

# Modified Glasgow Prognostic Score associated with survival in metastatic renal cell carcinoma treated with immune checkpoint inhibitors

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## ABSTRACT

**Background** The modified Glasgow Prognostic Score (mGPS) is a composite biomarker that uses albumin and C reactive protein (CRP). There are multiple immune checkpoint inhibitor (ICI)-based combinations approved for metastatic renal cell carcinoma (mRCC). We investigated the ability of mGPS to predict outcomes in patients with mRCC receiving ICI.

**Methods** We retrospectively reviewed patients with mRCC treated with ICI as monotherapy or in combination at Winship Cancer Institute between 2015 and 2020. Overall survival (OS) and progression-free survival (PFS) were measured from the start date of ICI until death or clinical/radiographical progression, respectively. The baseline mGPS was defined as a summary score based on pre-ICI values with one point given for CRP>10 mg/L and/or albumin<3.5g/dL, resulting in possible scores of 0, 1 and 2. If only albumin was low with a normal CRP, no points were awarded. Univariate analysis (UVA) and multivariate analysis (MVA) were carried out using Cox proportional hazard model. Outcomes were also assessed by Kaplan-Meier analysis.

**Results** 156 patients were included with a median follow-up 24.2 months. The median age was 64 years and 78% had clear cell histology. Baseline mGPS was 0 in 36%, 1 in 40% and 2 in 24% of patients. In UVA, a baseline mGPS of 2 was associated with shorter OS (HR 4.29, 95% CI 2.24 to 8.24, p<0.001) and PFS (HR 1.90, 95% CI 1.20 to 3.01, p=0.006) relative to a score of 0; this disparity in outcome based on baseline mGPS persisted in MVA. The respective median OS of patients with baseline mGPS of 0, 1 and 2 was 44.5 (95% CI 27.3 to not evaluable), 15.3 (95% CI 11.0 to 24.2) and 10 (95% CI 4.6 to 17.5) months (p<0.0001). The median PFS of these three cohorts was 6.7 (95% CI 3.6 to 13.1), 4.2 (95% CI 2.9 to 6.2) and 2.6 (95% CI 2.0 to 5.6), respectively (p=0.0216). The discrimination power of baseline mGPS to predict survival outcomes was comparable to the IMDC risk score based on Uno's c-statistic (OS: 0.6312 vs 0.6102, PFS: 0.5752 vs 0.5533).

**Conclusion** The mGPS is prognostic in this cohort of patients with mRCC treated with ICI as monotherapy

or in combination. These results warrant external and prospective validation.

## INTRODUCTION

Kidney cancer was diagnosed in 73,750 people in the USA and was responsible for approximately 13,830 deaths in 2020.<sup>1</sup> Renal cell carcinoma (RCC) comprises approximately 85% of primary cancers of the kidney with clear cell histology making up 75%–85% of RCC.<sup>2</sup> While the mainstay of therapy for localized disease is surgery, the 16% of patients who present with de novo metastatic disease and approximately half of the patients with locally advanced disease that recur after definitive surgery are treated with systemic therapy. This cohort with metastatic renal cell carcinoma (mRCC) has a 5-year survival rate of 13% based on population-level data from 2010 to 2016, although newer therapies are poised to improve outcomes.<sup>3</sup>

Several risk models exist to prognosticate and direct first-line therapy. The Memorial Sloan Kettering Cancer Center (MSKCC) prognostic model incorporates time from diagnosis to treatment, Karnofsky performance status (KPS), serum lactate dehydrogenase (LDH), calcium and hemoglobin, whereas the more widely used International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria replaces LDH with serum neutrophil and platelet count.<sup>4,5</sup> These risk scores have been used in clinical trials to risk stratify patients and have also been incorporated into the approved indications for new therapies. However, the IMDC criteria were developed based on survival data from patients treated with antiangiogenic therapies including sunitinib, sorafenib

and bevacizumab. The MSKCC model was derived from patients being treated with first-line interferon alfa-2a. Notably, neither prognostic model includes patients treated with contemporary immunotherapy, most commonly immune checkpoint inhibitors (ICIs) but also high-dose interleukin (IL)-2 in rare circumstances. Given our current practice, exploration of alternative and applicable prognostic tools is needed. Approved and commonly used in the first-line setting for clear cell histologies are the combinations of pembrolizumab and axitinib, pembrolizumab and lenvatinib, ipilimumab and nivolumab, axitinib and avelumab, and most recently, nivolumab and cabozantinib.<sup>6–10</sup> The ubiquitous presence of ICI in the treatment paradigm for mRCC warrants consideration of a prognostic score capable of predicting outcomes in patients treated specifically with immunotherapy.

Systemic inflammation has been identified as a contributor to resistance to ICI across multiple malignancies including RCC.<sup>11–15</sup> The original Glasgow Prognostic Score was developed by McMillan *et al* as a prognostic score in metastatic non-small cell lung cancer (NSCLC) and is based on inflammatory biomarkers; a point is assigned for a C reactive protein (CRP) of >10 mg/L and/or an albumin of <3.5 g/dL culminating in stratification of patients into low (0 points), intermediate (one point) and high (two points) risk.<sup>16</sup> The score's prognostic capabilities were improved on by the modified Glasgow Prognostic Score (mGPS), which differs in that a point is only awarded for a low albumin if the CRP is elevated, thus more heavily weighting the inflammatory component of the score.<sup>17</sup> The mGPS has been validated in non-metastatic clear cell RCC treated with nephrectomy<sup>18–20</sup> and more recently in a small cohort of patients with metastatic disease treated with nivolumab monotherapy in the second-line setting after targeted therapy.<sup>21</sup> We sought to investigate its prognostic significance more broadly in patients with mRCC treated with immunotherapy in any line of therapy.

## PATIENTS AND METHODS

We conducted a retrospective analysis of 156 patients with biopsy-proven mRCC. Included were those who received ICI in the form of an antiprogrammed cell death protein 1 (PD-1) or anti-programmed cell death protein ligand 1 (PD-L1) monoclonal antibody, either as monotherapy or in combination with an antiangiogenic agent, anti-CTLA4 therapy, or experimental therapy in any line of treatment at the Winship Cancer Institute of Emory University between the years of 2015 and 2020. Patients were identified through a drug administration pharmacy database. Demographic and clinical data including age, sex, race, smoking status, Eastern Cooperative Oncology Group (ECOG) performance status, tumor histology, sites of metastatic disease, body mass index (BMI), baseline laboratory data within 2 weeks of receiving treatment with ICI as well as treatment course and response were

extracted from the electronic medical record. Baseline laboratory values collected included albumin and CRP.

The primary outcomes assessed include progression-free survival (PFS), overall survival (OS) and clinical benefit rate (CBR). PFS was defined as the duration of time in months between ICI initiation and clinical or radiographical progression or death and OS as the time between ICI initiation and death. Radiographical response and progression were defined using the Response Evaluation Criteria in Solid Tumors (RECIST) V.1.1. Univariate (UVA) and multivariate (MVA) analyses were undertaken using Cox proportional hazard model for OS and PFS. In MVA, the model was fitted followed by backward variable elimination under a removal criterion of significance level  $p > 0.1$ . The covariates to be adjusted included age, sex, race, baseline BMI, sites of metastases, ECOG performance status, clear cell histology and prior lines of therapy. The HR and its 95% CI were reported. The overall significance level was set at  $p < 0.05$ . The relationship between mGPS and survival outcomes (OS and PFS) was assessed using Kaplan-Meier analysis. Statistical analysis was conducted using SAS V.9.4, and SAS macros were developed by the Biostatistics Shared Resource at Winship Cancer Institute.<sup>22</sup> The discrimination ability of baseline mGPS and IMDC risk score in predictive survival outcomes was measured by Uno's c-statistics.<sup>23</sup>

## RESULTS

### Baseline demographic and disease characteristics

We identified 156 patients who met the inclusion criteria (table 1). The median age was 64; 69% were male; and 80% were Asian or white. The majority of patients had a ECOG performance score 0 (36%) or 1 (49%). The predominant histology was clear cell (78%). Seventy-five percent of patients had lung metastases, while 37% and 29% had bone and liver metastases, respectively. Most patients were receiving first-line (38%) or second-line (44%) immunotherapy. Fifty-seven percent of patients received a PD-1 agent as monotherapy; 29% received combination anti-PD-1 and anticytotoxic T-lymphocyte-associated protein-4 (CTLA-4) therapy; 10% received an anti-PD-1 or anti-PD-L1 agent in combination with an antiangiogenic therapy (either a monoclonal antibody or tyrosine kinase inhibitor targeting vascular endothelial growth factor (VEGF)); and 4% were treated with an anti-PD-1 agent in addition to an experimental therapy. Baseline mGPS was 0 in 37%, 1 in 40% and 2 in 24% of patients. When stratified according to IMDC risk category, 15%, 61% and 24% of the cohort were favorable, intermediate and poor risk, respectively.

### Baseline mGPS and survival outcomes in univariate and multivariate analyses

Multiple variables including mGPS at baseline and their association with PFS and OS were investigated in univariate analysis (UVA) and multivariate analysis (MVA). In UVA, a baseline mGPS of 2 was associated with shorter OS

**Table 1** Patient characteristics

Characteristics	n=156 (% or range)
Age (years) (median)	64 (23–90)
Male gender	108 (69.2)
Race	
White/Asian	125 (80.1)
Black	31 (19.9)
Ever smoker	78 (50.0)
ECOG Performance Score	
0	56 (36.4)
1	75 (48.7)
2–3	23 (14.9)
Histology	
Clear cell	118 (78.1)
Non-clear cell	33 (21.9)
Sites of metastases	
Lymph node	93 (59.6)
Bone	58 (37.2)
Lung	117 (75)
Brain	18 (11.5)
Liver	45 (28.8)
Number of prior therapies	
0	59 (37.8)
1	69 (44.2)
2–6	28 (17.9)
Therapy type	
Anti-PD-1 monotherapy	89 (57.1)
Anti-PD-1+anti-CTLA-4	45 (28.8)
Anti-PD-1+anti-VEGF	10 (6.4)
Anti-PD-L1+anti-VEGF	5 (3.2)
Anti-PD-1+experimental therapy	7 (4.5)
BMI (median)	26.3 (16.3–56.4)
Baseline lab values	
Albumin (median)	3.75 (2.0–4.7)
CRP (median)	14.7 (0.76–297.0)
Baseline mGPS	
0	57 (36.6)
1	62 (39.7)
2	37 (23.7)
IMDC risk score	
Favorable	23 (14.8)
Intermediate	96 (61.5)
Poor	37 (23.7)

BMI, Body Mass Index; CRP, C reactive protein; CTLA-4, cytotoxic T-lymphocyte-associated protein-4; ECOG, Eastern Cooperative Oncology Group; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; mGPS, modified Glasgow Prognostic Score; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; VEGF, vascular endothelial growth factor.

(HR 4.29, CI 2.24 to 8.24,  $p < 0.001$ ) and PFS (HR 1.90, CI 1.20 to 3.01,  $p = 0.006$ ) relative to a score of 0 (table 2). The prognostic relevance of a high baseline mGPS persisted in MVA (table 3). An mGPS of 2 was associated with worse OS (HR 3.61, CI 1.78 to 7.31,  $p < 0.001$ ) and PFS (HR 1.87, CI 1.17 to 2.97,  $p = 0.008$ ). There was a trend in association of baseline mGPS of 1 and shorter OS (HR 1.82, CI 0.94 to 3.54,  $p = 0.076$ ), although this was not statistically significant.

### Baseline mGPS and survival outcomes in Kaplan-Meier analysis

Median follow-up was 24.2 months. The median overall survival (mOS) of the cohort was 20.8 months (95% CI 15.7 to not evaluable [NE]) with 66.6% of patients alive at 12 months and 48.6% at 24 months. The median progression-free survival (mPFS) was 4.4 months (95% CI 3.5 to 6.0) with 26% of patients without progression at 12 months and 18.7% at 24 months.

The mOS of patients with baseline mGPS of 0, 1 and 2 was 44.5 (95% CI 27.3 to NE), 15.3 (95% CI 11.0 to 24.2) and 10 (95% CI 4.6 to 17.5) months, respectively ( $p < 0.0001$ ) (figure 1A). The mPFS of these three cohorts was 6.7 (95% CI 3.6 to 13.1), 4.2 (95% CI 2.9 to 6.2) and 2.6 (95% CI 2.0 to 5.6) months, respectively ( $p = 0.0216$ ) (figure 2A). The mOS stratified by IMDC risk score differed significantly ( $p < 0.0001$ ), but the mPFS did not ( $p = 0.0728$ ) (figures 1B and 2B). The discrimination power of baseline mGPS to predict survival outcomes including OS and PFS was slightly improved compared with IMDC risk stratification based on Uno's c-statistic for each (table 3).

### DISCUSSION

Immunotherapy has been fully integrated into the first-line treatment of mRCC. The IMDC and MSKCC risk scoring systems help to prognosticate before the initiation of treatment but were developed during the era of targeted therapy, involve some subjectivity as they incorporate performance status and involve multiple factors which can make them more cumbersome to use. In the largest cohort of patients with mRCC examined to date, we found the mGPS to be prognostic in patients treated with immunotherapy in any line of therapy and comparable to the IMDC risk score in its ability to predict survival outcomes.

There are multiple risk scoring systems available for prognostication in mRCC, all of which include some combination of laboratory and clinical factors such as performance status. The French model was developed by Negrier *et al.*<sup>24</sup> based on the study of 782 patients treated with cytokine therapy (IL-2 or interferon). In their model, ECOG performance status, number of metastatic sites, time from diagnosis to metastatic disease, hemoglobin and biochemical evidence of inflammation (defined as erythrocyte sedimentation rate >100 or CRP >50) could be used to estimate the likelihood of rapid progression while

**Table 2** UVA and MVA\* analyses of mGPS and survival outcomes

Variable	UVA				MVA*			
	OS		PFS		OS		PFS	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Baseline mGPS	4.29 (2.24–8.24)	<0.001†	1.90 (1.20–3.01)	0.006†	3.61 (1.78–7.31)	<0.001†	1.87 (1.17–2.97)	0.008†
	2 (n=37)		2.78 (1.49–5.17)	0.001†	1.82 (0.94–3.54)	0.076	1.19 (0.77–1.85)	0.435
	1 (n=62)		–	–	–	–	–	–
	0 (n=57)		–	–	–	–	–	–

\*The Cox proportional hazard model was fitted followed by backward variable elimination with a significance level of  $p < 0.1$ . The covariables controlled for included age, sex, race, baseline Body Mass Index, sites of metastases, ECOG performance status, clear cell histology and prior lines of therapy.

†Statistical significance at  $\alpha < 0.05$ .

ECOG, Eastern Cooperative Oncology Group; mGPS, modified Glasgow Prognostic Score; MVA, multivariate analysis; OS, overall survival; PFS, progression-free survival; UVA, univariate analysis.

**Table 3** Discrimination power of mGPS and IMDC in predicting survival outcomes based on Uno's concordance statistic

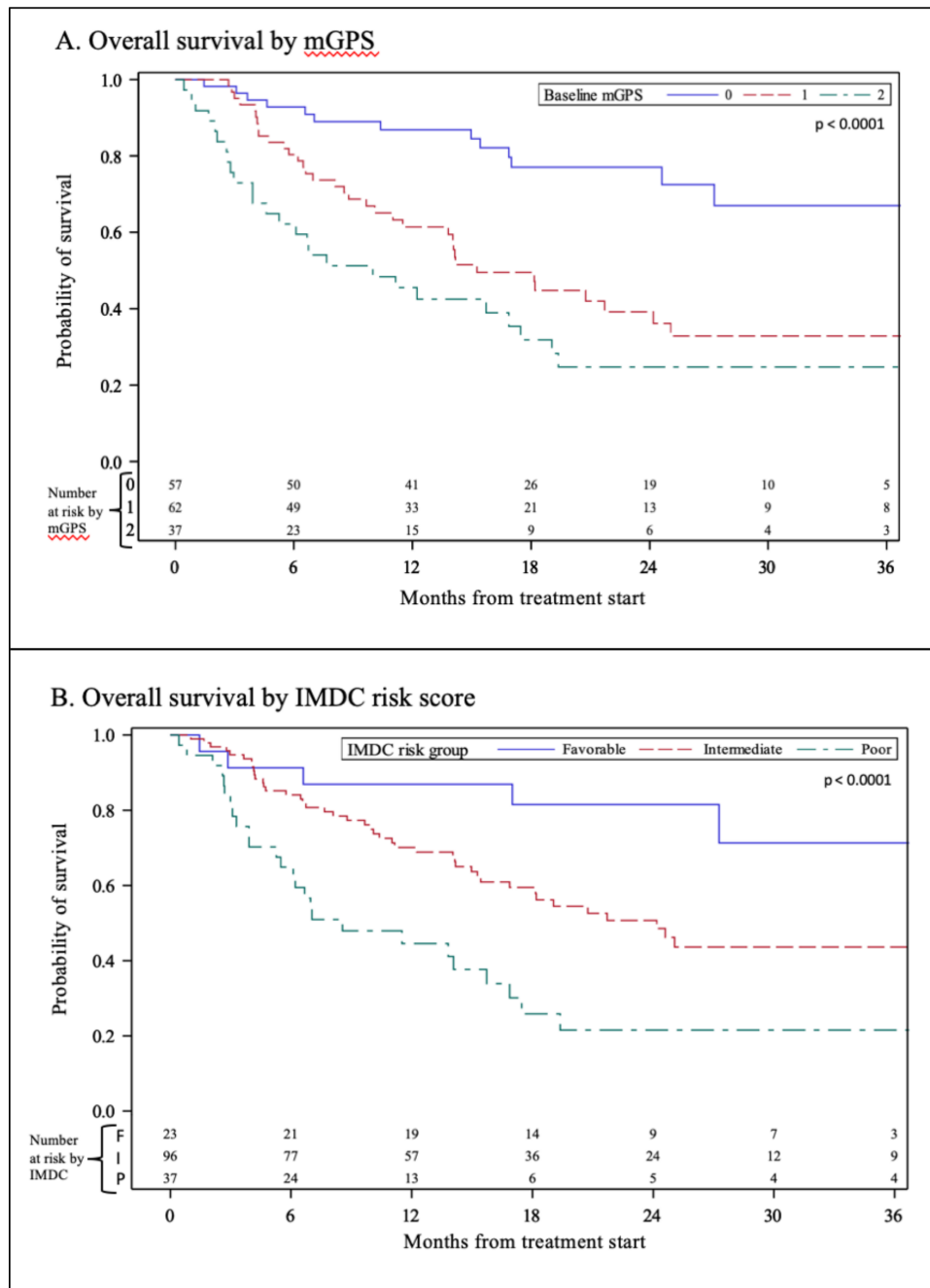
	OS		PFS	
	Estimate	SE*	Estimate	SE*
mGPS	0.6312	0.0435	0.5752	0.0385
IMDC	0.6102	0.0397	0.5533	0.0347

\*SEs are calculated using 5000 perturbation samples.

IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; mGPS, modified Glasgow Prognostic Score; OS, overall survival; PFS, progression-free survival.

receiving cytokine therapy. The Cleveland Clinic Foundation model was developed in 2007 via analysis of 120 patients treated with bevacizumab, sorafenib, sunitinib or axitinib during which a composite of five prognostic factors were found to predict mPFS, including corrected calcium, neutrophil count, platelet count, ECOG performance status and time from diagnosis to treatment of <2 years.<sup>25</sup> The International Kidney Cancer Working Group model incorporates nine factors total to prognosticate in patients also receiving antiangiogenic therapy: four clinical factors including treatment received, KPS, number of metastatic sites, and prior immunotherapy and five lab parameters including pre-treatment hemoglobin, LDH, alkaline phosphatase, neutrophils and calcium.<sup>26</sup> As mentioned previously, the IMDC model is the most widely used in clinical practice and trial development, differs only slightly from the MSKCC model and reflects many of the factors incorporated into in prior models: time from diagnosis to systemic therapy, KPS performance status, calcium, and CBC parameters including hemoglobin, neutrophil and platelet counts.<sup>5</sup> It was originally derived from a cohort of 1028 patients treated with targeted therapy and those with favorable, intermediate and poor risk scores were found to have a mOS of 43, 23 and 8 months, respectively. The IMDC model has been applied retrospectively as a prognostic tool in patients receiving second-line immunotherapy and acquired a predictive component when applied prospectively in the Checkmate214 phase III trial of ipilimumab and nivolumab versus sunitinib in mRCC.<sup>7 27</sup> However, the model has multiple components and incorporates some subjectivity in the form of performance status assessment, a facet worth noting since oncologists have been shown to overestimate performance status compared with how patients view their own functioning.<sup>28</sup> The applicability of the mGPS is intriguing given its two-factor composition, reliance solely on biomarkers and its reflection of underlying systemic inflammation, a suspected mode of resistance to immunotherapy.

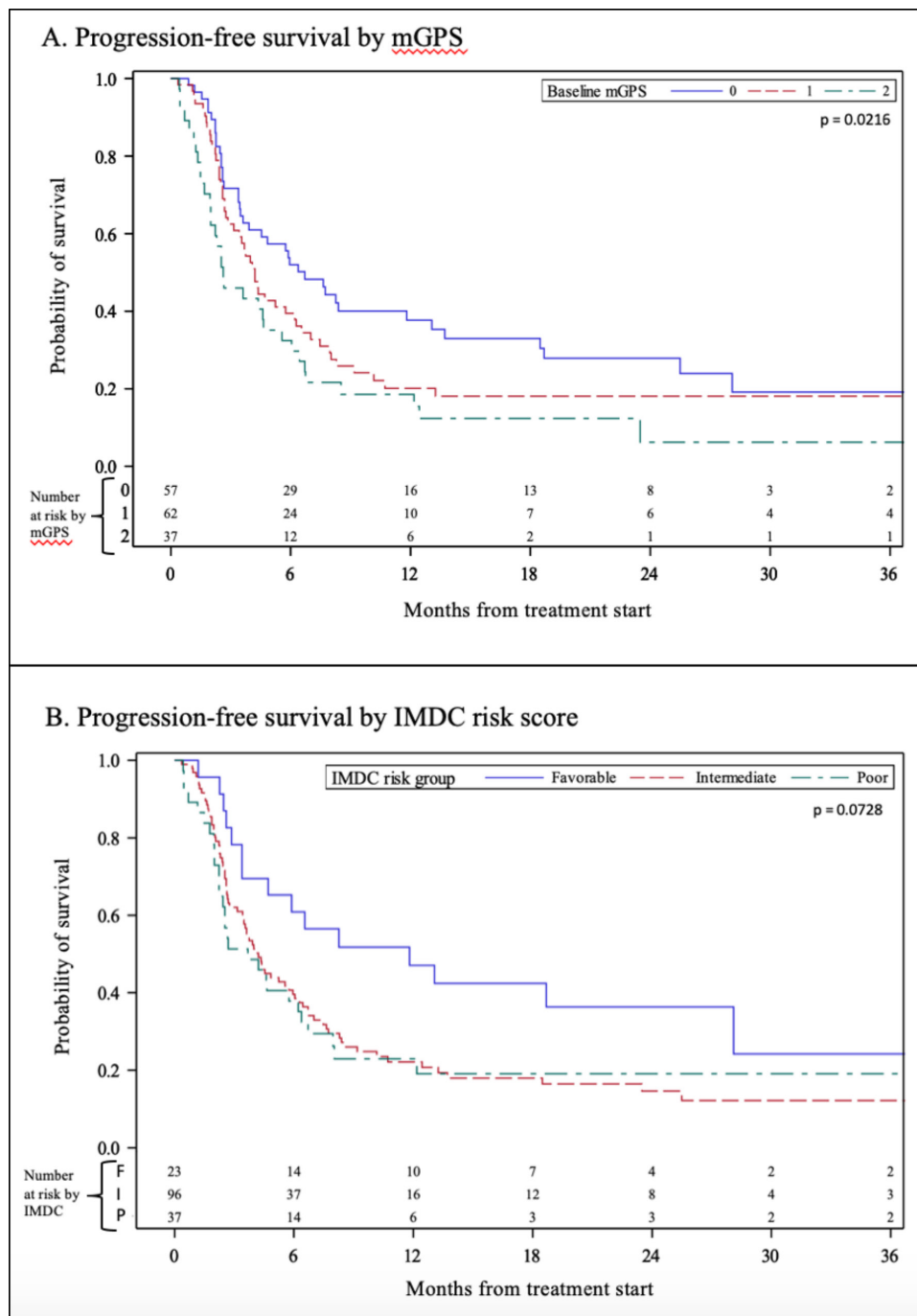
There are ample data to suggest that systemic inflammation portends poorer responses to ICI across genitourinary cancers including RCC.<sup>11–15 29</sup> Immune checkpoint blockade inhibits the attenuation of T-cell activation centrally in the secondary lymphoid organs in the case of



**Figure 1** Kaplan-Meier estimates of (A) baseline mGPS versus (B) IMDC risk group stratification and association with overall survival. IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; mGPS, modified Glasgow Prognostic Score.

anti-CTLA-4 agents and in peripheral tissues via the PD-1/PD-L1 targeted agents.<sup>30</sup> Intrinsic resistance to immunotherapy is felt to be related to low tumor immunogenicity and patient genetic factors affecting antigen presentation and T-cell tumor infiltration. However, outside of intrinsic tumor and host factors, an immunosuppressive milieu in the tumor microenvironment (TME) contributes as well.<sup>31–37</sup> The combination and interactions of tumor, immune, and endothelial cells, surrounding stromal cells of the extracellular matrix and soluble chemokines and cytokines constitute the very dynamic TME.<sup>38</sup> Adequate infiltration of a tumor by T cells may not be sufficient to

ensure response to checkpoint inhibition if an increased number of myeloid derived suppressor cells (MDSCs) and CD4+ regulatory T (Treg) cells locally dampen the cytotoxic antitumor effects mostly through cytokine signaling.<sup>39</sup> In metastatic urothelial carcinoma, a T-cell inflamed gene expression profile characterized by interferon gamma (IFN- $\gamma$ ) signaling predicted response to pembrolizumab in KEYNOTE052.<sup>40</sup> However, immunosuppressive cytokines like transforming growth factor- $\beta$  and IL-10 and proinflammatory mediators like IL-6, tumor necrosis factor (TNF) and IL-1 $\beta$  simultaneously contribute to MDSC upregulation and subsequent T-cell



**Figure 2** Kaplan-Meier estimates of (A) baseline mGPS versus (B) IMDC risk group stratification and association with progression-free survival. IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; mGPS, modified Glasgow Prognostic Score.

exhaustion.<sup>41,42</sup> Elevated levels of TNF and IL-6 are highly associated with malignancy and may further attenuate these ICI-induced cytotoxic T-cell responses.<sup>43</sup> Depletion of intratumoral MDSCs and Tregs has been shown to potentiate PD-1/PD-L1 blockade in melanoma and breast tumors, and MDSC enrichment has been associated with lack of response to ipilimumab in patients with metastatic melanoma.<sup>44–46</sup> Thus, chronic inflammation may contribute to tumor immune evasion at baseline but especially in the setting of ICI therapy.

The mGPS may be particularly relevant as a prognostic score in mRCC treated with ICI as it reflects some of these underlying mechanisms of immunotherapy resistance. IL-6, TNF- $\alpha$  and IL-1 $\beta$ , same inflammatory cytokines that lead to MDSC upregulation and T-cell anergy, are known to lead to increased production of CRP by hepatocytes and also correlate with larger tumor size and higher stage in RCC specifically.<sup>47</sup> Potentially in response to its angiogenic and antiapoptotic properties, elevated CRP correlates with poorer prognosis across urological

cancers, and in both patients with localized RCC undergoing nephrectomy as well as those with metastatic disease.<sup>48–50</sup> In fact, there are data to suggest that RCC tissue itself produces CRP in response to intratumoral IL-6 relative to adjacent normal kidney parenchyma.<sup>51</sup> We also know that this same cytokine profile has catabolic effects and plays a role in suppressing albumin production by the liver in malignant states.<sup>52,53</sup> It is not surprising then that the mGPS as the *composite* of these biomarkers of inflammation is capable of predicting response and survival in response to ICI. Fujiwara *et al* found the mGPS to be prognostic in 45 patients with mRCC treated with nivolumab in the second line.<sup>21</sup> We have expanded on their work to include a larger cohort treated with ICI as a single agent but also in combination with another ICI, antiangiogenic therapy or a novel experimental treatment. In addition, 38% of our cohort received ICI in the first line setting. This reflects the way that ICIs are used in our current treatment paradigm and further supports the use of the mGPS as a prognostic score in this patient population.

An easy-to-use, inexpensive and accessible score capable of prognosticating in patients with mRCC receiving immunotherapy like the mGPS is valuable. Both serum assays cost about 15 dollars, equating to a sum much smaller than those typically encountered in oncological care. However, the hunt for a *predictive* biomarker capable of helping clinicians navigate the crowded first-line therapy space and decide on an ICI and targeted therapy combination like axitinib and pembrolizumab versus an ICI duo such as ipilimumab and nivolumab is desperately needed. The IMDC remains the only prospectively applied predictive biomarker in mRCC to date.<sup>7</sup> While tumor PD-L1 expression has borne out in other malignancies, it is more controversial in RCC. In CHECKMATE214, among those with PD-L1 expression  $\geq 1\%$ , the mPFS was 22.8 vs 5.9 months (HR 0.46, 95% CI 0.31 to 0.67) in those who received ipilimumab plus nivolumab versus sunitinib, respectively; conversely, those with negative PD-L1 did not derive benefit from the ICI combination (11.0 vs 10.4 months, HR 1.00, 95% CI 0.80 to 1.26). However, the mOS and overall response rate benefit was seen with ipilimumab plus nivolumab over sunitinib regardless of PD-L1 status.<sup>7</sup> In the KEYNOTE426 trial of pembrolizumab plus axitinib versus sunitinib, mPFS, mOS and ORR were all improved with ICI-based therapy regardless of PD-L1 expression.<sup>6</sup> PD-L1 does not account for the entirety of response to ICI, potentially in part due to tumor heterogeneity within a tumor, between metastatic sites and over time as well as the variable threshold definitions for positivity across different assays. Another potential biomarker is tumor mutational burden (TMB), the concept being that tumors with higher TMB are more immunogenic due to an increase in neoantigen presentation. RCC has a low average TMB of 1.1 mutations/Mb compared as high as 300 mutations/Mb in other cancers like melanoma, although it does have the highest frequency of notably immunogenic insertion and

deletion mutations.<sup>54,55</sup> In practice, TMB has not manifested as the elusive predictive biomarker to ICI in RCC. In an exploratory analysis of patients treated in IMmotion150 with atezolizumab plus bevacizumab versus sunitinib, TMB quartile did not correlate with response.<sup>56</sup> This same study elegantly assessed whether an angiogenic gene expression signature or an immune signature characterized by increased CD8+ T-cell infiltration, and IFN- $\gamma$  signaling could predict response to anti-VEGF and ICI therapy, respectively. A high angiogenic signature did not impact PFS in response to atezolizumab plus bevacizumab versus sunitinib or atezolizumab monotherapy versus sunitinib; however, a high immune signature correlated with increased PFS with atezolizumab plus bevacizumab over sunitinib. A biomarker capable of determining who should see ICI versus ICI in combination with anti-VEGF therapy versus anti-VEGF monotherapy in the first-line remains one of the holy grail pursuits in mRCC at this time.

There are several limitations to our findings. While our cohort tripled the size of the only other existing investigation of mGPS in mRCC, it is still a retrospective analysis that warrants external validation in a larger group of patients. We attempted to combat selection bias by examining 156 contiguous patients treated at our institution between 2015 and 2020. While our look at ICI both as monotherapy and in combination with immunotherapy and non-immunotherapy treatments reflects the real-world use of immunotherapy both in clinical trials and community practice, there is the potential for the non-ICI component of the treatment to influence the findings. In addition, we selected patients who received an ICI of any kind. Approximately 10% of our cohort received an ICI in combination with an anti-VEGF agent, but the majority of first-line options fall into this category of combination therapy; thus, our study population is not entirely representative of current practice and a future exploration of the prognostic significance of mGPS in a more homogeneous cohort receiving ICI plus anti-VEGF therapy is needed. Because we investigated ICI given in any line of therapy, it is possible that baseline lab values could have been affected by the patient's status and response after the prior treatment. The mGPS two-factor composition makes it simple and easy-to-use, but it is worth noting that the half-life of CRP and albumin are 19 hours and 21 days, respectively. A strength of the score is its dynamicity with the downside of its susceptibility to impact by acute clinical status changes. Inflammatory markers can be affected by non-malignant conditions such as sepsis, and while we collected the values within 2 weeks of ICI initiation, it was not possible to account for all confounding factors, clinically known and unknown. Lastly, we investigated prognostic relevance of the baseline, pretreatment mGPS. Thus, we did not capture how the mGPS changes during the course of treatment. There are data to suggest that post-therapy mGPS and the delta across treatment timepoints hold prognostic significance in other malignancies such as esophageal cancer, colorectal cancer and

NSCLC.<sup>57–59</sup> We plan to investigate the significance of mGPS over time in patients with mRCC in future analyses.

## CONCLUSION

Higher baseline mGPS was found to be associated with shorter PFS and OS in patients with mRCC treated with ICI in any line of therapy. Given that the components of the score directly reflect systemic inflammation, a known factor in the presence or development of ICI resistance, it may have particular relevance as we navigate the ever-expanding first-line ICI combinations. Future work is needed to determine whether mGPS is prognostic in more homogeneous cohorts, including those receiving ICI as monotherapy, in tandem with other types of immunotherapy or in combination with antiangiogenic agents. As a prognostic biomarker, the intention of the score's use is not to prevent patients from receiving immunotherapy but rather to guide expectations about response to therapy. Our findings indicate that mGPS may be a useful clinical tool and should be validated prospectively.

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**Contributors** Conception/design: JTB, WBH, VAM, and MAB; provision of patients: EEH, GAR, SC, LY, SSJ, KO, BN, BCC, OK, WBH, VAM, and MAB; collection and/or assembly of data: JTB, JMS, DM, and DR; data analysis and interpretation: JTB, YL, and MAB; manuscript writing: JTB, YL, and MAB; final approval of the manuscript: JTB, YL, JMS, DM, DR, EEH, GAR, SC, LY, SSJ, HK, KO, BN, BCC, OK, WBH, VAM, and MAB.

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