, C-reactive protein; De Ritis, Aspartate transaminase/alanine transaminase ratio; ECOG PS, Eastern cooperative oncology group performance status; ENLM, Extranodal lymph node; GPS, Glasgow prognostic score; K, Potassium; KRAS, kirsten rat sarcoma viral oncogene; LDH, Lactate dehydrogenase; Na, Sodium; NLR, Neutrophil to lymphocyte ratio; PD-L1, Programmed cell death ligand 1; PLR, Platelet - lymphocyte ratio; PNI, Prognostic nutritional index; SD, standard deviation; SII, Systemic immune-inflammation index.

prognostic risk factors for PFS. However, the multivariate analysis did not support the univariate analysis finding that these two parameters were prognostic risk factors for PFS. Factors affecting PFS are shown in Table 2.

Risk Factors for Overall Survival

The median OS of our patients was 13 months. In the univariate risk assessment of the patients, age, gender, PD-L1, surgery history, metastasis status, brain metastasis, alcohol history, smoking history, BMI, blood group, GPS, NLR, PLR, PNI, and SII were not associated with OS. However, ECOG PS ($p = 0.010$), bone metastasis ($p = 0.047$), CAR ($p = 0.019$), and the De Ritis ratio ($p = 0.050$) were identified as prognostic risk factors of OS. In the multivariate analysis, ECOG performance status >1 (14.1 and 6.6 months, HR = 0.45, 95% CI 0.22–0.94, $p = 0.035$), the presence of bone metastases (17.9 and 7.3 months, HR = 0.38, 95% CI 0.19–0.78, $p = 0.008$), and the De Ritis ratio > 1

Table 2. Univariate and multivariate analysis of characteristic parameters and laboratory indices related to progression free survival.

PFS		Univariate Analysis		Multivariate Analysis	
Characteristics	**Category**	**HR(95% CI)**	**P**	**HR(95% CI)**	**P**
Age	<65 vs ≥65	0.95(0.54-1.67)	0.863		
Sex	Female vs male	1.04(0.47-2.30)	0.928		
ECOG PS	≤1 vs >1	1.74(1.00-3.02)	0.050	1.68(0.96-2.91)	0.067
Sub type	SCC vs AC	1.12(0.65-1.9)	0.686		
PD-L1	Negative vs positive	0.88(0.47-1.62)	0.654		
Surgery history	Negative vs positive	0.98(0.54-1.84)	0.992		
Metastasis status	Denovo vs recurrence	0.92(0.53-1.60)	0.756		
Brain metastasis	Negative vs positive	1.07(0.50-2.23)	0.867		
Alcohol history	Yes vs /no	0.64(0.31-1.30)	0.215		
Smoking history	Yes vs no	1.01(0.99-1.00)	0.898		
BMI	<25 vs ≥25	0.63(0.37-1.06)	0.083		
Bone metastasis	Negative vs positive	1.16(0.69-1.97)	0.574		
Blood group	O/A/B/AB	0.99(0.0.76-1.30)	0.950		
	RH- vs RH+	0.64(0.28-1.46)	0.290		
CAR	≤5.73 vs >5.73	0.58(0.34-0.99)	0.046	1.57(0.93-2.66)	0.093
De-ritis	≤1 vs >1	0.66(0.39-1.12)	0.124		
GPS	≤1 vs >1	1.04(0.60-1.80)	0.895		
NLR	≤3.74 vs >3.74	1.02(0.60-1.72)	0.946		
PLR	≤223.5 vs >223.5	1.09(0.65-1.84)	0.747		
PNI	≤46 vs >46	0.97(0.58-1.62)	0.895		
SII	≤970.2 vs >970.2	1.03(0.61-1.73)	0.926		

AC, Adenocarcinoma; BMI, Body mass index; CAR, C-reactive protein/albumin ratio; CI, Confidence interval; De Ritis, Aspartate transaminase/alanine transaminase ratio; ECOG PS, Eastern cooperative oncology group performance status; GPS, Glasgow prognostic score; HR, Hzard ratio; NLR, Neutrophil to lymphocyte ratio; PFS, progression free survival; PLR, Platelet - lymphocyte ratio; PNI, Prognostic nutritional index; SII, Systemic immune-inflammation index; SCC,Squamous cell carcinoma.

Table 3. Univariate and multivariate analysis of characteristic parameters and laboratory indices related to overall survival.

OS		Univariate Analysis		Multivariate Analysis	
Characteristics	**Category**	**HR(95% CI)**	**P**	**HR(95% CI)**	**P**
Age	<65 vs ≥65	1.08(0.52-2.23)	0.840		
Sex	Female vs male	1.04(0.37-2.96)	0.943		
ECOG PS	≤1 vs >1	2.62(1.26-5.44)	0.010	0.45(0.22-0.94)	0.035
Sub type	SCC vs AC	1.13(0.54-2.4)	0.744		
PD-L1	Negative vs positive	1.09(0.54-2.20)	0.803		
Surgery history	Negative vs positive	1.05(0.36-3.10)	0.925		
Metastasis status	Denovo vs recurrence	0.88(0.25-3.12)	0.841		
Brain metastasis	Negative vs positive	1.10(0.42-2.88)	0.849		
Alcohol history	Yes vs /no	0.55(0.20-1.50)	0.242		
Smoking history	Yes vs no	1.32(0.54-3.20)	0.540		
BMI	<25 vs ≥25	0.46(0.21-1.00)	0.051		
Bone metastasis	Negative vs positive	2.95(1.02-8.58)	0.047	0.38(0.19-0.78)	0.008
Blood group	O/A/B/AB	1.06(0.75-1.50)	0.732		
	RH- vs RH+	0.64(0.28-1.46)	0.290		
CAR	≤5.73 vs >5.73	0.43(0.21-0.87)	0.019	1.58(0.72-3.47)	0.253
De-ritis	≤1 vs >1	2.02(0.99-4.11)	0.050	0.47(0.23-0.96)	0.037
GPS	≤1 vs >1	1.65(0.75-3.64)	0.217		
NLR	≤3.74 vs >3.74	0.85(0.43-1.68)	0.644		
PLR	≤223.5 vs >223.5	1.09(0.55-2.15)	0.806		
PNI	≤46 vs >46	0.95(0.48-1.88)	0.890		
SII	≤970.2 vs >970.2	1.07(0.54-2.10)	0.846		

AC, Adenocarcinoma; BMI, Body mass index; CAR, C-reactive protein/albumin ratio; CI, Confidence interval; De Ritis, Aspartate transaminase/alanine transaminase ratio; ECOG PS, Eastern cooperative oncology group performance status; GPS, Glasgow prognostic score; HR, Hzard ratio; NLR, Neutrophil to lymphocyte ratio; PFS, progression free survival; PLR, Platelet - lymphocyte ratio; PNI, Prognostic nutritional index; SII, Systemic immune-inflammation index; SCC,Squamous cell carcinoma.

Table 4. Adverse event associated with nivolumab.

Events	N	%
Anemia	37	44.0
Thrombocytopenia	7	8.3
Thyroiditis	4	4.7
Neutropenia	3	3.5
Pneumonitis	2	2.3
Nephritis	1	1.2
Hypophysitis	1	1.2
Febrile neutropenia	0	0

(14.2 and 9.2 months, HR = 0.47, 95% CI 0.23-0.96, p = 0.037) were identified as risk factors for shorter OS (Figure 2). Table 3 shows the factors affecting OS.

Best Objective Response Rate

In our patients, 2.4% had a complete response, 31% had a partial response, 17.9% had stable disease, and 48.8% had progressive disease (Figure 3).

Adverse Events

During nivolumab treatment, 44.0% of the patients had anemia, 8.3% had thrombocytopenia, 4.7% had thyroiditis, 3.5% had neutropenia, 2.3% had pneumonitis, 1.2% had nephritis, and 1.2% had hypophysitis. Table 4 gives details of side effects.

DISCUSSION

This study examined the relationship between prognostic factors and survival in patients with NSCLC receiving nivolumab as second-line therapy. Studies of the use of nivolumab as second-line treatment in patients diagnosed with NSCLC have generally focused on patients with ECOG PS ≤ 1 (8,9). A study evaluating the treatment effectiveness of nivolumab, including patients with ECOG PS > 1, found that patients with an ECOG PS > 1 had a similar OS advantage to patients with ECOG PS ≤ 1 (12). However, meta-analyses and studies have shown that patients with ECOG PS ≤ 1 have better PFS and OS than patients with ECOG PS > 1 (13,14). We observed that patients with ECOG PS ≤ 1 had better PFS and OS than patients with ECOG PS > 1.

The presence of bone metastases in patients diagnosed with NSCLC is not only a poor prognostic factor but is also associated with a lower ICI treatment response (15,16). Similarly, in our patients, the presence of bone metastases was associated with a shorter OS.

Many recent studies have addressed the prognostic significance of different inflammatory markers in different types of cancer, such as GPS, NLR, PLR, PNI, SII, CAR, and the De Ritis ratio (17-20). In patients with NSCLC, a high CAR was found to be associated with earlier recurrence, worse local control, and shorter PFS and OS (21-26). In our cohort, a higher CAR was also associated with a shorter PFS and OS in univariate analyses, but not in the multivariate analysis.

A high De Ritis ratio has prognostic importance for many tumors, especially colon, pancreas, and renal cell cancers. Although the De Ritis ratio has been studied in colon, pancreatic, and renal cancers, its role in NSCLC remains underexplored (20,27,28). In our patients, a high De Ritis ratio was associated with a shorter OS.

The limitations of our study are that it was single-center, retrospective, and enrolled a small number of patients. ICI-related side effects may develop up to 12 months after discontinuing ICI treatment and therefore some side effects may not have been evaluated. Its strengths are that it is the first study to evaluate the prognostic value of the De Ritis ratio in patients with NSCLC using ICI.

CONCLUSION

In our study, a poor ECOG PS, the presence of bone metastases, and a De Ritis ratio > 1 were found to be prognostic risk factors for poor survival in patients with NSCLC using ICI. These risk factors, especially the De Ritis ratio, need to be evaluated in more comprehensive, prospective, and randomized controlled studies.

Ethical Statement

This study was conducted in accordance with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee (KAEK/2023.12.652). Written informed consent was obtained from all patients before the conduct of the study.

Author Contribution

TK and NB conducted the literature review and designed the study. GUE wrote the first draft of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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