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Research Article

Gustave Roussy Immune Score in Nivolumab Treated Metastatic Renal Cell Carcinoma

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Abstract

Aim: The aim of this study is to evaluate the Gustave Roussy immune (GRIm) score as a biomarker for survival in metastatic renal cell carcinoma (mRCC) patients receiving nivolumab following first-line treatment.
Material and Method: 41 mRCC patients who were given nivolumab beyond first line were included in this retrospective study. Data on ratio of neutrophile to lymphocyte, albumin, and LDH levels were utilized to determine GRIm score. Patients scoring 2–3 were grouped into the high GRIm score, whereas those scoring 0–1 were grouped as the low GRIm score. The association between the GRIm score and progression-free survival (PFS) with overall survival (OS) was examined.
Results: Thirty patients exhibited a low GRIm score, whereas eleven presented a high GRIm score. Prolonged median PFS and OS, with values of 7.06 months compared to 2.89 months (p=0.002) and 20.34 months compared to 4.27 months (p<0.001), are found respectively in low GRIm score group. In terms of PFS, a higher GRIm score was identified as an independent prognostic indicator but lacked prognostic significance for OS in multivariable analysis.
Conclusion: The GRIm score may be used as an accessable and cost-effective prognostic biomarker in mRCC patients receiving nivolumab, and may assist clinicians in patient selection, thus improving therapeutic efficacy and the efficient use of clinical resources.

Keywords: Renal cell carcinoma, metastatic, Gustave Roussy immune score, nivolumab, prognosis

INTRODUCTION

There have been major changes in how metastatic renal cell carcinoma (mRCC) is treated in the last 20 years. One of the pivotal advancements was the tyrosine kinase inhibitors, they extended progression free survival (PFS) and became a standard treatment during the 2000s (1,2). However, despite initial efficacy, the majority of patients eventually develop resistance to vascular endothelial growth factor (VEGF)-targeted therapies, prompting the exploration of immune checkpoint inhibitors (ICIs) as an alternative treatment strategy. Nivolumab was the first ICI licensed for mRCC after the phase III CheckMate-025 study showed improved survival rates (3). Standard first-line treatment among all the risk groups of International Metastatic RCC Database Consortium (IMDC) have recently become ICI-based combination therapies. These therapies have shown significant benefits for patients with intermediate-poor prognostic features (4,5).

Following Vascular endothelial growth factor receptor thyrosine kinase inhibitor (VEGFR-TKI) failure, nivolumab is considered as an alternative therapeutic option (6). In Türkiye, clinical practice is shaped by national reimbursement policies, which currently authorize the use of nivolumab beyond first line treatment following VEGFR-TKI failure. This means that most of the real-world data show how nivolumab worked for people who had already failed TKI treatment. However, only a subset of these patients experience durable clinical benefit, underscoring the need for robust biomarkers that can predict response to ICIs (7,8).

Readily available markers derived from routine blood tests have garnered interest as potential predictors of immunotherapy outcomes in various cancers, including mRCC (9-12).

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The Gustave Roussy immune (GRIm) score is a composite indicator based on neutrophil to lymphocyte ratio, albumin, and LDH values (13). While the GRIm score has shown prognostic relevance in several malignancies including lung cancers and gastrointestinal tumors, evidence regarding its utility in mRCC remains limited (14-19).

In this study, the GRIm score's significance on prognosis in patients treated with nivolumab is evaluated, its potential role in stratifying patients based on anticipated clinical benefit from ICI therapy is emphasized.

MATERIAL AND METHOD

Data Collection

Patients with mRCC treated with nivolumab beyond the first line at Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital between January 1, 2017, and January 1, 2023 were included in this retrospective analysis. The review of electronic medical records provided data on demographics, Eastern Cooperative Oncology Group performance status (ECOG PS), IMDC risk group, line of nivolumab therapy, time to disease progression, and time to death from the initiation of treatment. This study was approved by the Ethics Committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (Approval No: 2023-09/80, Date: September 14, 2023).

GRIm Score Calculation

GRIm score was calculated with three peripheral blood markers: NLR, serum albumin concentration, and LDH. The scoring system was defined as follows:

- **Serum albumin:** ≤35 g/L =1 point; >35 g/L =0 point
- **LDH:** >220 IU/L =1 point; ≤220 IU/L =0 point
- **NLR:** >75th percentile of the cohort =1 point; ≤75th percentile =0 point
- **GRIm score:** low group: 0 or 1 points
- **GRIm score:** high group: 2 or 3 points (15).

Statistical Analysis

IBM SPSS Statistics for Windows, Version 25.0 is used. Continuous variables were described as mean±standard deviation (SD). Frequencies and percentages summarized categorical variables. PFS and overall survival (OS) were explored using Kaplan Meier analysis. Prognostic factors are described with Cox regression models. Statistical significance was defined as a two-sided p-value less than 0.05 for all tests.

RESULTS

41 mRCC patients received nivolumab beyond first line were included. Most patients were male (n=34, 82.9%), while 7 patients (17.1%) were female. At treatment initiation, 32 patients (78%) had ECOG PS 1, and 9 patients (22%) had ECOG PS 2. The median age was 63 years (range: 37–86). Nivolumab was administered in second-line in 25 patients (61%) and in third-line in 16 patients (39%). 31 patients (75.6%) were in the intermediate, 6 (14.6%) were in the poor, and 4 (9.8%) in the favorable IMDC risk group. Based on the GRIm score, 30 patients (73.2%) were classified into the low GRIm group (score 0–1), while 11 patients (26.8%) were in the high GRIm group (score 2–3). Disease progression was observed in 35 patients (85.4%). A total of 33 patients (80.5%) had died, whereas 8 patients (19.5%) were alive at the last follow-up.

A statistically significant moderate positive correlation was observed between IMDC risk classification and GRIm score grouping, as determined by Spearman's rank correlation analysis (r_s=0.505, p=0.001, n=41).

Median PFS was 7.06 months (95% CI: 1.99–12.13) vs 2.89 months (95% CI: 1.93–3.85) (p=0.002) between low and high GRIm groups respectively (Figure 1). Median OS was 20.34 months (95% CI: 5.57–35.11) in the low GRIm group compared to 4.27 months (0–8.95) in the high group (p<0.001) (Figure 2).

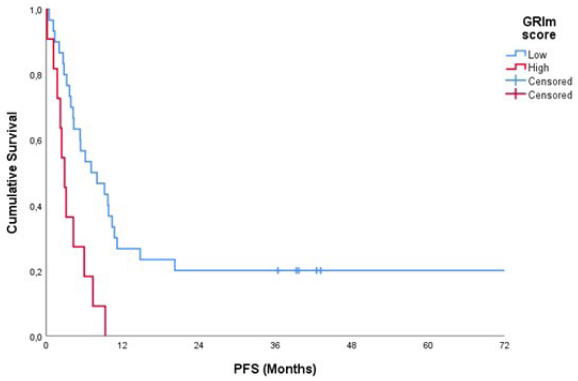

Figure 1. Kaplan–Meier analysis of PFS based on GRIm score classification (low vs high)

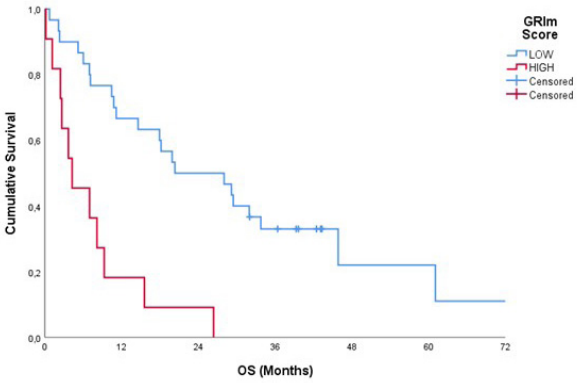

Figure 2. Kaplan–Meier analysis of OS based on GRIm score classification (low vs high)

According to univariate analyses ECOG performance status, IMDC risk classification, and GRIm score were significantly related to both PFS and OS. High GRIm group exhibited a significantly reduced median PFS of 2.9 months compared to 7.06 months in the low GRIm group (p=0.002). Similarly, OS was markedly reduced within high GRIm group, with a median of 4.27 months versus 20.34 months in the low GRIm group (p<0.001). In multivariance analysis, the GRIm score was the sole significant independent predictor for PFS (p=0.003) (Table 1).

Table 1. Univariate and multivariate cox regression analyses for PFS and OS

Variable	Univariate PFS Median (95% CI)	p value	Univariate OS Median (95% CI)	p value	Multivariate PFS HR (95% CI)	Multivariate PFS p-value	Multivariate OS HR (95% CI)	Multivariate OS p-value
Sex								
Female	9.17 (4.4–13.9)	0.27	18.17 (3.0–33.3)	0.57	-	-	-	-
Male	4.34 (2.7–5.98)		14.59 (4.48–24.7)					
Age								
≤63 years	5.40 (0.97–9.8)	0.90	18.17 (2.3–34.0)	0.45	-	-	-	-
>63 years	5.30 (1.8–8.9)		7.13 (4.67–9.59)					
ECOG PS								
0–1	6.10 (3.7–8.9)	0.06	18.17 (0.9–35.0)	0.01*	1.47 (0.64-3.4)	0.37	2.09 (0.8-5.5)	0.134
2–3	3.10 (1.1–5.1)		3.68 (0.7–6.65)					
IMDC score								
Favorable	7.10 (0–20.8)		29.47 (15.8–43.1)					
Intermediate	5.40 (2.0–8.7)	0.045*	15.58 (6.5–24.59)	0.012*	0.82 (0.26-2.59)	0.74^60	0.81 (0.24-2.74)	0.52774^
Poor	0.24 (1.76–2.7)		2.66 (0.45–8.87)					
Line of therapy								
2nd line	4.23 (2.52–5.95)	0.18	10.77 (4.6–16.96)	0.36	-	-	-	-
≥3rd line	7.32 (1.14–13.5)		18.17 (13.4–22.8)					
GRIm score								
Low	7.06 (2.0–12.0)	0.002*	20.34 (5.57-35.1)	<0.001*	0.31 (014-0.67)	0.003*47*	0.34 (0.11-1.1)	0.06473
High	2.90 (1.9–3.8)		4.27 (0–8.9)					

*Significant, ^Poor vs Favorable

DISCUSSION

We investigated the usefulness of the GRIm score as a prognostic indicator in mRCC patients undergoing nivolumab treatment beyond first-line settings. We found a significant association between a high GRIm score and decreased PFS. Notably, the GRIm score was independently associated with PFS in multivariate analysis, highlighting its potential role in risk stratification for mRCC patients receiving immune checkpoint inhibitors. Although the GRIm score was significantly associated with PFS in both univariate and multivariate analyses, its association with OS did not reach statistical significance in the multivariate model. This may be attributed to the limited sample size and potential confounding effects of post-progression treatments and other non-tumor-related factors that influence OS.

The GRIm score, which combines serum albumin, LDH, and NLR, was originally developed as a simple immune-inflammatory biomarker to predict outcomes in patients treated with ICIs (13). These results support previous evidence demonstrating that systemic inflammation-based indicators like NLR and LDH have prognostic relevance in mRCC (20-22). High NLR levels have repeatedly been accompanied by unfavorable outcomes in patients receiving ICIs. Similarly, low albumin levels and increased LDH are indicative of malnutrition, high tumor burden, and metabolic stress, all of which are linked to poor clinical outcomes.

In this study population, a higher GRIm score was linked to unfavorable prognosis, as evidenced by notably lower median PFS and OS in the high-risk category. These results highlight the GRIm score's practical utility as a low-cost, non-invasive biomarker that can be easily integrated into daily oncology practice, particularly in settings where molecular profiling is unavailable or resource-limited. GRIm score may complement existing risk models, such as the IMDC classification, by providing additional biologically relevant information derived from systemic inflammation and nutritional status.

While the implications of this study are encouraging, its retrospective and single-center design, along with the small sample size, may reduce the extent to which the findings can be generalized. Additionally, our analysis excluded patients treated with contemporary first-line ICI combinations, which have become standard care in many settings. Validation of these results in future multicenter, prospective cohorts is essential to fully establish the GRIm score's predictive capacity in varied oncologic treatment landscapes.

CONCLUSION

The GRIm score functions as a practical survival biomarker for mRCC patients receiving nivolumab after first-line treatment. In this retrospective cohort, a high GRIm score had a significant association with reduced progression-free survival and overall survival. It continued to serve as an independent predictor of PFS in the multivariate analysis; however, no statistically significant association was found with OS.

These findings support the GRIm score's potential role in clinical risk stratification and point out the need for further validation in broader, prospective studies.

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Conflict of interest: *The authors have no conflicts of interest to declare.*

Ethical approval: *This study was approved by the Ethics Committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital (Approval No: 2023-09/80, Date: September 14, 2023) and was conducted in accordance with the ethical principles of the Declaration of Helsinki.*

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