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Prognostic Value of a New Marker, IBI Score and NLR Change in Non-Small Cell Lung Cancer Patients Receiving Immune Checkpoint Inhibitors (Prognostic value of IBI score and NLR change in NSCLC)

İmmün Kontrol Noktası İnhibitörleri Alan Küçük Hücreli Dışı Akciğer Kanseri Hastalarında Yeni Bir Belirtecin, IBI Skorunun ve NLR Değişiminin Prognostik Değeri (IBI skor ve NLR değişiminin NSCLC'de prognostik değeri)

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Öz

Bu çalışma, IBI skoru (inflamatuar ben chmark index) ve tedavi sırasındaki NLR (nötrofil lenfosit oranı) değişiminin nonsmall cell lung cancer (NSCLC) hastalarında genel sağkalım (OS) ve progresyonsuz sağkalım (PFS) için prognostik değerini araştırmayı amaçlamaktadır. Driver mutasyonu olmayan ve tedavi basamaklarında immün kontrol noktası inhibitörü (ICI) uygulanan 155 NSCLC tanılı hasta çalışmaya alındı. ICI tedavi başlangıcında ve tedavinin üçüncü ayında değerlendirilen laboratuvar ve klinik parametreler retrospektif olarak kaydedildi. CRP, nötrofil, lenfosit ve trombosit değeri kullanılarak; IBI skor, NLR oranı ve NLR change değerlerinin prognostik değeri analiz edildi. Ortalama takip süresi 26.07 aydı. Hastaların kemoterapi ve ICI alma durumları kaydedildi. İmmünoterapiyi kaçıncı basamakta alırsa alsın, ICI sonrası hastaların 34.8%'inde (54 hasta) progresyon görülmedi. 101 hasta (65.2%) ise ICI sonrası progrese oldu. NLR≥10.25 (p<0.001) ve NLR Change≥3.60 (p<0.001) olduğunda mortalitedeki artış anlamlı bulundu. Yaş (p=0.021), ECOG performans (p=0.043), tanıdaki evre (p=0.013), NLR change (p<0.001) ve NLR (p<0.001) ile mOS arasındaki ilişki anlamlı bulundu. Yaş (p=0.013), tanıdaki evre (p=0.004), IBI skor (p=0.027), NLR change (p=0.001) ve NLR (p=0.002) PFS için prognostik olduğu bulundu. Tüm bu sonuçlar 'IBI skor ve NLR change''in NSCLC hastalarında ICI tedavi yanıtı için prognostik belirteç olarak kullanılabileceğini düşündürmektedir.

Anahtar Kelimeler: IBI Skor, NLR Değişimi, NSCLC

Abstract

This study aims to investigate the prognostic value of IBI score (inflammatory benchmark index) and NLR (neutrophil lymphocyte ratio) change during treatment for overall survival (OS) and progression-free survival (PFS) in nonsmall cell lung cancer (NSCLC) patients. A total of 155 NSCLC patients without driver mutations who were treated with immune checkpoint inhibitor (ICI) were included in the study. Laboratory and clinical parameters evaluated at the beginning and third month of ICI treatment were retrospectively recorded. The prognostic value of IBI score, NLR ratio and NLR change values were analysed using CRP, neutrophil, lymphocyte and platelet values. The median follow-up period was 26 months. Chemotherapy and ICI status of the patients were recorded. Regardless of the stage of immunotherapy, 34.8% of the patients (54 patients) did not progress after ICI. 101 patients (65.2%) progressed after ICI. The increase in mortality was significant when NLR≥10.25 (p<0.001) and NLR Change≥3.60 (p<0.001). Age (p=0.021), ECOG performance (p=0.043), stage at diagnosis (p=0.013), NLR change (p<0.001) and NLR (p<0.001) were significantly associated with mOS. Age (p=0.013), stage at diagnosis (p=0.004), IBI score (p=0.027), NLR change (p=0.001) and NLR (p=0.002) were prognostic for PFS. All these results suggest that 'IBI score and NLR change' can be used as prognostic markers for ICI treatment response in NSCLC patients.

Keywords: IBI Score, NLR Change, NSCLC

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Introduction

The foundations of oncology and immunology were laid with William Coley's clinical study with ten cases and the response obtained by stimulating the immune system by repeated injection of bacteria obtained from erysipelas into the masses (1). It has been reported that 1.8 million people worldwide lost their lives due to lung cancer in 2020. Lung cancer is the most common cause of cancer-related deaths regardless of gender. Since lung cancer is a heterogeneous disease group, the reflection of therapeutic and diagnostic algorithms on treatment practice and obtaining effective treatment in each

patient group takes a long time. In the literature, the process started with chemotherapy and continued with the elucidation of driver mutations in the heterogeneous molecular substructure of lung cancer and treatments for these mutations (2). In today's practice, the number of clinical studies showing a significant increase in overall survival (OS) in nonsmall cell lung cancer (NSCLC) patients with the inclusion of immune checkpoint inhibitors (ICI) in treatment is increasing day by day (3-6). One of these clinical trials included 21 randomised controlled trials and concluded that ICI alone significantly improved progression-free-survival (PFS) in the treatment of 9826 NSCLC patients (7). Immunotherapy is a treatment that enables the cancer cell to be destroyed by the patient's own immune system by inhibiting the inhibition points of the immune system. It is not clearly defined in which patient group immune checkpoint inhibitors are more effective. Clinical research is also a matter of curiosity. There is no defined prognostic marker other than PDL 1. It is thought that prognostic markers that can be calculated with laboratory and clinical parameters will guide the clinician for treatment selection and treatment follow-up. Inflammatory response is important in the life cycle and pathogenesis of cancer cells. Different inflammatory markers have been defined based on the clinical reflection of this. The study aims to investigate the prognostic significance of IBI score (inflammatory marker index) and NLR change during treatment for OS and PFS in NSCLC patients. To our knowledge, IBI score and NLR change during treatment have not been evaluated for their ability to predict the prognosis of NSCLC patients receiving ICI.

Material and Method

Patient characteristics and data collection

This study evaluated the efficacy of ICI treatments in single-centre NSCLC patients without driver mutations and which markers may be prognostic for OS and PFS. Between June 2010 and December 2023, 155 NSCLC patients admitted to the medical oncology clinic were included with regular follow-up and complete data. Inclusion criteria were; all patients over 18 years of age with NSCLC, without driver mutations, and receiving an ICI at any stage of treatment. Exclusion criteria were; patients younger than 18 years, patients with a second primary malignancy, patients with missing data and patients with driver mutations. Clinical and demographic characteristics of the patients were retrospectively recorded from the patient file and hospital laboratory system. Age at diagnosis, gender, stage, systemic treatment, treatment responses, progression and survival data were recorded.

Purposes of use and calculation of prognostic markers

All these scores were calculated by recording the hematological and biochemical values of the patients routinely examined and placing them into formulas. As a result of this analysis, we evaluated which inflammatory markers could be prognostic for OS and PFS. PFS was defined as the time from the date of diagnosis to the first progression of the disease. OS was defined as the time from the date of diagnosis to the time of death or last follow-up.

IBI score: This score showing inflammatory response is based on CRP and neutrophil-to-lymphocyte ratio. It was calculated by the formula 'CRP×(neutrophil/lymphocyte) (8).

Neutrophil-lymphocyte ratio: This marker, which predicts inflammatory response, is calculated by dividing the number of neutrophils by the number of lymphocytes with the formula 'neutrophil÷lymphocyte'. It has been defined as a prognostic marker in different solid tumours in the literature (9).

Neutrophil-to-lymphocyte ratio change (NLR change): The change in the NLR ratio recorded at the time of diagnosis and the NLR ratio repeated at each visit predicts the treatment response. Increasing NLR change favours progressive disease. It is calculated with the formula 'NLR last-NLR diagnosis' (9, 10). Roc curve analysis was then performed for the cut-off value of the prognostic markers. The prognostic value of results below and above this value for two-year and five-year OS and PFS rates were analysed.

43 pack-years of smoking history; the cutoff value in the study evaluating the prognostic power of EPSILON score in NSCLC patients in the literature was taken (11).

Cachexia; was defined as ≥5% weight loss or ≥2% weight loss in the last 6 months and BMI<20 (12).

Statistical analysis

Statistical analyses were carried out with the use of 'IBM SPSS Statistics for Windows. Version 25.0 (Statistical Packing for the Social Sciences, IBM Corp., Armonk, NY, USA). Descriptive statistics are expressed as n and % for categorical variables and median for continuous variables. Prognostic cut-off values for survival of various laboratory parameters were determined using ROC curve analysis. Positive likelihood ratio was used. Chi-Square test was mainly applied to measure the significance of the difference between observed and expected frequencies in categorical data. Kaplan-Meier method was used for comparison of OS and PFS duration between different clinical parameter groups. $p<0.05$ was considered to be statistically significant.

Results

Clinical and demographic data of the patients included in the study are presented in Table 1.

Table 1. Clinical and demographic characteristics of NSCLC patients receiving ICI

Variables	Total n:155
Age, median	63
Gender, n(%)	
Male	141 (91%)
Female	14 (9%)
Smoking history, n (%)	
None	17 (11%)
<43 packs/year	54 (34.8%)
≥43 packs/year	84 (54.2%)
ECOG, n (%)	103 (66.5%)
0	49 (31.6%)
1	3 (1.9%)
2	
Progression after immunotherapy,n(%)	54 (34.8%)
None	101 (65.2%)
+	
Mortality, n(%)	
Live	72 (46.5%)
Deceased	83 (53.5%)
Follow-up time,month median	26

The median age was 63 years and 141 of the patients were male (91%). The median follow-up period was 26 months. The treatments, chemotherapy and ICI received by the patients in the treatment steps were recorded. Regardless of the stage of immunotherapy, 34.8% of the patients (54 patients) did not progress after ICI (Table1). The power to predict increased mortality was statistically significant when NLR≥10.25 ($p<0.001$) and NLR Change≥3.60 ($p<0.001$) (Table2).

Table 2. Prognostic power of NLR and NLR change in predicting mortality

Variables	AUC	95%CI	Cut-off	Sensitivity (%)	Spesificity (%)	*p*
NLR	0.741	0.646-0.835	≥10.25	68.3	68.1	**<0.001**
NLR change	0.802	0.713-0.890	≥3.60	73.0	72.3	**<0.001**

The power of prognostic markers to predict two and five year OS and PFS in NSCLC patients receiving ICI was evaluated. In the whole patient group, median OS (mOS):31 months (min-max:21.9-40.1); median PFS (mPFS):23months (min-max:18.19-27.80) was the median time to first progression after ICI. Statistically significant correlations were found between age (p= .021), ECOG performance (p=0.043), stage at diagnosis (p=0.013), NLR change ($p<0.001$) and NLR ($p<0.001$) and mOS (Figure1 and Table 3).

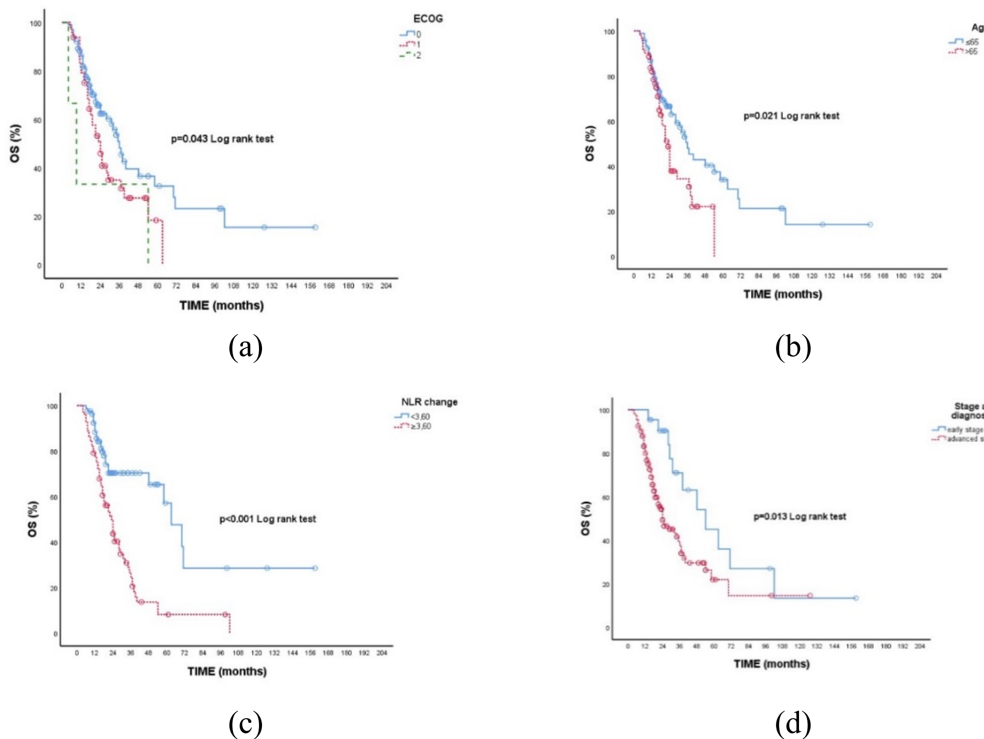

Figure 1. Kaplan-Meier estimate of overall survival; ECOG performance (a), age (b), NLR change (c), stage at diagnosis (d).

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Table 3. Prognostic markers and two year and five year OS in NSCLC patients receiving ICIs Predictive effect on PFS

OS (months)	**2 years %**	**5 years %**	**median (95%CI)**	***p***
General	60.0	26.4	31.0 (21.9-40.1)	
Age				
≤65	86.0	34.1	36.0 (27.69-44.30)	0.021
>65	48.7	-	23.0 (19.52-26.47)	
Gender				
Male	57.3	26.2	32.0 (22.96-41.03)	0.470
Female	44.9	22.4	24.0 (14.62-33.37)	
Smoking history				
None	34.9	-	18.0 (11.14-24.85)	0.102
<43packs/year	58.8	34.2	34.0 (22.58-45.42)	
≥43packs/year	63.9	27.9	29.0 (18.95-39.05)	
BMI				
Normal	56.6	27.2	32.0 (22.42-41.58)	0.05
Cachexia	40.0	-	15.0 (6.41-23.58)	
ECOG				
0	62.4	32.5	36.0 (30.10-41.89)	0.043
1	46.0	18.4	24.0 (18.81-29.18)	
TM type				
Squamous carcinoma	57.7	23.3	28.0 (18.41-37.58)	0.888
Nonsquamous carcinoma	62.3	29.7	31.0 (18.51-43.48)	
Stage at diagnosis				
Early stage	90.4	45.1	54.0 (28.74-79.25)	0.013
Advanced stage	54.4	22.0	31.0 (16.11-31.89)	
PDL				
0	55.8	24.1	24.0 (17.01-30.98)	0.173
1-49	50.1	23.0	25.0 (17.49-32.50)	
≥50	69.2	28.9	38.0 (31.01-44.98)	
IBI skor				
<10	49.1	27.8	24.0 (14.81-33.18)	0.135
≥10	66.7	26.1	37.0 (32.47-41.52)	
NLR Change				
<3.60	70.4	57.2	63.0 (48.20-77.79)	<0.001
≥3.60	50.0	8.3	23.0 (18.27-27.73)	
PFS (months)	2 years %	5 years %	median (%95 CI)	p
General	47.9	20.1	23.0 (18.19-27.80)	
Age				
≤65	59.1	25.8	28.0 (21.41-34.58)	0.013
>65	35.2	-	17.0 (13.63-20.36)	
Gender				
Male	48.6	21.4	24.0 (18.45-29.54)	0.383
Female	41.7	10.4	17.0 (6.84-27.15)	
Smoking history				
None	29.4	-	14.0 (8.95-19.04)	0.232
<43packs/year	50.3	26.7	27.0 (15.02-38.98)	
≥43packs/year	53.7	17.0	25.0 (21.63-28.36)	
BMI				
Normal	50.1	20.7	24.0 (17.84-30.15)	0.162
Cachexia	40.0	-	11.0 (8.85-13.14)	
ECOG				
0	52.4	26.4	28.0 (17.32-38.67)	0.296
1	40.5	11.6	21.0 (16.34-25.65)	
TM type				
Squamous carcinoma	46.0	15.1	21.0 (15.85-26.14)	0.735
Nonsquamous carcinoma	49.6	24.9	24.0 (13.55-34.45)	
Stage at diagnosis				
Early stage	85.9	38.9	44.0 (18.39-69.60)	0.004
Advanced stage	43.4	16.7	19.0 (14.55-23.44)	
PDL				
0	38.8	16.4	17.0 (10.33-23.66)	0.067
1-49	44.5	12.1	19.0 (11.14-26.85)	
≥50	56.0	24.6	30.0 (18.21-41.79)	
IBI skor				
<10	39.7	15.0	18.0 (14.13-21.86)	0.027
≥10	56.3	24.7	26.0 (16.48-35.51)	
NLR Change				
<3.60	55.6	39.9	44.0 (13.95-74.04)	0.001
≥3.60	43.8	6.8	21.0 (14.25-27.74)	

BMI:body mass index, IBI score:inflammatory marker index, NLR:neutrophil lymphocyte ratio, NLR-change:last NLR-NLR value at diagnosis, p<0.05 was considered statistically significant.

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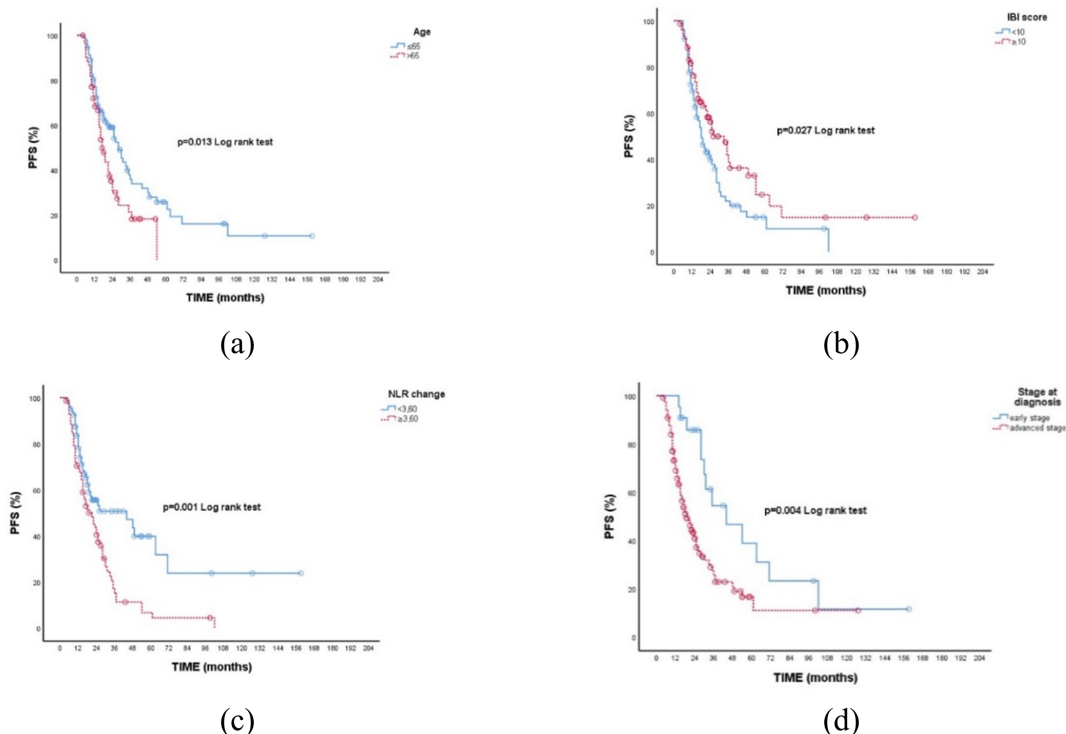

Figure 2. Kaplan-Meier estimate of progression free survival; age(a), IBI score(b), NLR change(c), stage at diagnosis (d).

There were statistically significant associations between mPFS and age (p=0.013), stage at diagnosis (p=0.004), IBI score (p=0.027), NLR change (p=0.001) and NLR (p=0.002) groups (Table 3 and Figure 2). In patients aged <65years, OS was 86% at 2 years and 34.1% at 5 years (p=0.021). In patients aged >65 years, OS was 48.7% at 2 years and 0.7% at 5 years (p=0.021). For patients with ECOG PS '0', two-year and five-year OS rates were 62.4% and 32.5%, respectively. For patients with ECOG PS '1', two-year and five-year OS rates were 46% and 18.4%, respectively (p=0.043). For patients with early-stage disease at diagnosis, two-year and five-year OS rates were 90.4% and 45.1%, respectively; for patients with advanced-stage disease, two-year and five-year OS rates were 54.4% and 22% (p=0.013) (Table 3).

Two and five year OS rate in patients with NLR change <3.6 was 70.4% and 57.2%, respectively, while two and five year OS rate in patients with "≥3.6" was 50% and 8.3%, respectively (p<0.001). Patients with IBI score≥10 had two and five year OS rates of 66.7% and 26.1%, respectively; patients with '<10' had two and five year OS rates of 49.1% and 27.8%, respectively (p=0.135). An IBI score of ≥10 was associated with an increased survival rate. This result was numerically significant. However, it was not statistically significant. Patients younger than 65 years (p=0.013), early stage at diagnosis (p=0.004), IBI score ≥10 (p=0.027), last NLR ≥10.2 (p=0.002) and change in NLR ≥3.6 (p=0.001) had a higher two and five year PFS (Table 3).

Discussion

The aim of this study was to investigate the prognostic significance of IBI score and NLR change during ICI treatment in NSCLC patients. We investigated whether it is a marker suitable for practical use in predicting survival together with prognostic indicators defined in current practice. The markers that we considered to be prognostic for two- and five-year survival in NSCLC patients receiving ICI were calculated using the retrospectively recorded laboratory data of the patients. Age at diagnosis, ECOG performance status, stage, NLR change and NLR were significantly associated with survival. Age, stage at diagnosis, IBI score, NLR change and NLR were significantly associated with progression-free survival (Table 3). This study suggests that a patient's age under 65 years, ECOG PS '0' and early stage at diagnosis may predict a higher two and five year survival. Patients who did not meet these parameters had a worse prognosis.

Patients with low NLR change had higher 2- and 5-year OS rates. Although 2 and 5-year OS rates were higher in patients with high IBI score, there was no statistical significance, respectively. High IBI score was associated with increased survival. Although this result was numerically significant, it was not statistically significant. It was found that progression was less common on high IBI score.

The hypothesis of our study is based on the inflammation in the tumour microenvironment and the response of the immune system to cancer cells. The effect of inflammation and nutritional status on

the prognosis of patients with many types of cancer has been reported. It has been shown that there is a bidirectional link between cancer and inflammation in the early stage of cancer. The inflammatory reaction induced by cancer causes cancer growth, progression and suppression of the immune system. Thus, both an escape from the immune system and an uncontrollable inflammatory response occur. This process, which continues one after the other, determines the continuity and prognosis of the cancer cell in the life cycle (13-15).

In a clinical study including 701 HCC patients who underwent HCC resection, the prognostic value of IINS and IBI was analysed. The cut-off value of IBI score was found to be 7.2 by X-tile analysis. The prognosis of patients above this value was worse ($p<0.001$). As a result, the use of IBI as a prognostic marker after hepatectomy in HCC patients was recommended (8).

It was concluded that when the variables that make up the IBI score are evaluated in combination, it allows us to predict postoperative treatment efficacy and prognosis. This result showed that the IBI score is a prognostic marker that can be used when evaluating treatment response in other treatment alternatives. Neutrophil increase in immune system response and peritumoural immunosuppressive environment due to lymphopenia are indicators of poor prognosis. CRP increase is prognostic for peritumoural inflammation and immune response to the tumour as well as infection. Although CRP increase alone is poor prognostic, the combined evaluation of this parameter with different variables increases its prognostic power. For this reason, IBI score is a feasible and easily accessible marker that can be used prognostically.

Virchow et al. first described the relationship between cancer and inflammation in 1863. It was observed that cell proliferation increased with inflammation and based on this, it was concluded that cancer originated in areas of chronic inflammation (15). Later clinical studies showed that cell proliferation is not the only cause of cancer. Growth factors, inflammatory cells, DNA damage and peritumoural stroma were found to increase neoplastic risk and consequently tumour tissue behaves like a chronic non-healing wound. The cellular response of the immune system during the healing process is blamed for tumour proliferation, invasion and metastasis (16). We think that the change in IBI score and NLR level during treatment can be used in the evaluation of the peritumoural cellular response with prognostic markers that enable us to predict the immunotherapy response. Treatment efficacy occurs with the reorganisation of peritumoural immunosuppression caused by inflammation with ICI treatment and activation of the individual's own immune system. The decrease in NLR level indicates the change in tumour microenvironment and treatment response. Repeated calculations and changes in the NLR ratio during treatment follow-up were found to be more prognostic than a single measurement. It is thought that this result will contribute to clinical practice.

When CRP, neutrophil, lymphocyte, which are the variables that make up the IBI score and NLR ratio, are evaluated individually, there will be clinical and laboratory reflections. CRP is a noninvasive marker synthesised in response to acute infection produced in the liver. Increased CRP activates complement and causes a more severe inflammatory response. In this case, peritumoural immunosuppression also increases. Increased CRP is a harbinger of poor prognosis. Lymphocytes are important defence cells in the immune system against tumour cell proliferation. Therefore, peritumoural lymphocyte increase is associated with a good prognosis. Neutrophils also exhibit anti-tumour properties by providing the collection of immunosuppressed macrophages and Treg cells from the tumour microenvironment (17-19). As a result of all these effects, it is thought that 'IBI score and NLR change' will contribute to the oncology practice since different antitumour mechanisms can be evaluated with a single prognostic marker.

In a clinical trial of patients with stage IIIC or stage 4 epithelial ovarian cancer, there was no statistical significance in the use of NLR, PLR and CA-125 to predict suboptimal resection. A decrease of more than 70% in NLR levels predicts optimal resection. (9). These markers should be used at each patient visit, not at a single time point, as this was thought to be more meaningful. A review of the literature suggests that an increase in NLR can predict whether surgery is appropriate for advanced ovarian cancer.

The clinical study that found that PD-L1 expression, which we often use in clinical practice, was not prognostic suggested that different markers should be used together rather than a single marker. Smoker history, ECOG performance status and NLR have been associated with survival in NSCLC patients who received ICI (20). This has been attributed to the fact that the NLR is an indicator of chronic inflammation (21). Markers that have been created by combining different markers in patients with NSCLC who are receiving ICI therapy have been described in the literature. Modified Lung Immune Prognostic Index (mLIPI), Lung Immune Prognostic Index (LIPI), Advanced Lung Cancer Inflammation Index (ALI), Scottish Inflammatory Prognostic Score (SIPS), Prognostic Nutrition Index (PNI), EPSILoN and SII have been investigated (22).

Increased NLR levels during ICI treatment have been shown to be associated with worse survival in several studies examining dynamic changes in prognostic markers (23-25). In another study suggesting that dynamic changes in NLR and PLR

are more valuable than a single measurement, decreased NLR and PLR were associated with prolonged mPFS (26). In particular, tracking the change in NLR has shown a better AUC in predicting both OS and response to treatment (27, 28). Monitoring IBIscore, NLR and change in NLR prior to treatment with ICIs in NSCLC patients may be a promising indicator for monitoring response to immunotherapy. A clinical trial found that the NLR ratio was the strongest prognostic marker in gastric cancer patients receiving neoadjuvant chemotherapy. NLR ratio values were recorded at follow-up. They were grouped into continuous descending (CDG), stable (SG) and ascending descending (ADG) groups. SG survived longer than ADG and CDG (mOS:69 months vs 41 and 30 months) (p=0.0018) (29). It is thought that the calculation of prognostic markers at each control of the patient, as in this study, will enable reflex decision making on the treatment of the patient, early recognition of progression and ICI treatment response.

This study had limitations that may affect the results of this study; the small number of patients, the analysis of single centre data and the retrospective collection of data make it difficult to draw definite conclusions. Therefore, it is thought that statistical significance will increase if our data are evaluated in prospective studies with a higher number of patients. Similar limitations are also found in retrospective studies in the literature. It was thought that prognostic markers based on cancer and inflammation would help clinicians in their routine practice. The fact that these prognostic markers enable us to evaluate more than one parameter, are costless and easy to use will increase their prevalence.

Conclusion

The variables investigated in this study, NLR change and IBI score, when evaluated in combination, enabled us to predict the prognosis in NSCLC patients receiving ICI without driver mutation. In this study, NLR change and IBI score are prognostic markers that can be used when evaluating immunotherapy response. High NLR value, fluctuations/increase in NLR ratio and high IBI score are associated with high mortality and poor prognosis. Since different antitumour mechanisms can be evaluated with a single prognostic marker, 'IBI score and NLR change' is thought to contribute to oncology practice.

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Conflict of interest statement

No conflict of interest was declared by the authors.

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