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Novel Risk Scoring System for Patients with Metastatic Renal Cell Carcinoma Treated with Immune Checkpoint Inhibitors

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Immunotherapy • Prognostic markers • Renal cell carcinoma • Risk scoring system • Inflammation • Body composition

Abstract

Background. The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria are the gold standard for risk-stratifying patients with metastatic renal cell cancer (mRCC). We developed a novel risk scoring system for patients with mRCC treated with immune checkpoint inhibitors (ICIs).

Methods. We performed a retrospective analysis of 100 ICI-treated patients with mRCC at Winship Cancer Institute from 2015 to 2018. Several baseline variables were collected, including markers of inflammation, body mass index (BMI), and sites of metastatic disease, and all were considered for inclusion in our risk scoring system. Upon variable selection in multivariable model, monocyte-to-lymphocyte ratio (MLR), BMI, and number and sites of metastases at baseline were used for risk score calculation. Patients were categorized using four-level risk groups as good (risk score = 0), intermediate (risk score = 1), poor (risk score = 2), or very poor (risk score = 3–4). Cox's proportional hazard model and the Kaplan-Meier method were implemented for survival outcomes.

Results. Most patients were male (66%) with clear cell renal cell carcinoma (72%). The majority (71%) received anti–programmed cell death protein-1 monotherapy. Our risk scoring criteria had higher Uno's concordance statistics than IMDC in predicting overall survival (OS; 0.71 vs. 0.57) and progression-free survival (0.61 vs. 0.58). Setting good risk (MLR <0.93, BMI ≥24, and D_Met = 0) as the reference, the OS hazard ratios were 29.5 (95% confidence interval [CI], 3.64–238.9), 6.58 (95% CI, 0.84–51.68), and 3.75 (95% CI, 0.49–28.57) for very poor, poor, and intermediate risk groups, respectively.

Conclusion. Risk scoring using MLR, BMI, and number and sites of metastases may be an effective way to predict survival in patients with mRCC receiving ICI. These results should be validated in a larger, prospective study. ***The Oncologist*** 2020;25:e484–e491

Implications for Practice: A risk scoring system was created for patients with metastatic renal cell carcinoma treated with immune checkpoint inhibitors. The results of this study have significant implications for practicing oncologists in the community and academic setting. Importantly, these results identify readily available risk factors that can be used clinically to risk-stratify patients with metastatic renal cell carcinoma who are treated with immune checkpoint inhibitors.

Introduction

Immunotherapy has changed the landscape of treatment of metastatic renal cell carcinoma (mRCC) since nivolumab, a programmed cell death protein-1 (PD-1) inhibitor, was approved for vascular endothelial growth factor (VEGF)–refractory mRCC in November 2015 [1]. The first immune checkpoint inhibitor (ICI) combination regimen, nivolumab and ipilimumab, was recently approved for first-line intermediate or poor risk mRCC, and results from ongoing trials

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Table 1. Emory risk scoring system

Variable	Score
MLR ≥0.93	1
MLR <0.93	0
Baseline BMI <24	1
Baseline BMI ≥24	0
D_Met = 2	2
D_Met = 1	1
D_Met = 0	0

Abbreviations: BMI, body mass index; D_Met, metastatic site variable; MLR, monocyte-to-lymphocyte ratio.

of ICI and anti-VEGF combination regimens have been very promising [1–4]. Given the increasing number of treatment options for patients with mRCC, including several ICI-based regimens, it is becoming increasingly important to identify risk factors that make patients with mRCC more likely to respond to ICI.

The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk criteria are currently the gold standard for predicting survival in patients with renal cell cancer (RCC) [5, 6]. This method includes six risk factors: time from RCC diagnosis to first-line systemic therapy <1 year, elevated platelet count, elevated absolute neutrophil count, anemia, hypercalcemia, and Karnofsky performance status <80. The IMDC criteria have been validated in patients treated with VEGF-targeted therapy [7] and are widely used to risk-stratify patients in trials of patients with RCC. Although the IMDC criteria capture both laboratory values and clinical findings that accurately predict survival in patients with mRCC, they do not take into account number and sites of metastatic disease, systemic inflammation, or body composition, which all likely affect the host's systemic immune responses to ICI therapy [8–11].

Patients treated with ICI may require specific risk stratification given the unique mechanism of action of ICI. Updated prognostic models may more accurately predict survival and optimize selection of patients who are most likely to respond to ICI-based treatment regimens. In this study, we created a novel risk stratification system, the Emory risk scoring system, for patients with mRCC treated with ICI. We categorized patients into four groups using three variables to capture risk from systemic inflammation, number and sites of metastatic disease, and body composition.

Materials and Methods

Patients and Data Collection

We performed a retrospective analysis of 100 patients with mRCC who received ICI at Winship Cancer Institute of Emory University between 2015 and 2018. Overall survival (OS) and progression-free survival (PFS) were measured from first dose of ICI to date of death or hospice referral and radiographic or clinical progression, respectively. RECIST version 1.1 was used to evaluate response to ICI [12]. Neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) were obtained from the complete blood count prior to treatment with ICI and used as surrogates of systemic inflammation. Body mass index (BMI) at the time of ICI initiation was obtained and used to represent body composition. Number and sites of metastasis at the time of first dose of ICI were obtained from radiology reports and clinic notes. Other variables collected included demographic information, drug allergies, prior lines of systemic therapy, post-ICI treatments, immune-related adverse events, eosinophil count, basophil count, and IMDC risk group criteria.

The study was approved by the Emory University Institutional Review Board and was conducted in accordance with Good Clinical Practice Guidelines and the Declaration of Helsinki. Informed consent for publication has been obtained, and the consent forms are held by the authors. All data generated or analyzed during this study are included in this published article.

Statistical Analysis

The analyses were done using SAS 9.4 and SAS macros [13], and the significance level was set at .05 by two-sided tests. Given that the presence of liver metastases was associated with shorter OS in univariate analysis (UVA), we created a new variable, D_Met, to more accurately represent risk related to metastatic sites: D_Met = 0 indicates fewer than two metastatic sites, D_Met = 1 indicates at least two metastatic sites without liver metastasis, and D_Met = 2 indicates at least two metastatic sites with liver metastasis. OS was set as the primary outcome. For prognostic factors with continuous values, the optimal cut regarding OS was searched at all unique values, and the value that was chosen was the one that gave the maximum separation [14]. The following variables, which were collected prior to treatment with ICI, were under consideration for inclusion in our model: age, gender, race, smoking status, medication allergies, D_Met, Eastern Cooperative Oncology Group performance status, NLR, MLR, PLR, BMI, eosinophils, and basophils. With all possible prognostic variables under consideration, a backward variable selection was implemented in Cox's proportional hazard model regarding OS with $p < .05$. Based on the parameter estimated in the final model, a score was assigned based on Sullivan's weighting schema [15, 16]. The final variables selected were baseline MLR, D_Met, and baseline BMI.

The Emory risk scoring system is shown is Table 1. MLR ≥0.93, BMI <24, and D_Met = 1 each counted as one point in the risk score, whereas D_Met = 2 counted as two points in the risk score. Patients were categorized as good risk (Emory risk score = 0), intermediate risk (Emory risk score = 1), poor risk (Emory risk score = 2), or very poor risk (Emory risk score = 3 or 4). Uno's concordance statistics (C-statistics) were calculated and compared for the Emory risk scoring system and the IMDC criteria regarding the discrimination for OS or PFS [17]. The C-statistics for each risk scoring system were calculated at the initiation of ICI therapy. Cox's proportional hazard model and the Kaplan-Meier method were used for association with OS and PFS in UVA and multivariable analysis (MVA) for the Emory risk scoring system.

Results

Baseline Patient Characteristics

The baseline descriptive statistics are presented in Table 2. Most patients (66%) were male, and the median age was 65 years. The majority (72%) had clear cell renal cell carcinoma histology. The distribution of metastatic sites was as follows: 56% had lymph node metastases, 37% had bone metastases, 25% has liver metastases, 17% had brain metastases, and 71% had lung metastases. Most patients (60%) were overweight or obese at baseline (BMI ≥25), and the median BMI was 26.7. The majority of patients (83%) had at least two sites of metastatic disease at the time of first dose of ICI. The IMDC risk group distribution was as follows: 15% favorable, 55% intermediate, 22% poor risk, and 8% missing. The median baseline NLR, MLR, and PLR were 3.1, 0.40, and 196.02, respectively. Anti–PD-1 monotherapy (71%) was the most common ICI treatment regimen, and 29% received combination therapy. Most patients (45%) received one prior line of systemic therapy before ICI, and 31% received ICI as first-line treatment. Less than one-quarter (24%) of patients received two or more lines of systemic therapy before ICI initiation.

Emory Risk Scoring System Analysis

The UVA and MVA of the association between the Emory risk scoring system and survival are presented in Table 3. Very poor risk patients had significantly shorter OS (hazard ratio [HR], 37.72; 95% confidence interval [CI], 4.76–298.70; $p < .001$) and PFS (HR, 3.87; CI, 1.50–9.96; $p = .005$) than good risk patients in UVA. Poor risk patients also had significantly shorter OS than good risk patients (HR, 8.49; CI, 1.11–64.75; $p = .039$), and they showed a trend toward shorter PFS (HR, 2.13; CI, 0.90–5.02; $p = .085$) in UVA. In MVA, very poor risk patients had significantly shorter OS (HR, 29.50; CI, 3.64–238.9, $p = .002$) and PFS (HR, 2.80; CI, 1.10–7.11; $p = .030$) compared with good risk patients. Poor and intermediate risk patients also trended toward shorter OS (poor risk HR, 6.58; CI, 0.84–51.68; $p = .073$; intermediate HR, 3.75; CI, 0.49–28.57; $p = .203$) and PFS (poor risk HR, 1.36; CI, 0.55–3.33; $p = .506$; intermediate HR, 1.70; CI, 0.73–3.94; $p = .218$) compared with the good risk group. The median OS and PFS was significantly shorter for very poor risk patients (OS, 4.2 months; PFS, 2.6 months) compared with poor risk (OS, 16.9 months; PFS, 4.5 months), intermediate risk (OS, 29.7 months; PFS, 6.1 months), and good risk patients (OS, not reached; PFS, 12.3 months) per Kaplan-Meier estimation (Figs. 1 and 2; OS, $p < .001$; PFS, $p = .068$).

Given that MLR, PLR, and NLR measure systemic inflammation and were highly correlated (Pearson correlation coefficients >0.678, all $p < .0001$; supplemental online Fig. 1), risk groups using NLR or PLR instead of MLR were also created. The Kaplan-Meier plots for the NLR-based and PLR-based models are given in supplemental online Figures 2 and 3. The C-statistics were similar for each of the models in predicting OS (MLR-based model, 0.711; NLR-based model, 0.687; PLR-based model, 0.682) and PFS (MLR-based model, 0.610; NLR-based model, 0.611; PLR-based mode, 0.594).

Table 2. Demographics and baseline patient characteristics

Variable, category	*n* (%)
Gender	
M	66 (66)
F	34 (34)
Race	
White/Asian	83 (83)
Black	17 (17)
ECOG PS	
0–1	69 (69)
2+	15 (15)
Missing	16 (16)
Histology	
ccRCC	72 (72)
nccRCC	20 (20)
Unknown	8 (8)
Number of metastatic sites	
0–1	17 (17)
2+	83 (83)
IMDC risk group	
Favorable	15 (15)
Intermediate	55 (55)
Poor	22 (22)
Missing	8 (8)
Metastatic site distribution	
Lymph node	56 (56)
Lung	71 (71)
Brain	17 (17)
Bone	37 (37)
Liver	25 (25)
Baseline BMI (median: 26.7)	
≥25	60 (60)
<25	39 (39)
Missing	1 (1)
Type of ICI	
PD-1 monotherapy	71 (71)
ICI combination	29 (29)
Number of prior lines of systemic therapy	
0	31 (31)
1	45 (45)
2+	24 (24)
Median NLR	3.1
Median MLR	0.40
Median PLR	196.0

Abbreviations: BMI, body mass index; ccRCC, clear cell renal cell cancer; ECOG PS, Eastern cooperative oncology group performance status; F, female; ICI, immune checkpoint inhibitor; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; M, male; MLR, monocyte-to-lymphocyte ratio; nccRCC, non-clear cell renal cell cancer; NLR, neutrophil-to-lymphocyte ratio; PD-1, programmed cell death protein-1; PLR, platelet-to-lymphocyte ratio.

Table 3. UVA and MVA of risk groups and survival

	UVA				MVA[a]			
	OS		PFS		OS		PFS	
Risk groups	HR (CI)	*p* value	HR (CI)	*p* value	HR (CI)	*p* value	HR (CI)	*p* value
Very poor risk: Risk score = 3–4 (*n* = 13)	37.72 (4.76–298.70)	<.001[b]	3.87 (1.50–9.96)	.005[b]	29.50 (3.64–238.90)	.002[b]	2.80 (1.10–7.11)	.030[b]
					Median survival: 4.2 months		Median survival: 2.6 months	
Poor risk: Risk score = 2 (*n* = 28)	8.49 (1.11–64.75)	.039[b]	2.13 (0.90–5.02)	.085	6.58 (0.84–51.68)	.073	1.36 (0.55–3.33)	.506
					Median survival: 16.9 months		Median survival: 4.5 months	
Intermediate risk: Risk score = 1 (*n* = 45)	4.22 (0.55–32.17)	.165	1.40 (0.61–3.19)	.422	3.75 (0.49–28.57)	.203	1.70 (0.73–3.94)	.218
					Median survival: 29.7 months		Median survival: 6.1 months	
Good risk: Risk score = 0 (*n* = 13)	1		1		1		1	
					Median survival: Not reached		Median survival: 12.3 months	

[a]MVA controlled for gender, race, International Metastatic Renal Cell Carcinoma Database Consortium risk group, number of distant metastases, age, clear cell renal cell carcinoma histology, programmed cell death protein-1 monotherapy, and number of prior lines of systemic therapy.
[b]Statistical significance at $\alpha < .05$.
Abbreviations: CI, 95% confidence interval; HR, hazard ratio; MVA, multivariate analysis; OS, overall survival; PFS, progression-free survival; UVA, univariate analysis.

Comparison with IMDC

A discrimination by the prediction model was measured by Uno's C-statistics. Regarding predicting OS, the Emory risk scoring system had a C-statistic of 0.711, compared with 0.566 by IMDC ($p = .053$). The C-statistic was also higher for the Emory risk scoring system in predicting PFS (0.610) compared with 0.575 for the IMDC risk grouping ($p = .587$).

Discussion

Optimal risk stratification is important for practicing oncologists to predict survival and manage treatment for patients. This is becoming increasingly important in mRCC, given that there have been several recently approved treatments with distinct targets such as cabozantanib, nivolumab, and ipilimumab and lenvatinib and everolimus [4, 18–20]. Risk scoring is particularly important for patients treated with immunotherapy because durable clinical benefit is only observed in a subset of patients [21]. Furthermore, results from the CA209-214 study showed that nivolumab and ipilimumab was only superior to sunitinib, a VEGF inhibitor, in intermediate and poor risk patients [19]. In this study, we developed a hypothesis-generating risk scoring system using three variables to represent risk from number and sites of metastatic disease (D_Met), body composition (BMI), and inflammation (MLR). This builds upon previously established data on the effectiveness of the IMDC criteria in predicting survival in patients with mRCC treated with VEGF-targeted therapy [6, 7, 22]. The results from our study indicate that incorporation of risk factors such as sites of metastatic disease, body composition, and a more accurate inflammatory marker may improve prediction of survival in patients with mRCC treated with ICI.

It is becoming increasingly recognized that the tumor microenvironment (TME) influences responses to immunotherapy and that the TME differs significantly between metastatic sites depending on the organ tropism [23]. Therefore, sites of metastatic disease likely influence responses to immunotherapy. This is particularly true for the liver, which is a secondary lymphoid organ that synthesizes acute phase reactants, complement proteins, and chemokines and houses a significant population of lymphoid cells such as T lymphocytes [24, 25]. Unsurprisingly, liver metastases are a poor prognostic factor in patients treated with ICI [8, 26–28]. A recent study suggests that this may be because liver metastases decrease the ratio of $CD8^+/Foxp3^+$ regulatory T cells and the number of activated $PD\text{-}1^+/CTLA\text{-}4^+$ T cells, indicating that liver metastases may have a systemic influence on tumor immunity [29]. The results from this study as well as several previous studies suggest that liver metastases are a poor prognostic factor in patients treated with ICI. Therefore, updated prognostic models may be improved by including a variable to account for number of metastatic sites and the presence of liver metastases.

Body composition has been an increasingly studied prognostic factor in patients with cancer. The most easily accessible and clinically useful marker of body composition is BMI. Although obesity is a risk factor for the development and progression of some cancers [30, 31], several studies have shown that BMI may be protective in patients with RCC, in both the perioperative and metastatic settings [32, 33]. A recent article showed that increased BMI was independently associated with improved survival in patients with melanoma treated with ICI [11]. Although the underlying biology explaining these clinical findings has not been elucidated, there are several potential biological explanations for this. Obesity has been shown to alter fatty acid metabolism, which plays a role in both oncogenesis and responses to therapy [34, 35]. Adipocyte PD-L1 expression increases during adipogenesis, suggesting that obesity

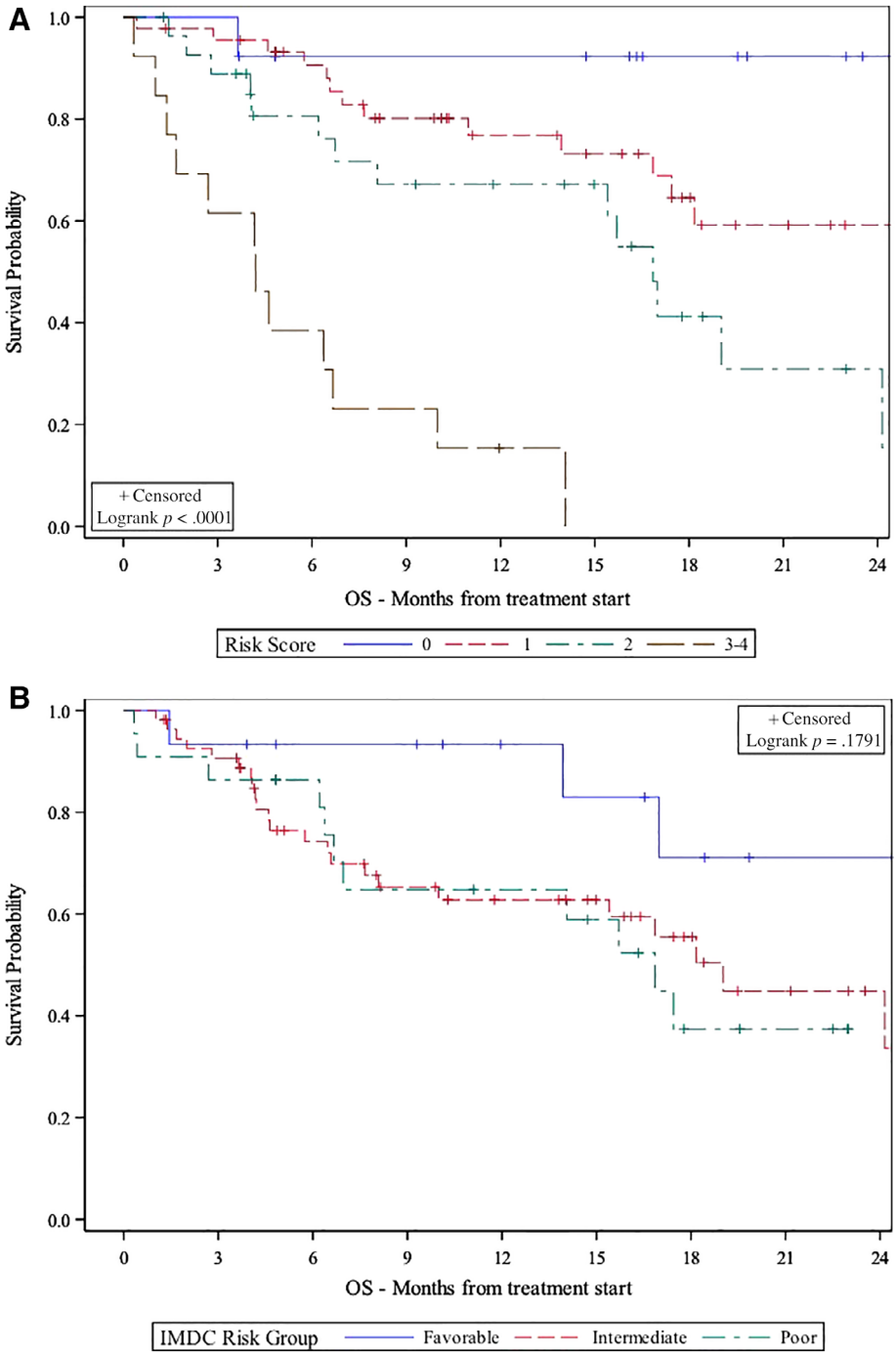

Figure 1. Emory risk group versus IMDC risk group stratification and association with OS. **(A):** Emory risk group stratification. 0 = good risk, 1 = intermediate risk, 2 = poor risk, 3–4 = very poor risk. **(B):** IMDC risk group stratification.
Abbreviations: IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; OS, overall survival.

promotes tumor immune evasion, and this process can be reversed with treatment with ICI via increased activity of effector T cells [36, 37]. Taken together, inclusion of a body composition marker such as BMI in updated prognostic models may improve prediction of survival in patients with mRCC treated with ICI.

Inflammation has been described as one of the hallmarks of cancer [38, 39]. NLR, MLR, and PLR have been used as markers of systemic inflammation [40]. Increased NLR, MLR, and PLR have been shown to be associated with poor outcomes in patients with cancer treated with immunotherapy [40–43]. This may be due to the fact that ICIs rely on the host immune system for their efficacy [44]. Therefore, immune dysfunction likely decreases the likelihood that patients will respond favorably to ICI. Although tissue-based macrophages have differing effects on the inflammatory process depending on whether they are M1 or M2 macrophages [45], MLR was a stronger predictor of survival in our model. It should be noted that NLR, MLR, and PLR were highly correlated (Pearson correlation

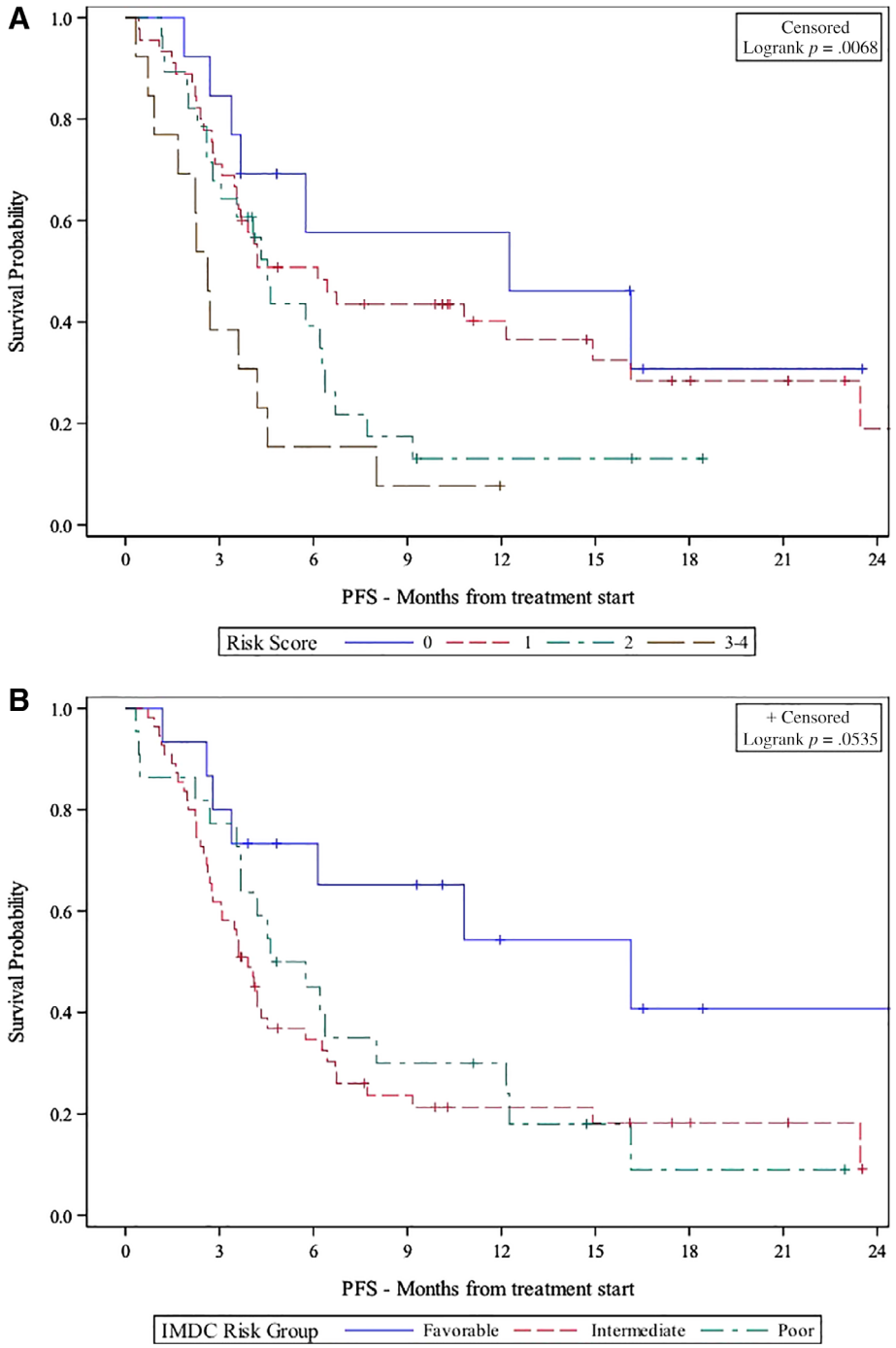

Figure 2. Emory risk group versus IMDC risk group stratification and association with PFS. **(A):** Emory risk group stratification. 0 = good risk, 1 = intermediate risk, 2 = poor risk, 3–4 = very poor risk. **(B):** IMDC risk group stratification.
Abbreviations: IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; PFS, progression-free survival.

coefficients >0.678, all $p < .0001$) and had similar C-statistics in our model. Therefore, any of these values may provide value as a prognostic biomarker in patients with mRCC treated with ICI. Although the IMDC criteria include thrombocytosis and neutrophilia as risk factors, MLR may be a more effective predictor of survival. The results of this study build upon previous evidence that suggests that the inclusion of a systemic inflammation variable may be helpful in updated prognostic scoring models for patients treated with ICI.

Although this study has significant clinical relevance, the results are hypothesis-generating, and several limitations should be mentioned. First, this is a retrospective cohort that is subject to selection bias. We attempted to decrease the effect of this on the results of the study by including all patients at our center who received at least one dose of ICI regardless of their RCC histology or other baseline characteristics. It should also be mentioned that BMI is an imperfect marker of body composition, particularly given the increasing prevalence of obesity in the U.S. [46]. We chose

BMI as a marker of body composition because it is cheap and readily available to practicing oncologists. Finally, we included all patients in our survival analysis regardless of the number of lines of therapy prior to treatment with ICI. Given that survival is likely affected by the number of prior lines of therapy, we attempted to minimize the confounding effect by controlling for this in MVA. Future studies are required to validate the results of this study and to elucidate the underlying biology explaining how metastatic sites, body composition, and systemic inflammation affect host immune responses to ICI.

Conclusion

We developed a novel risk scoring system for patients with mRCC treated with ICI-based treatment regimens. The results from this study suggest that it may be useful to update prognostic scoring systems for ICI-treated patients with mRCC to include BMI as a body composition marker, number and sites of metastatic disease to capture the effect of the TME, and MLR as a surrogate of systemic inflammation. Risk scoring may be particularly useful for patients being considered for treatment with immunotherapy, given that durable clinical responses are only seen in a subset of patients. This study is hypothesis generating, and future studies are needed to validate these findings in a larger, prospective study.

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Disclosures

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