Gustave Roussy Immune Score (GRIm-Score) Predicts Prognosis in Non-Small Cell Lung Cancer Patients Undergoing Nivolumab: A Multicenter Retrospective Study from Turkiye

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ABSTRACT

The Gustave Roussy Immune Score (GRIm-Score) is a prognostic marker used for predicting the survival outcomes of cancer patients who are undergoing immunotherapy. The purpose of this study is to evaluate the prognostic significance of the GRIm-Score in advanced NSCLC patients treated with nivolumab, and to explore its role in clinical decision-making and treatment optimization. This two-center retrospective study included 285 patients with metastatic NSCLC treated with nivolumab between 2021 and 2024. Clinico-pathologic characteristics, laboratory parameters and treatment responses were evaluated. GRIm-Score was calculated by neutrophil-to-lymphocyte ratio (NLR), baseline albumin and lactate dehydrogenase (LDH) levels. The median age of the patients was 64 years and men were 86.7% of all patients. Compared to those with a high GRIm-Score (2-3), those with a low GRIm-Score (0-1) had significantly better disease control rates (DCR) and objective response rates (ORR) (DCR: 79.7% vs. 32.8%, p= 0.0001; ORR: 56.5% vs. 18.5%; p= 0.0001). In multivariate analysis, serum albumin level, de novo metastatic disease and NLR outcome were predictive of overall survival. Low GRIm-score was associated with long-term survival. The GRIm-Score is an important prognostic factor in patients with advanced NSCLC treated with nivolumab. The GRIm-Score can guide clinicians in selecting patients for nivolumab therapy, optimizing treatment outcomes and resource allocation in clinical practice.

Keywords: Non-small cell lung cancer, Gustave Roussy Immune Score, Peripheral blood inflammatory markers, Nivolumab, Immunotherapy

INTRODUCTION

Lung cancer is the most common type of malignancy worldwide and the leading cause of cancer-related mortality.[1] Approximately 85% of all malignancies are non-small cell lung cancers (NSCLC), which are very frequent tumors.[2] While NSCLC was previously treated with chemotherapy alone, immunotherapies (e.g. nivolumab) have emerged as a prominent treatment option for this malignancy with a poor prognosis and a low survival rate (5-year survival rate less than 20%).[3,4]

Immunotherapies are frequently used, highly effective medicines applied in various cancer types, especially renal cell carcinoma, malignant melanoma and lung cancer.[5-8] Patients with NSCLC at any stage have demonstrated an overall survival benefit from nivolumab, an inhibitor of programmed cell death protein 1 (PD-1).[8] Unfortunately, because the response to nivolumab varies greatly among patients, finding accurate prognostic indicators is essential for predicting treatment outcomes.

Many laboratory parameters have been used to predict survival in different cancer types.[9-11] One of these biomarkers, the Gustave Roussy Immune Score (GRIm-Score) is calculated using albumin levels, neutrophil-to-lymphocyte ratio (NLR) and lactate dehydrogenase (LDH) levels to predict the prognosis of cancer patients receiving immunotherapy.[12] Although the GRIm-Score has been shown to be associated with survival outcomes in many cancer types, its merits in nivolumab-treated NSCLC patients is still unclear.[13-15]

The aim of this study was to examine the association between GRIm-Score and survival outcomes in advanced non-small cell lung cancer patients treated with nivolumab. Finding the predictive significance of GRIm-Score will shed light on clinical decision-making and lead to better patient outcomes.

PATIENTS AND METHODS

Patients with metastatic non-small cell lung cancer who treated with nivolumab are analyzed retrospectively in this study. The research comprised information from two centers between 2021 and 2024, involving 285 individuals who fulfilled the inclusion criteria. The study included patients who received single-agent nivolumab at any line in metastatic NSCLC. Serum albumin levels, NLR, LDH levels are the three clinical indicators that were used to calculate the GRIm-Score. Each parameter was scored as 0 or 1 according to defined thresholds and the total score ranged from 0 to 3. As an example, albumin levels equal to or greater than 35 g/L are assigned a score of 0, whilst levels below 35 g/L are assigned a score of 1. Similarly, normal LDH levels are scored as 0, while those above each center's upper limit of normal (ULN) (247 U/L in these hospitals) are scored as 1. For NLR, values ≤ 3.3 are scored as 0 and those >3.3 are scored as 1. The sum of the scores for each variable gives a total GRIm-Score of 0, 1, 2 or 3, which is used to classify patients into three separate categories: Group 0 (GRIm-Score 0), Group 1 (GRIm-Score 1) and Group 2 (GRIm-Score 2 or 3). Patients were then divided into low (GRIm-Score 0-1) or high (GRIm-Score 2-3) groups according to their total score.

Age, tumor histological characteristics, Eastern Cooperative Oncology Group-Performance score (ECOG-PS), clinical and pathological features of the cancer, laboratory parameters and treatment responses of patients with NSCLC treated with nivolumab were retrospectively recorded from the files.

Follow-up time, progression-free survival (PFS) and overall survival (OS) data were also calculated. The time from nivolumab initiation to first progression, death or last disease-free visit was determined as the primary outcome of PFS. OS was defined as the time from the date of diagnosis to the last visit or death.

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethics committee approval was obtained (Gaziantep City Hospital 16.10.2024.75).

Statistical Analysis

Each piece of data was analyzed using SPSS 23.0 software. Both univariate and multivariate analysis were performed. Standard deviation was indicated by the symbol (±). Independent variable t test was used to compare parametric variables between groups. Nonparametric variables were evaluated using the chi-square test. Cox Regression was used for multivariate analysis. Kaplan-Meier test was used to analyze survival. 95% confidence interval was assigned. A significant p value < 0.05 was defined.

RESULTS

The study included 285 patients with metastatic NSCLC treated with nivolumab. Both male and female patients were included in the study, with the majority being male (86.7%), with a median age of 64 years (range 24-88 years). Most patients (67.4%) had ECOG-PS 0 and the predominant histologic subtype was non-squamous cell carcinoma (61.1%). Approximately 54.7% of patients were metastatic at diagnosis. Of the patients included in the study, 70 received nivolumab in the first-line setting (45 patients in first-line metastatic disease after chemoradiotherapy for locally advanced dis-

Table 1. Demographic and clinical characteristics of the patients

Characteristics	n (%)
Age, year	
Median (Interquartile range)	64 (24-88)
Gender	
Female	38 (13.3)
Male	247 (86.7)
ECOG-performance score	
0	192 (67.4)
1-2	93 (32.6)
Histological classification	
Non-squmous cell carcinoma	174 (61.1)
Squmous cell carcinoma	111 (38.9)
De novo metastatic stage	156 (54.7)
Metastatic site	
Lung	120 (42.1)
Bone	48 (16.8)
Adrenal	11 (3.9)
Brain	40 (14.0)
Multi-organ	83 (29.1)
Nivolumab line	
1-2	223 (78.2)
> 2	62 (21.8)
Treatment response	
Complete Response	17 (6.0)
Partial Regression	94 (33.0)
Stable Disease	57 (20.0)
Progressive Disease	112 (39.3)
Not Evaluated	5 (1.8)
BMI	
Median (Interquartile range)	24.9 (15.5-42.2)
LDH, U/L	
< 247	209 (73.3)
≥ 247	76 (26.7)
Albumin, gr/L	
< 35	44 (15.4)
≥ 35	241 (84.6)
NLR	
< 3.3	135 (47.4)
≥ 3.3	150 (52.6)
Progression	
Yes	170 (59.6)
No	115 (40.4)
Status	
Alive	169 (59.3)
Death	116 (40.7)

ECOG= Eastern Cooperative Oncology Group performance status; LDH= lactate dehydrogenase; NLR= neutrophil-to-lymphocyte ratio; BMI= body mass index

ease and 25 patients in the first-line after progression following adjuvant chemotherapy), 153 in the second-line setting, and 62 in later lines of treatment. All patients were treated with nivolumab as a single agent. Progression under nivolumab was seen in 39.3% of the patients (Table 1).

Two groups of patients were created: one for low GRIm-Score (0-1) and another for high GRIm-Score (2-3). The objective response rate (ORR) was significantly lower in the high GRIm-Score group (p= 0.0001) and 56.5% in the low GRIm-Score group when evaluated based on treatment response. Similarly, the disease control rate (DCR) was 32.8% in the high GRIm-Score group and 79.7% in the low GRIm-Score group (p= 0.0001). The findings show that better treatment outcomes are associated with a lower GRIm-Score in individuals receiving nivolumab (Table 2).

Median PFS was 8.9 months (95% CI: 6.9-10.9) in the GRIm-Score low group and 3.5 months (95% CI: 2.4-4.6) in the GRIm-Score high group (p< 0.001). Median OS was similarly shorter in the high GRIm-Score group (low GRIm-Score 52.6 months (95% CI: 36.9-68.4) vs high GRIm-Score 22.6 months (95% CI: 15.4-29.8); p< 0.001). When evaluated as Group 0, 1 and 2-3, the duration of PFS and OS shortened significantly as the score increased (p< 0.001) (Figure1-4).

Univariate analysis showed a significant association between the ECOG-PS, de novo metastatic disease, body mass index (BMI), nivolumab treatment line, albumin level, LDH level, NLR, and GRIm-Score, and overall survival. Multivariate analysis results revealed that BMI (HR 0.66, 95% CI: 0.44-0.97, p= 0.039), nivolumab treatment line (HR 0.41, 95% CI: 0.25-0.66, p< 0.001) and de novo metastatic disease (HR 2.60, 95% CI: 1.71-3.95, p< 0.001) were the variables that independently predicted overall survival. The GRIm-Score was significant in both in the univariate analysis (HR 2.39, 95% CI: 1.64-3.48, p= 0.0001) and in the multivariate model (HR 2.69, 95% CI: 1.84-3.92, p< 0.001) (Table 3).

DISCUSSION

According to our findings, patients with lower GRIm-Scores responded to treatment considerably better than those with higher GRIm-Scores. The low GRIm-Score group had significantly greater

Table 2. Response evaluation between the GRIm-Score groups

Characteristics	Group 0 (Low Group)	Group 1 (Low Group)	Group 2-3 (High Group)	Total	p
Objective response, n (%)					0.0001
CR	12 (12.1)	4 (3.4)	1 (1.4)	17 (5.9)	
PR	44 (44.4)	38 (32.7)	12 (17.1)	94 (32.9)	
SD	23 (23.2)	24 (20.6)	10 (14.2)	57 (20.0)	
PD	19 (19.1)	49 (42.2)	44 (62.8)	112 (39.2)	
NE	1 (1.0)	1(0.8)	3 (4.2)	5 (1.7)	
Objective response rate (%)	56 (56.5)	42 (36.2)	13 (18.5)	111 (38.9)	0.0001
Disease control rate (%)	79 (79.7)	66 (56.8)	23 (32.8)	168 (58.9)	0.0001

GRIm-Score: Gustave Roussy Immune score; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; NE: inevaluable

ORR and DCR compared to the high GRIm-Score group (56.5% and 79.7% respectively, as opposed to 18.5% and 32.8% respectively). The GRIm-Score was significant in predicting OS in both the univariate and the multivariate analysis (p< 0.001). This demonstrates that GRIm-Score is a very dependable measure of therapy efficacy, which could aid in the process of choosing appro-

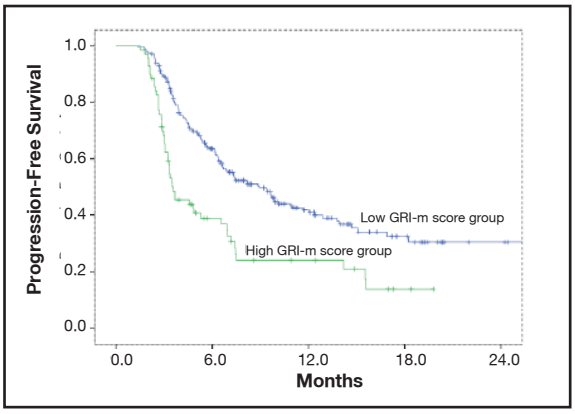

Figure 1. Association between GRI-m score and progression-free survival

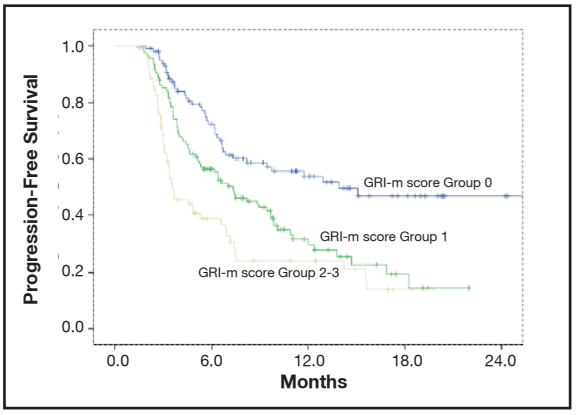

Figure 2. Association between GRI-m score and progression-free survival

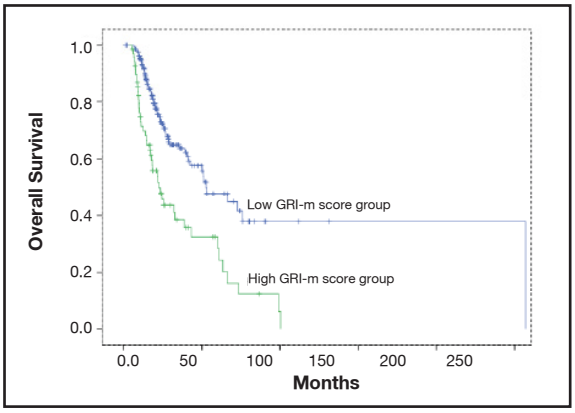

Figure 3. Association between GRI-m score and overall survival

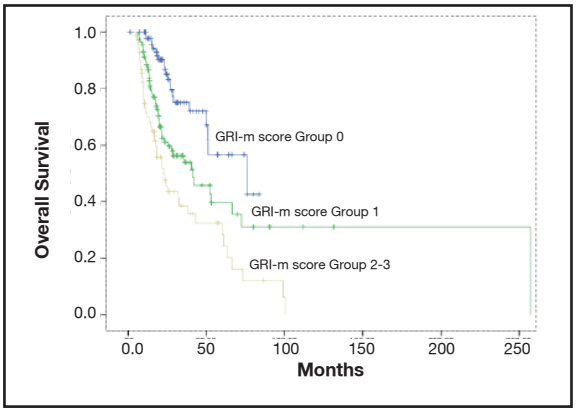

Figure 4. Association between GRI-m score and progression-free survival

Table 3. Univariate and multivariate analysis of potential prognostic factors for overall survival

Parametres	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	p
Age (< 65 vs ≥ 65)	1.21 (0.83-1.74)	0.300	-	-
Gender (female vs male)	0.71 (0.44-1.16)	0.170	-	-
ECOG-PS (0 vs 1-2)	1.51 (1.04-2.19)	0.030	1.42 (0.97-2.07)	0.067
De novo metastatic (no vs yes)	1.98 (1.34-2.91)	<0.001	2.60 (1.71-3.95)	<0.001
BMI (< 25 vs > 25)	0.64 (0.44-0.93)	0.020	0.66 (0.44-0.97)	0.039
Histological (squamous vs nonsquamous)	0.99 (0.68-1.44)	0.970	-	-
Brain metastasis (no vs. yes)	1.00 (0.59-1.71)	0.970	-	-
Adrenal metastasis (no vs. yes)	1.09 (0.40-2.98)	0.850	-	-
Bone metastasis (no vs. yes)	1.54 (0.95-2.49)	0.070	-	-
Nivolumab line (1-2 vs > 2)	0.53 (0.34-0.82)	0.005	0.41 (0.25-0.66)	<0.001
GRIm-Score (low vs high)	2.39 (1.64-3.48)	<0.001	2.69 (1.84-3.92)	<0.001

ECOG-PS= Eastern Cooperative Oncology Group performance status; GRIm-Score= Gustave Roussy Immune Score; BMI= Body mass index; HR= hazard ratio; CI= confidence interval

priate treatments. The correlation between a higher GRIm-Score and worse outcomes may indicate the influence of systemic inflammation and nutritional status on the progression of cancer and its response to treatment.

The study's findings highlight the significance of clinicopathology characteristics and treatment response in predicting survival for patients with metastatic NSCLC receiving nivolumab in any stage.

The study also showed that other variables important in predicting overall survival were de novo metastatic disease and BMI. As we know from previous studies, de novo metastatic disease was associated with a poor prognosis for overall survival in our study, as in all cancers.[16,17] Patients with de novo metastatic disease had an almost three times higher risk of death (HR= 2.60, p< 0.001), indicating that their NSCLC was aggressive. On the other hand, a BMI above 25 was associated with a protective effect and a lower chance of death (HR= 0.66, p= 0.039). This finding is consistent with other research suggesting that a higher BMI may be linked to improved outcomes in NSCLC.[18,19]

Patients who received nivolumab as first- or second-line treatment had better outcomes than those who received it later in their treatment course, giving nivolumab treatment line another significant determinant of survival. Even in first- or second-line treatment, less than 50% of patients respond to this treatment, while response rates are less than 20% when used as part of other lines treatments.[20-24] This finding highlights the potential benefits of initiating rapid and effective treatment in the early lines of metastatic NSCLC, similar to other cancer types. We think that the reason why nivolumab and other therapies are more effective in metastatic NSCLC in early lines is related to the higher number of treatment naive cells in the early period.

As we have emphasized previously, many treatment options are recommended in guidelines for metastatic NSCLC. At the same time, nivolumab is an effective treatment for metastatic NSCLC but it is costly. Therefore, we need markers to select patients in order to optimize treatment efficacy. The GRIm-Score, which classifies patients according to expected treatment response and survival, could be a useful tool to develop more personalized treatment strategies in metastatic NSCLC prior to nivolumab treatment. Furthermore, the importance of inflammatory markers and nutrition on survival outcomes highlights the necessity of comprehensive patient management that takes into account these modifiable factors. Similar prognostic scores using parameters such as neutrophil-to-

lymphocyte ratio, albumin and LDH are often used to predict prognosis in oncology. Such biomarkers are commonly applied in combination with the GRIm-Score.

Limitations of the Study: Although our study yielded significant findings, there are certain limitations. The limited generalizability of the results could be attributed to the retrospective character of the investigation, the short follow-up period and small sample size. In order to validate these findings and investigate the underlying mechanisms of the observed relationships, further extensive prospective studies with larger populations are required.

Conclusion

The GRIm-Score, by integrating inflammatory and nutritional biomarkers, serves as a simple and practical tool to predict survival outcomes in NSCLC patients undergoing nivolumab therapy. Future prospective studies are warranted to validate these findings and optimize personalized treatment strategies. The GRIm score, which is calculated from laboratory parameters such as albumin, neutrophil count, neutrophil count, lymphocyte count and LDH in peripheral blood before immunotherapy treatment, may be useful to identify fragile patients who require close follow-up or additional measures.

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