Original Article

Sarcopenia and Modified Glasgow Prognostic Score Predict Postsurgical Outcomes in Localized Renal Cell Carcinoma

Michelle I. Higgins, BA [1]; Dylan J. Martini, BA[2,3]; Dattatraya H. Patil, MBBS, MPH [1]; Reza Nabavizadeh, MD[1]; Sean Steele, BA[1]; Milton Williams, MD[4]; Shreyas S. Joshi, MD, MPH[1]; Vikram M. Narayan, MD[1]; Aarti Sekhar, MD[5]; Sarah P. Psutka, MD, MS [6]; Kenneth Ogan, MD[1]; Mehmet Asim Bilen, MD [2,3]; and Viraj A. Master, MD, PhD[1]

BACKGROUND: Body composition and inflammation are gaining importance for prognostication in cancer. This study investigated the individual and combined utility of the preoperative skeletal muscle index (SMI) and the modified Glasgow Prognostic Score (mGPS) for estimating postoperative outcomes in patients with localized renal cell carcinoma (RCC) undergoing nephrectomy. **METHODS:** The authors performed a retrospective review of 352 patients with localized RCC. SMI was measured via computed tomography or magnetic resonance imaging. Patients met the criteria for sarcopenia by body mass index– and sex-stratified thresholds. Multivariable and Kaplan-Meier analyses of associations of sarcopenia and mGPS with overall survival (OS), recurrence-free survival (RFS), and cancer-specific survival (CSS) were performed. Variables were analyzed independently and combined into risk groups: low risk (nonsarcopenic, low mGPS), medium risk (sarcopenia only), medium risk (inflammation only), and high risk (sarcopenic, high mGPS). Receiver operating characteristic (ROC) curves were used to analyze risk groups in comparison with the Stage, Size, Grade, and Necrosis (SSIGN) score and the modified International Metastatic RCC Database Consortium (IMDC) score. **RESULTS:** The majority of the patients were at stage pT3 (63%), 39.5% of the patients were sarcopenic, and 19.3% had an elevated mGPS at the baseline. The median follow-up time was 30.4 months. Sarcopenia and mGPS were independently associated with worse OS (hazard ratio for sarcopenia, 1.64; $P = .006$; hazard ratio for mGPS, 1.72; $P = .012$), CSS, and RFS. Risk groups had an increasing association with worse RFS ($P = .015$) and CSS ($P = .004$) but not OS ($P = .087$). ROC analyses demonstrated a higher area under the curve for risk groups in comparison with the SSIGN and IMDC scores at 5 years. **CONCLUSIONS:** Sarcopenia and an elevated mGPS were associated with worse clinical outcomes in this study of patients with localized RCC. This has implications for preoperative prognostication and treatment decision-making. ***Cancer* 2021;127:1974-1983**.

LAY SUMMARY:

- Kidney cancer is a disease with a wide variety of outcomes. Among patients undergoing surgical removal of the kidney for cancer that has not spread beyond the kidney, many are cured, but some experience recurrence.
- Physicians are seeking ways to better predict who is at risk for recurrence or death from kidney cancer.
- This study has evaluated body composition and markers of inflammation before surgery to predict the risk of recurrence or death after surgery. Specifically, low muscle mass and an elevated inflammation score (the modified Glasgow Prognostic Score) have been associated with an increased likelihood of recurrence of kidney cancer and death.

KEYWORDS: body composition, inflammation, prognosis, renal cell carcinoma, risk stratification, sarcopenia.

INTRODUCTION

Renal cell carcinoma (RCC) is the 6th most common type of cancer in men and the 10th most common in women worldwide and is estimated to cause more than 140,000 deaths annually.[1] The prognosis for RCC is heterogeneous: patients with localized RCC have a 5-year overall survival (OS) rate of 92% versus 53% for patients with locally advanced (stage III) disease and 8% for patients with metastatic disease.[2] Treatment options for localized RCC include active surveillance, thermal ablation, and surgery. Approximately one-quarter of patients experience tumor recurrence within 5 years of surgery.[3] Therefore, prognostication regarding the risk of local or metastatic recurrence is of critical importance for informing treatment election. Current prognostic models focus on tumor pathologic and histologic characteristics available only after definitive surgery, such as the TNM staging system. For instance, a commonly used grading system is the Stage, Size, Grade, and Necrosis (SSIGN) score.[4] Although these tumor-centric prognostic models are validated in RCC, a growing body of evidence suggests that patient-specific factors,

Corresponding Author: Viraj A. Master, MD, PhD, Department of Urology, Emory University School of Medicine, 1365 Clifton Rd NE, Building B, Ste 1400, Atlanta, GA 30322 (vmaster@emory.edu).

[1]Department of Urology, Emory University School of Medicine, Atlanta, Georgia; [2]Department of Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, Georgia; [3]Winship Cancer Institute of Emory University, Atlanta, Georgia; [4]Department of Urology, University of Alabama, Birmingham, Alabama; [5]Department of Radiology and Imaging Sciences, Emory University School of Medicine, Atlanta, Georgia; [6]Department of Urology, University of Washington, Seattle, Washington

Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.33462, **Received:** November 17, 2020; **Revised:** December 18, 2020; **Accepted:** December 22, 2020, **Published online** March 24, 2021 in Wiley Online Library (wileyonlinelibrary.com)

such as body composition and systemic inflammation, can improve prognostication for many types of cancer, but they remain largely underused.[5,6]

Body mass index (BMI), the most commonly used descriptor of body composition, is a nonspecific measure with limited prognostic utility in RCC.[7,8] Skeletal muscle mass provides an alternative, more nuanced assessment of body composition. Sarcopenia, the severe deficiency of skeletal muscle mass, is associated with an increased risk of mortality and recurrence after nephrectomy in both localized and metastatic RCC.[8-10] In addition, inflammation is a hallmark of cancer in both localized and metastatic settings and plays an important role in RCC.[6] In fact, a well-established prognostic model for metastatic RCC, the International Metastatic RCC Database Consortium (IMDC) score, relies on a combination of serum inflammation markers and patient performance status.[11] Inflammatory markers associated with a worse prognosis in localized RCC include elevated levels of C-reactive protein (CRP), the neutrophil-to-lymphocyte ratio, and IL-6 as well as hypoalbuminemia.[12,13] The modified Glasgow Prognostic Score (mGPS) is a 0- to 2-point scale that incorporates 1 point for elevated CRP and 1 additional point for a decreased albumin level, which is commonly used as a surrogate metric for systemic inflammation.[14] An elevated mGPS is well established to portend worse outcomes in RCC, although this accessible measure is underused in clinical practice.[15-19] Because of their independent impacts on RCC outcomes, sarcopenia and inflammatory markers may together provide preoperative prognostic value. This has not yet been studied in localized RCC.

In this study, we investigate the independent and combined associations between preoperative sarcopenia and systemic inflammation, as measured by mGPS, and clinical outcomes in patients undergoing nephrectomy for localized RCC. We compare these metrics with conventional prognostic tools used in RCC. We hypothesize that a preoperative deficiency of skeletal muscle mass and elevated serum markers of systemic inflammation are associated with increased risks of cancer recurrence, mortality, and all-cause mortality in patients with surgically treated localized RCC.

MATERIALS AND METHODS

Study Population

This study was a retrospective review of patients who underwent partial or radical nephrectomy for localized RCC between 2005 and 2015. This study was approved by Emory University's institutional review board. The inclusion criteria were 1) a confirmed histologic diagnosis of RCC without evidence of metastatic disease, 2) preoperative computed tomography (CT) or magnetic resonance imaging (MRI) within 90 days of surgery, and 3) available preoperative laboratory tests (CRP and albumin). We obtained the following additional preoperative clinical data: age, sex, race, height and weight, Charlson Comorbidity Index (CCI), Eastern Cooperative Oncology Group (ECOG) performance status (PS), and American Society of Anesthesiologists physical status classification. The mGPS was calculated as follows: a CRP level > 10 mg/L scored 1 point, and a concurrent albumin level < 3.5 g/dL yielded a classification of high mGPS (2 points).[14]

Postoperatively, we obtained the tumor pathologic T and N stages, Fuhrman grade, SSIGN score, and recurrence and death rates. As a comparison prognostic model, we calculated a previously described modified IMDC risk score using the performance status and hemoglobin, calcium, neutrophil, and platelet counts.[11] Scores ranged from 0 to 5 with the exclusion of the sixth criterion of time to systemic therapy, as previously done to adjust for localized RCC.[20]

Skeletal Muscle Measurement

Axial images from preoperative noncontrast CT and MRI scans were obtained at the mid-L3 vertebral level.[21] Images were analyzed by 4 observers (M.I.H., D.J.M., S.S., and M.W.) who were trained in segmentation with <1% intra-observer variability and blinded to patient information. All images were analyzed via Slice-O-Matic software (version 5.0; TomoVision) with previously defined threshold values for skeletal muscle of –29 to +150 Hounsfield units on CT and with the region-growing preview tool on MRI.[9,21] The total lumbar skeletal muscle area was measured on all scans in centimeters squared, including the cross-sectional area of the psoas major, quadratus lumborum, erector spinae, and abdominal wall muscles (rectus abdominis, transversus abdominis, external and internal obliques, and linea alba). The skeletal muscle area was normalized by the height in meters squared to calculate the skeletal muscle index (SMI). SMI thresholds for sarcopenia were defined by a receiver operating characteristic (ROC) analysis and grid-search best fit method to optimally stratify by BMI and sex in our population, as done in previous studies.[21-23] Sarcopenia was defined as SMI < 47 cm^2/m^2 for males and SMI < 38 cm^2/m^2 for females with a BMI < 30 kg/m^2 and as SMI < 54 cm^2/m^2

for males and SMI < 47 cm^2/m^2 for females with a BMI ≥ 30 kg/m^2.

Statistical Analysis

Univariable analyses and multivariable analyses (MVAs) were performed with Cox proportional hazards models to evaluate the association of sarcopenia and mGPS with OS, recurrence-free survival (RFS), and cancer-specific survival (CSS). MVA models controlled for age, sex, race, BMI, CCI, Fuhrman grade, presence of necrosis, pathologic T and N stages, and ECOG PS. The final model was derived after the testing of interaction assessment and proportionality assumptions. Kaplan-Meier analysis was used to evaluate OS, RFS, and CSS.

We then used the results of the sarcopenia and inflammation marker analysis to create a prognostic model. In our model, we established the following risk groups: low risk (nonsarcopenic, low mGPS), medium risk (sarcopenia only; sarcopenic, low mGPS), medium risk (inflammation only; nonsarcopenic, high mGPS), and high risk (sarcopenic, high mGPS). Time-dependent ROC curves were used to analyze the predictive ability of risk groups versus established nomograms such as the SSIGN score and the modified IMDC scale 5 years after treatment. In addition, to further interrogate the comparison between our prognostic risk groups and the SSIGN score, we obtained the distribution of patients in each of those groups. We performed the Cochran-Mantel-Haenszel (CMH) mean score test using rank scores to evaluate for differences in the discrete categories. For all analyses, a 2-sided *P* value < .05 was considered statistically significant, and SAS 9.4 (SAS, Cary, North Carolina) was used.

RESULTS

Patient Baseline Characteristics

Among 583 patients with RCC who underwent partial or radical nephrectomy, we identified 352 patients with localized RCC and CT or MRI imaging, 305 of whom also had CRP and albumin values available. The median number of days between preoperative imaging and surgery was 34 (interquartile range, 18-53 days). Of the 352 patients with preoperative SMI measurements, 139 (39.5%) were sarcopenic, and 213 (60.5%) were nonsarcopenic. In total, 59 (19.3%) met the criteria for a high mGPS, whereas 246 (80.7%) had a low mGPS.

The demographic data and baseline characteristics of the patients are presented in Table 1. The median age at the time of surgery was 62.7 years, 236 patients (67.0%) were male, 224 (63.3%) were White, 107 (30.4%) were Black, and 21 (5.9%) were other or unknown. The median BMI was 29.0 kg/m^2. The majority of our cohort had T3 (63.1%) and N0 disease (84.1%) with a Fuhrman grade of 3 or 4 (70.9%). In an analysis of variance, age, BMI, CCI, ECOG PS, Fuhrman grade, SSIGN score, recurrence, and death were significantly associated with the presence of sarcopenia. The median follow-up time was 30.4 months (interquartile range, 13.2-50.9 months), and the follow-up

TABLE 1. Baseline Characteristics of Patients With Localized Renal Cell Carcinoma (N = 352)

Characteristic	Value
Age, median, y	62.7
Sex, No. (%)	
Female	116 (33.0)
Male	236 (67.0)
Race, No. (%)	
White	224 (63.6)
Black	107 (30.4)
Other	11 (3.1)
Unknown	10 (2.8)
BMI, median, kg/m^2	29.0
Charlson Comorbidity Index, No. (%)	
0	37 (10.5)
1-2	139 (39.5)
≥3	176 (50)
ECOG performance score, No. (%)	
0	291 (82.7)
≥1	61 (17.3)
Pathologic T stage, No. (%)	
pT1	98 (27.8)
pT2	23 (6.5)
pT3	222 (63.1)
pT4	9 (2.6)
Pathologic N stage, No. (%)	
N0	296 (84.1)
N1	56 (15.9)
Fuhrman grade, No. (%)	
1-2	102 (29.1)
3-4	249 (70.9)
SSIGN score	
0-2	89 (25.3)
3-5	126 (35.8)
≥6	137 (38.9)
Modified IMDC score, No. (%)[a]	
0	111 (31.5)
1	146 (41.5)
2	77 (21.9)
3	13 (3.7)
4	5 (1.4)
Recurrence, No. (%)	
Yes	90 (25.7)
No	260 (74.3)
Death, No. (%)	
Yes	130 (36.9)
No	222 (63.1)

Abbreviations: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; IMDC, International Metastatic RCC Database Consortium; SSIGN, Stage, Size, Grade, and Necrosis.
[a]The modified IMDC score is 0 to 5 (excluding the criterion of time to systemic therapy). Zero patients scored 5.

TABLE 2. Multivariable Analysis of Sarcopenia and the mGPS Score as a Combined Prognostic Model for Survival and Recurrence After Surgery for Localized Renal Cell Carcinoma (N = 305)

	Overall Survival		Recurrence-Free Survival		Cancer-Specific Survival	
Risk Group	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Sarcopenia per SMI only						
No	1 (reference)		1 (reference)		1 (reference)	
Yes	1.64 (1.15-2.34)	.006	1.51 (0.99-2.31)	.055	2.01 (1.19-3.39)	.009
mGPS only[a]						
Low	1 (reference)		1 (reference)		1 (reference)	
High	1.72 (1.13-2.64)	.012	1.85 (1.11-3.07)	.018	1.33 (0.71-2.48)	.372
Sarcopenia + mGPS[b]		.004		.015		.087
Low risk (nonsarcopenic, low mGPS)	1 (reference)		1 (reference)		1 (reference)	
Medium risk (sarcopenia only)	1.78 (1.12-2.82)	.014	1.76 (1.02-3.04)	.042	2.30 (1.12-4.71)	.023
Medium risk (inflammation only)	2.13 (1.14-3.97)	.018	2.93 (1.44-5.96)	.003	1.72 (0.68-4.38)	.255
High risk (sarcopenic, high mGPS)	2.62 (1.48-4.62)	<.001	1.83 (0.95-3.52)	.069	2.55 (1.07-6.03)	.034

Abbreviations: CI, confidence interval; HR, hazard ratio; mGPS, modified Glasgow Prognostic Score; SMI, skeletal muscle index.
The multivariable analysis controlled for age, race, sex, body mass index, Charlson Comorbidity Index, Fuhrman grade, Eastern Cooperative Oncology Group performance status, necrosis, and pathologic T and N stages.
[a]A low mGPS score is 0 or 1; a high mGPS score is 2.
[b]Type 3 *P* values (overall) are shown in this row.

time did not differ by sarcopenia or inflammatory marker status.

Sarcopenia and mGPS Independent Analysis

On MVA, sarcopenia was an independent predictor of worse OS (hazard ratio [HR], 1.64; 95% confidence interval [CI], 1.15-2.34; $P = .006$) and CSS (HR, 2.01; 95% CI, 1.19-3.39; $P = .009$), and it trended toward worse RFS (HR, 1.51; 95% CI, 0.99-2.31; $P = .055$), as demonstrated in Table 2. The mGPS was an independent predictor of worse OS (HR, 1.72; 95% CI, 1.13-2.64; $P = .012$) and RFS (HR, 1.85; 95% CI, 1.11-3.07; $P = .018$) but was not an independent predictor of CSS (Table 2). A Kaplan-Meier analysis by sarcopenia status demonstrated that an absence of sarcopenia was associated with longer median OS (102.7 vs 61.1 months; $P = .0004$), RFS, and CSS (Fig. 1). A Kaplan-Meier analysis stratified by mGPS demonstrated that a low mGPS was associated with longer median OS (88.3 vs 61.3 months; $P = .0003$), RFS, and CSS (Fig. 1).

Combined Prognostic Model Analysis

The MVAs including the composite risk groups incorporating sarcopenia and mGPS for the outcomes of recurrence, cancer-specific mortality, and all-cause mortality are presented in Table 2. The risk groups demonstrated incremental associations with oncologic outcomes. Compared with the low-risk group, both medium-risk groups and the high-risk group had HRs of increasing magnitude for worse OS, RFS, and CSS (the *P* values from the grouped MVAs were .004 for OS and .015 for RFS, and they trended toward significance with $P = .087$ for CSS). The medium-risk (sarcopenia only) group HRs were 1.78 for shorter OS (95% CI, 1.12-2.82; $P = .014$), 1.76 for shorter RFS (95% CI, 1.02-3.04; $P = .042$), and 2.30 for shorter CSS (95% CI, 1.12-4.71; $P = .023$). The medium-risk (inflammation only) group HRs were 2.13 for OS (95% CI, 1.14-3.97; $P = .018$) and 2.93 for RFS (95% CI, 1.44-5.96; $P = .003$) and did not reach significance for CSS. The high-risk group HRs were 2.62 for OS (95% CI, 1.48-4.62; $P < .001$) and 2.55 for CSS (95% CI, 1.07-6.03; $P = .034$) and trended toward significance for RFS. A Kaplan-Meier analysis of OS, CSS, and RFS for the sarcopenia and mGPS prognostic model is shown in Figure 2. The high-risk group had significantly shorter OS, RFS, and CSS than both medium-risk groups and the low-risk group per Kaplan-Meier estimation (OS, 61.2 [high risk] vs 65.4 [medium risk: inflammation] vs 73.8 [medium risk: sarcopenia] vs 104.4 months [low risk]; $P < .0001$; Fig. 2).

Comparative Analyses of Prognostic Models

Time-dependent ROC analyses demonstrated comparable areas under the curve (AUCs) for sarcopenia and mGPS alone in comparison with the SSIGN score at 5 years (Table 3). The combined prognostic risk groups demonstrated higher AUCs than the SSIGN score (OS,

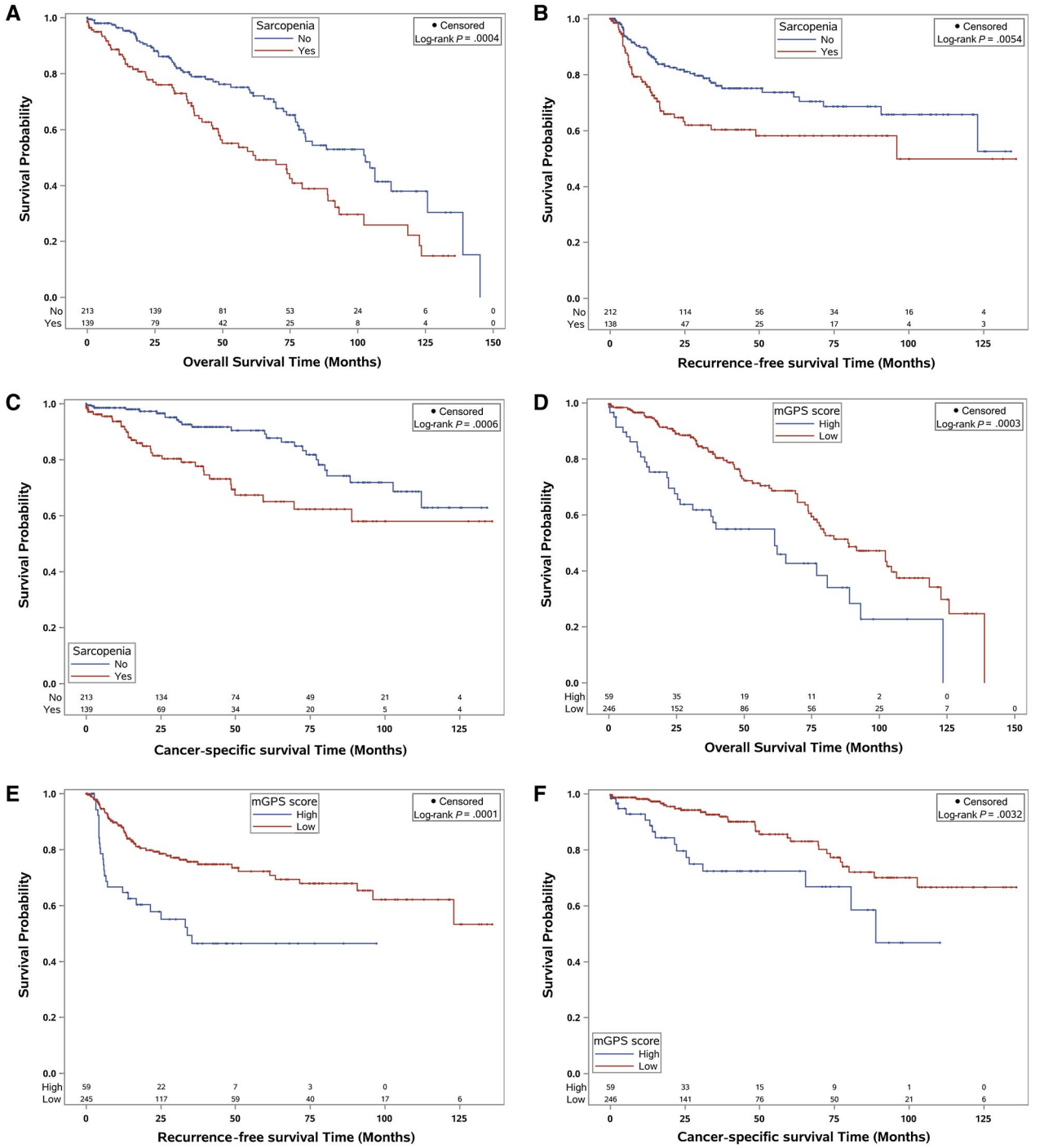

Figure 1. Kaplan-Meier analyses of median survival and time to recurrence in patients with localized renal cell carcinoma by (A-C) sarcopenia status and (D-F) mGPS (high score, 2; low score, 0 or 1) independently: (A,D) overall survival, (B,E) recurrence-free survival, and (C,F) cancer-specific survival. mGPS indicates modified Glasgow Prognostic Score.

0.705 vs 0.676; RFS, 0.778 vs 0.776; and CSS, 0.834 vs 0.778), although these differences were not statistically significant. The prognostic model also demonstrated higher AUCs than the modified IMDC score, which had an AUC of 0.534 for OS, an AUC of 0.621 for RFS, and an AUC of 0.619 for CSS.

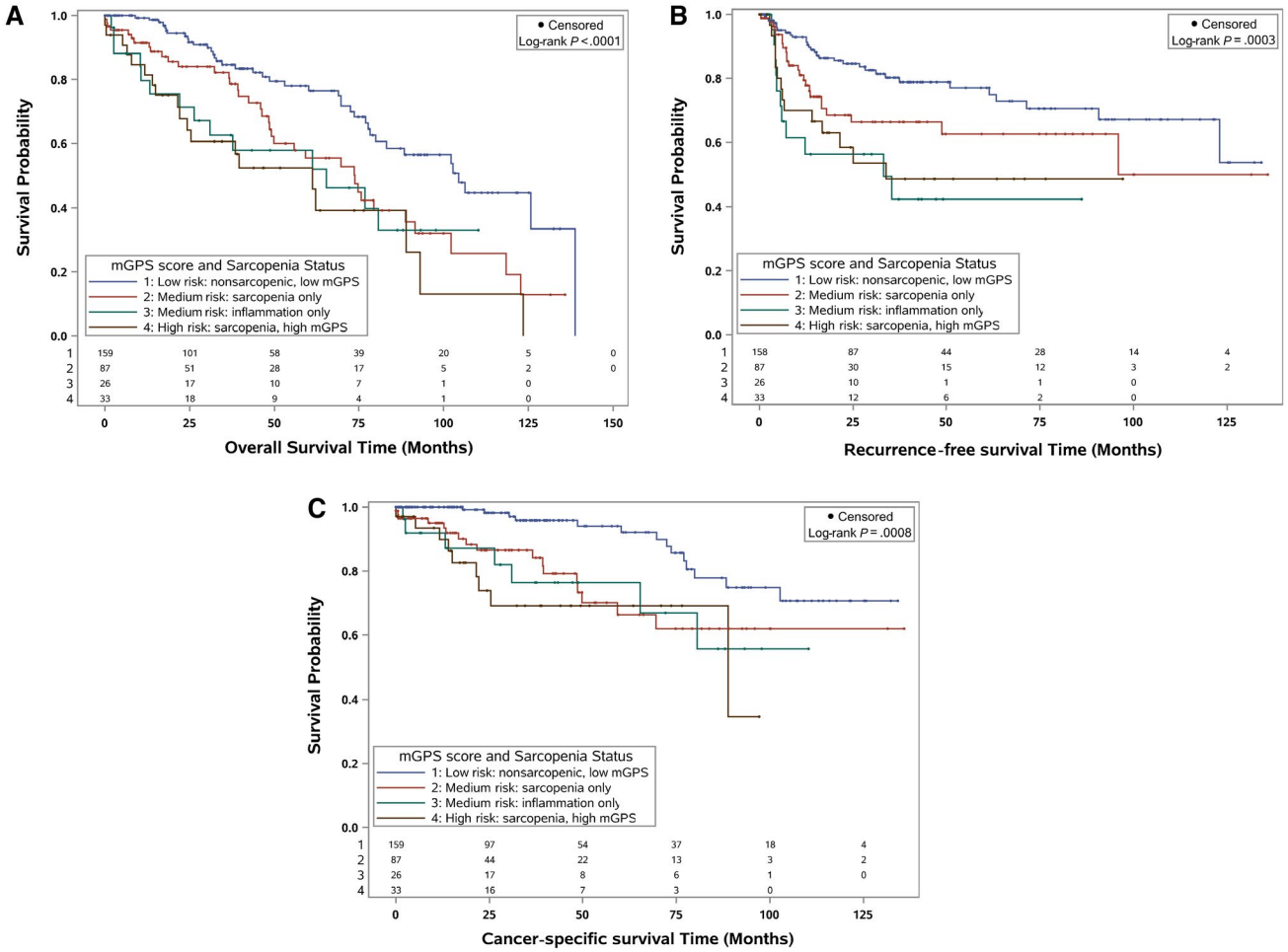

Figure 2. Kaplan-Meier analyses of median survival and time to recurrence in patients with localized renal cell carcinoma by combined mGPS and sarcopenia status prognostic risk group: (A) overall survival, (B) recurrence-free survival, and (C) cancer-specific survival. mGPS indicates modified Glasgow Prognostic Score.

TABLE 3. Time-Dependent Receiver Operating Characteristic Analysis of the Prognostic Model Versus the SSIGN Score and the Modified IMDC Score 5 Years After Treatment

	AUC (95% CI)		
Prognostic Model	Overall Survival	Recurrence-Free Survival	Cancer-Specific Survival
Sarcopenia only	0.613 (0.528-0.698)	0.580 (0.505-0.655)	0.711 (0.612-0.811)
mGPS only	0.578 (0.496-0.659)	0.703 (0.625-0.780)	0.598 (0.499-0.697)
Sarcopenia + mGPS	0.705 (0.608-0.802)	0.778 (0.698-0.856)	0.834 (0.750-0.918)
SSIGN score	0.676 (0.586-0.763)	0.776 (0.701-0.851)	0.778 (0.697-0.860)
Modified IMDC score[a]	0.534 (0.457-0.610)	0.621 (0.539-0.703)	0.619 (0.520-0.718)

Abbreviations: AUC, area under the curve; CI, confidence interval; IMDC, International Metastatic RCC Database Consortium; mGPS, modified Glasgow Prognostic Score; SSIGN, Stage, Size, Grade, and Necrosis.
[a]The modified IMDC score is 0 to 5 (excluding the criterion of time to systemic therapy).

To further interrogate these comparisons, we analyzed the distribution of mGPS and sarcopenia risk groups by SSIGN score. A mosaic plot of these results is shown in Supporting Figure 1. The distribution of patients was as follows: in the low-risk group, 48 had an SSIGN score of 0 to 2, 60 had an SSIGN score of 3 to 5, and 51 had an SSIGN score ≥ 6; in the medium-risk (sarcopenia) group, 16 had an SSIGN score of 0 to 2, 41 had

an SSIGN score of 3 to 5, and 30 had an SSIGN score ≥ 6; in the medium-risk (inflammation) group, 4 had an SSIGN score of 0 to 2, 4 had an SSIGN score of 3 to 5, and 18 had an SSIGN score ≥ 6; and in the high-risk group, 3 had an SSIGN score of 0 to 2, 4 had an SSIGN score 3 to 5, and 26 had an SSIGN score ≥ 6. The CMH mean score test gave an association statistic value of 25.58 (1 degree of freedom; $P < .0001$).

DISCUSSION

There is a critical unmet need for improved preoperative prognostication of outcomes in localized RCC. In this study, we examined the relationships between preoperative sarcopenia and inflammatory markers and OS, RFS, and CSS. We observed that sarcopenia, as measured on axial imaging, and systemic inflammation, as measured by the mGPS, were associated with inferior survival and earlier recurrence after surgery for localized RCC. We then combined these variables into a prognostic composite model that demonstrated an association with both CSS and recurrence in a stepwise fashion. Notably, our cohort included only patients who underwent nephrectomy and, therefore, reflected more locally advanced disease than the average of all patients presenting with nonmetastatic RCC (63% of patients had pT3 stage disease, and 15.9% had lymph node invasion). This is the first study, to our knowledge, to examine the association of sarcopenia and inflammation with clinical outcomes in localized RCC. These data have implications for preoperative clinical risk assessment and decision-making for urologists and oncologists who evaluate and treat patients with localized RCC.

The prognostic potential of both body composition measures and inflammatory markers is being increasingly explored in many types of cancer in nonmetastatic and metastatic settings.[5,14,22-26] However, these accessible tools have yet to be incorporated into standard clinical practice for cancer, including localized RCC.[12] Currently, clinicians primarily use the TNM staging system and histologic features of the tumor, such as the SSIGN score, to risk-stratify patients with localized RCC,[4] and this may limit prognostic abilities in the preoperative space. Using ROC analyses, we found that our prognostic model predicted 5-year outcomes comparatively to the SSIGN score (Table 3). Also, further distribution between risk groups and SSIGN scores using CMH mean score testing was suggestive of strong overlapping of the 2 prognostic models. This supports the validity of the new prognostic stratification system of mGPS and sarcopenia in comparison with preexisting models and may suggest the potential of the combined utility of the 2 scoring systems.

The IMDC risk score incorporates both serum inflammatory markers and patient clinical characteristics (performance status) that can be obtained preoperatively as well as the time from diagnosis to systemic therapy to account for the aggressiveness of underlying disease. Despite the availability and potential utility of these serum markers in the nonmetastatic setting, the IMDC risk score has mostly been validated for metastatic RCC in patients receiving systemic therapy.[11,27] In an effort to use the IMDC in a broader range of settings, modifications have been made to the criterion of time to systemic therapy in the IMDC, such as excluding it altogether or using the interval from nephrectomy to the appearance of metastases.[20,28] We used this previously proposed modified IMDC for localized RCC, with the sixth criterion excluded, as an additional comparator for our prognostic model. Using ROC analyses, we found that our model of sarcopenia and mGPS predicted 5-year OS, RFS, and CSS outcomes comparatively to the modified IMDC criteria with higher AUC values that did not reach statistical significance (Table 3). This finding and the SSIGN score comparison suggest that the novel strata presented herein may improve upon available risk stratification systems for localized RCC in the preoperative setting.

The intersection of sarcopenia and the body's inflammatory response is an important current topic of interest in cancer. In patients with metastatic RCC, sarcopenia has been correlated with worse survival, and individuals with more skeletal muscle have been observed to have a better response to targeted therapies and immunotherapy with lower rates of dose-limiting toxicity.[26,29-31] A large study of operable colorectal cancer demonstrated that sarcopenia, myosteatosis (as measured by skeletal muscle density), and mGPS predicted OS and that patients with high inflammatory states were more likely to have lower muscle mass.[22] Moreover, systemic inflammatory markers such as CRP predict an accelerated loss of lean muscle mass.[32] Although the mechanisms underpinning these observations remain to be defined at this point, the cross-talk between muscle and proinflammatory mediators stimulated by tumor cells appears to play a critical role in the clinical syndrome of cancer cachexia, which portends worse outcomes.[21,33] Although cachexia is a manifestation of late-stage cancer, assessing these markers during

early stages of disease may further delineate who is at risk for poor clinical outcomes.

The use of CRP as an inflammation marker in cancer is well established, and the mGPS has been validated in a wide range of settings in diverse cancers, including RCC.[12,34] Importantly, several studies in localized RCC have found a strong association between the mGPS and CSS, which underscores the prognostic power of this marker in operable RCC.[17-19] In fact, an elevated mGPS was a worse prognostic marker than sarcopenia alone in 2 of the 3 outcomes in our model in accordance with the previously demonstrated role of inflammation in RCC.

Overall, a preoperative evaluation of body composition and inflammation has the potential to aid in treatment decision-making for urologists and oncologists. They may help to identify who would most benefit from radical nephrectomy over partial nephrectomy or active surveillance because of a more aggressive disease outlook. Importantly, these markers may aid in patient selection for clinical trials of neoadjuvant or adjuvant treatment. Currently, there is only 1 Food and Drug Administration–approved systemic therapy for patients with RCC in the neoadjuvant or adjuvant setting.[35] Because of the paucity of available treatments and the interaction of muscle mass, the immune system, and systemic therapies discussed previously, incorporating new markers of body composition and systemic inflammation may be helpful in stratifying patients for treatment or trial enrollment. With improved prognostic models, clinicians may better identify which patients are most likely to derive clinical benefit from more aggressive medical and surgical interventions to improve outcomes for patients with localized RCC.

Additionally, a notable advantage of identifying patients with a higher inflammatory and sarcopenic preoperative status is to invoke early intervention to change the disease trajectory. Some anti-inflammatory agents such as nonsteroidal anti-inflammatory drugs and steroids have shown utility at advanced cancer stages.[6,36] These have not been studied in earlier stage disease. Early interventions with exercise programs designed to build muscle could potentially offset the long-term risks of sarcopenia and, in this way, improve survival. Several studies have demonstrated the benefit of a preoperative exercise regimen in decreasing hospital length of stay, postoperative complications, and costs for patients with cancer undergoing surgery.[37,38] However, prospective data are needed to evaluate the impact of exercise interventions on long-term survival and recurrence in localized RCC, with consideration given to the potential risks conferred by delaying definitive treatment. Because of the interaction of body composition and the body's inflammatory response to cancer, a multimodal approach early on in the disease process may provide benefit to those at elevated risk of developing metastatic disease.

There are relevant limitations that should be acknowledged. First, this study was a retrospective review and, therefore, was limited in number and subject to selection bias. These data are hypothesis-generating, and they should be validated in larger studies with longer follow-up periods. Because the population studied included patients with localized RCC who underwent nephrectomy, these patients likely represented more advanced disease, in both tumor and lymph node pathologic stage and grade, than all-comers with localized RCC (see Table 1). In addition, the inclusion requirement of preoperative imaging for sarcopenia evaluation may also have biased the cohort toward more advanced disease (eg, patients who received preoperative imaging for evaluation for possible lymph node metastases). This may limit the extrapolation of these data to patients with lower stage (pT1, N0) disease.

As another important limitation, sarcopenia was analyzed as a binary variable, and it was defined on the basis of a best fit model that closely matched cutoffs created for similar studies.[21,22] However, there is heterogeneity in the cutoffs that are applied across sarcopenia research, and this leads to difficulty in generalizing these cutoffs to broader populations. Finally, the software used to measure SMI (Slice-O-Matic) is expensive and requires specialized training, and thus it may not be accessible or practical in all clinical environments. Notably, techniques to measure muscle mass using more rapid and accessible methods have been proposed, although more studies are needed to verify the generalizable clinical validity of these methods.[39,40]

In conclusion, traditional methods of predicting recurrence and survival in localized RCC focus on TNM stage and grade. This study demonstrates that preoperative sarcopenia and an elevated mGPS, both independently and combined, predicted survival and recurrence in a cohort of patients who underwent surgery for localized RCC. This has potential implications for improving prognostication and informing surgical and medical treatment decisions in patients with localized RCC.

FUNDING SUPPORT

Michelle I. Higgins was a 2020 American Urological Association summer medical student fellow of the American Urological Association Urology Care Foundation (sponsored by the Herbert Brendler, MD, Research Fund).

CONFLICT OF INTEREST DISCLOSURES

Mehmet Asim Bilen has acted as a paid consultant for and/or as a member of the advisory boards of Calithera Biosciences, Exelixis, Bayer, Bristol-Myers Squibb, Eisai, Pfizer, AstraZeneca, Janssen, Genomic Health, Nektar, and Sanofi and has received grants for his institution from Xencor, Bayer, Bristol-Myers Squibb, Genentech/Roche, Seattle Genetics, Incyte, Nektar, AstraZeneca, Tricon Pharmaceuticals, Genome & Company, AAA, Peleton Therapeutics, and Pfizer for work performed outside the current study. Vikram M. Narayan reports other from Ciox LLC, SWOG, TELIX International Pty, Ltd, and Blue Earth Diagnostics outside the submitted work. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

All authors contributed to the conceptualization, methodology, investigation, and writing and editing of the manuscript and approved the final version of the manuscript.

REFERENCES

1. Capitanio U, Bensalah K, Bex A, et al. Epidemiology of renal cell carcinoma. *Eur Urol*. 2019;75:74-84.
2. National Cancer Institute. Cancer Stat Facts: Kidney and Renal Pelvis Cancer. Accessed July 12, 2020. https://seer.cancer.gov/statfacts/html/kidrp.html
3. Dabestani S, Thorstenson A, Lindblad P, Harmenberg U, Ljungberg B, Lundstam S. Renal cell carcinoma recurrences and metastases in primary non-metastatic patients: a population-based study. *World J Urol*. 2016;34:1081-1086.
4. Sengupta S, Lohse CM, Leibovich BC, et al. Histologic coagulative tumor necrosis as a prognostic indicator of renal cell carcinoma aggressiveness. *Cancer*. 2005;104:511-520.
5. Boutin RD, Yao L, Canter RJ, Lenchik L. Sarcopenia: current concepts and imaging implications. *AJR Am J Roentgenol*. 2015;205:W255-W266.
6. Roxburgh CS, McMillan DC. Cancer and systemic inflammation: treat the tumour and treat the host. *Br J Cancer*. 2014;110:1409-1412.
7. Ebadi M, Martin L, Ghosh S, et al. Subcutaneous adiposity is an independent predictor of mortality in cancer patients. *Br J Cancer*. 2017;117:148-155.
8. Sharma P, Zargar-Shoshtari K, Caracciolo JT, et al. Sarcopenia as a predictor of overall survival after cytoreductive nephrectomy for metastatic renal cell carcinoma. *Urol Oncol*. 2015;33:339.e17-339.e23.
9. Psutka SP, Boorjian SA, Moynagh MR, et al. Decreased skeletal muscle mass is associated with an increased risk of mortality after radical nephrectomy for localized renal cell cancer. *J Urol*. 2016;195:270-276.
10. Fukushima H, Nakanishi Y, Kataoka M, Tobisu K, Koga F. Prognostic significance of sarcopenia in patients with metastatic renal cell carcinoma. *J Urol*. 2016;195:26-32.
11. Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor–targeted agents: results from a large, multicenter study. *J Clin Oncol*. 2009;27:5794-5799.
12. Ramsey S, Lamb GW, Aitchison M, McMillan DC. Prospective study of the relationship between the systemic inflammatory response, prognostic scoring systems and relapse-free and cancer-specific survival in patients undergoing potentially curative resection for renal cancer. *BJU Int*. 2008;101:959-963.
13. Roxburgh CS, McMillan DC. Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. *Future Oncol*. 2010;6:149-163.
14. McMillan DC. Systemic inflammation, nutritional status and survival in patients with cancer. *Curr Opin Clin Nutr Metab Care*. 2009;12:223-226.
15. Shim SR, Kim SJ, Kim SI, Cho DS. Prognostic value of the Glasgow Prognostic Score in renal cell carcinoma: a meta-analysis. *World J Urol*. 2017;35:771-780.
16. Kim SI, Kim SJ, Kim SJ, Cho DS. Diagnostic test accuracy of Glasgow Prognostic Score as a prognostic factor for renal cell carcinoma: a meta-analysis. *Am J Clin Oncol*. 2020;43:393-398.
17. Lamb GW, Aitchison M, Ramsey S, Housley SL, McMillan DC. Clinical utility of the Glasgow Prognostic Score in patients undergoing curative nephrectomy for renal clear cell cancer: basis of new prognostic scoring systems. *Br J Cancer*. 2012;106:279-283.
18. Qayyum T, McArdle PA, Lamb GW, et al. Prospective study of the role of inflammation in renal cancer. *Urol Int*. 2012;88:277-281.
19. Cho DS, Kim SI, Choo SH, Jang SH, Ahn HS, Kim SJ. Prognostic significance of modified Glasgow Prognostic Score in patients with non-metastatic clear cell renal cell carcinoma. *Scand J Urol*. 2016;50:186-191.
20. Warren H, Fernando A, Thomas K, Austin C, Chowdhury S, O'Brien T. Surgery for high-risk locally advanced (pT3c) renal tumours: oncological outcomes and prognostic significance of a modified International Metastatic Renal Cell Cancer Database Consortium (IMDC) score. *BJU Int*. 2019;124:462-468.
21. Martin L, Birdsell L, Macdonald N, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol*. 2013;31:1539-1547.
22. Dolan RD, Almasaudi AS, Dieu LB, Horgan PG, McSorley ST, McMillan DC. The relationship between computed tomography–derived body composition, systemic inflammatory response, and survival in patients undergoing surgery for colorectal cancer. *J Cachexia Sarcopenia Muscle*. 2019;10:111-122.
23. Feliciano EMC, Kroenke CH, Meyerhardt JA, et al. Association of systemic inflammation and sarcopenia with survival in nonmetastatic colorectal cancer: results from the C SCANS study. *JAMA Oncol*. 2017;3:e172319.
24. Martini DJ, Liu Y, Shabto JM, et al. Novel risk scoring system for patients with metastatic renal cell carcinoma treated with immune checkpoint inhibitors. *Oncologist*. 2020;25:e484-e491.
25. Deng JP, Hua X, Long ZQ, Zhang WW, Lin HX, He ZY. Prognostic value of skeletal muscle index and monocyte-to-lymphocyte ratio for lymph node–positive breast cancer patients after mastectomy. *Ann Transl Med*. 2019;7:775.
26. Bilen MA, Martini DJ, Liu Y, et al. Combined effect of sarcopenia and systemic inflammation on survival in patients with advanced stage cancer treated with immunotherapy. *Oncologist*. 2020;25:e528-e535.
27. Heng DY, Xie W, Regan MM, et al. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. *Lancet Oncol*. 2013;14:141-148.
28. Bimbatti D, Ciccarese C, Fantinel E, et al. Predictive role of changes in the tumor burden and International Metastatic Renal Cell Carcinoma Database Consortium class during active surveillance for metastatic renal cell carcinoma. *Urol Oncol*. 2018;36:526.e13-526.e18.
29. Cushen SJ, Power DG, Teo MY, et al. Body composition by computed tomography as a predictor of toxicity in patients with renal cell carcinoma treated with sunitinib. *Am J Clin Oncol*. 2017;40:47-52.
30. Antoun S, Baracos VE, Birdsell L, Escudier B, Sawyer MB. Low body mass index and sarcopenia associated with dose-limiting toxicity of sorafenib in patients with renal cell carcinoma. *Ann Oncol*. 2010;21:1594-1598.
31. Huillard O, Mir O, Peyromaure M, et al. Sarcopenia and body mass index predict sunitinib-induced early dose-limiting toxicities in renal cancer patients. *Br J Cancer*. 2013;108:1034-1041.
32. Wallengren O, Ireslo BM, Lundholm K, Bosaeus I. Loss of muscle mass in the end of life in patients with advanced cancer. *Support Care Cancer*. 2015;23:79-86.
33. Baracos VE, Martin L, Korc M, Guttridge DC, Fearon KCH. Cancer-associated cachexia. *Nat Rev Dis Primers*. 2018;4:17105.
34. McMillan DC. The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer. *Cancer Treat Rev*. 2013;39:534-540.
35. Ravaud A, Motzer RJ, Pandha HS, et al. Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy. *N Engl J Med*. 2016;375:2246-2254.

36. Solheim TS, Blum D, Fayers PM, et al. Weight loss, appetite loss and food intake in cancer patients with cancer cachexia: three peas in a pod?—analysis from a multicenter cross sectional study. *Acta Oncol*. 2014;53:539-546.
37. Englesbe MJ, Grenda DR, Sullivan JA, et al. The Michigan Surgical Home and Optimization Program is a scalable model to improve care and reduce costs. *Surgery*. 2017;161:1659-1666.
38. Sebio Garcia R, Yanez Brage MI, Gimenez Moolhuyzen E, Granger CL, Denehy L. Functional and postoperative outcomes after preoperative exercise training in patients with lung cancer: a systematic review and meta-analysis. *Interact Cardiovasc Thorac Surg*. 2016;23:486-497.
39. Cespedes Feliciano EM, Avrutin E, Caan BJ, Boroian A, Mourtzakis M. Screening for low muscularity in colorectal cancer patients: a valid, clinic-friendly approach that predicts mortality. *J Cachexia Sarcopenia Muscle*. 2018;9:898-908.
40. Avrutin E, Moisey LL, Zhang R, et al. Clinically practical approach for screening of low muscularity using electronic linear measures on computed tomography images in critically ill patients. *JPEN J Parenter Enteral Nutr*. 2018;42:885-891.