EJMI

DOI: 10.14744/ejmi.2022.66227
EJMI 2022;6(3):374–382

Research Article

Association of Low Muscle Mass as a Marker of Sarcopenia with Survival in Metastatic Renal Cell Carcinoma Patients Receiving Nivolumab

Seher Yildiz Tacar,[1] Mesut Yilmaz,[1] Deniz Tural,[1] Ilkay Gulturk,[1] Mustafa Orhan Nalbant,[2] Ercan Inci,[2] Gulistan Bahat[3]

[1]Department of Medical Oncology, Bakırköy Sadi Konuk Training and Research Hospital, Istanbul, Türkiye
[2]Department of Radiology, Bakırköy Sadi Konuk Training and Research Hospital, Istanbul, Türkiye
[3]Department of Internal Medicine, Division of Geriatrics, Istanbul Medical School, Istanbul University, Istanbul, Türkiye

Abstract

Objectives: We aimed to evaluate the prognostic effect of low muscle mass (LMM), a marker of sarcopenia, in patients with metastatic RCC (mRCC) receiving nivolumab.

Methods: We analyzed the data of 33 patients retrospectively. Total skeletal muscle index (SMI) and psoas muscle index (PMI) were measured using computed tomography scans at lumbar vertebra level. Low SMI was detected by use of population-specificcut-offs. Median PMI was calculated for men and women.

Results: The median patient age was 61 (range: 55-65); 75.8% was male. Considering total skeletal muscle index, LMM was found in 10 (30.3%) patients. In the low SMI group, OS and PFS were significantly shorter compared to the normal SMI group (OS, median 6.76 vs. 56.26 months; PFS, median 5.13 vs. 39.41 months, respectively). In the patients having PMI lower than thesex-specific median PMI, OS and PFS were significantly shorter compared to the others (OS, 4.5 vs 61.82 months for male; OS 3.5 vs 64.83 months for female; PFS, 3.30 vs 53.65 months for male; PFS, 3 vs 49.91 months for female). In multivariate analysis, the only factor related to OS was ECOG-PS and to PFS was Fuhrman grade.

Conclusion: In mRCC patients treated with nivolumab, those with low muscle mass had shorter OS and PFS. Future prospective randomized studies with higher number of participants are required to clarify the potential association of LMM with outcomes.

Keywords: Sarcopenia, renal cell ccarcinoma, nivolumab

Cite This Article: *Yildiz Tacar S, Yilmaz M, Tural D, Gulturk I, Nalbant MO, Inci E, et al. Association of Low Muscle Mass as a Marker of Sarcopenia with Survival in Metastatic Renal Cell Carcinoma Patients Receiving Nivolumab. EJMI 2022;6(3):374–382.*

Kidney cancer is a significant cause of cancer-related deaths worldwide.[1] 70% of the patients have a local disease at the time of diagnosis, and approximately 20% of them develop recurrence or metastatic disease.[2,3] The treatment options for metastatic renal cell carcinoma (mRCC) include cytoreductive nephrectomy, tyrosine kinase inhibitors (TKI), cytokine therapy, and immune checkpoint inhibitors (ICI).[3]

The prognostic significance of markers such as Fuhrman nuclear grade, ECOG (Eastern Cooperative Oncology Group) performance status, C-reactive protein (CRP), Glasgow prognostic score (GPS), neutrophil-lymphocyte

Address for correspondence: Seher Yildiz Tacar, MD. Bakirkoy Sadi Konuk Egitim ve Arastirma Hastanesi Tibbi Onkoloji Anabilim Dali, Istanbul, Türkiye
Phone: +90 507 034 21 11 **E-mail:** sehertcr@gmail.com

Submitted Date: March 10, 2022 **Accepted Date:** August 01, 2022 **Available Online Date:** September 30, 2022

ratio (NLR), platelet-to-lymphocyte ratio (PLR),and hemoglobin, albumin, lymphocyte, and platelet (HALP) score has been suggested in RCC.[4-6]

Cachexia and weight loss due to cancer have adverse effects on survival and treatment response in patients.[4,7] Sarcopenia can occur as a result of cancer cachexia.[4,8] Currently, sarcopenia is defined as a decrease in muscle strength and/or functions accompanied by low muscle mass.[9,10] Sarcopenia and/or components, i.e low muscle strength and low muscle mass; has been associated with prognosis in various solid tumors, including hepatocellular carcinoma, gastroesophageal cancers, colorectal cancer, and urothelial cancers.[11] It was observed that RCC patients suffered from high prevalence of sarcopenia, as, 39-47% in localized RCC and 29-68% in metastatic RCC.[12-15]

Nivolumab, a programmed death 1 (PD-1) immune checkpoint inhibitör (ICI) monoclonal antibody and is used to treat many solid organ tumors, including metastatic RCC. It also has a different efficacy and side effect profile than standard cytotoxic treatments.[16] In some patients, persistent and long-lasting responses have been observed. [17] Clinical or pathological biomarkers that will predict the efficacy of ICI and treatment resistance in metastatic RCC patients have not been fully yet.

An association has been shown between increased inflammatory cytokine level and decreased muscle strength and mass. With the increase of inflammatory cytokines, protein synthesis decreases and the catabolic process begins. Proteins involved in the immune response are consumed from the skeletal muscle pool.[18] In the chronic inflammation process, the increase of cytokines such as transforming growth factor-β, interleukin (IL) -6 and decrease in the level of myokines such as IL-15 and IL-5 contribute to the development of sarcopenia and the number of T-cells decreases and the immune response becomes weaker; thus the effectiveness of ICIs reduces.[19-21]

There are a limited number of studies evaluating sarcopenia and its components as a prognostic marker in metastatic RCC patients.[22,23] These studies include mRCC patients receiving VEGF-targeted therapy.[22,23] There is no study in the literature evaluating the prognostic effect of sarcopenia and/or components in mRCC patients receiving ICI. This study aimed to evaluate the prognostic effect of muscle mass, a marker of sarcopenia, in mRCC patients specifically receiving nivolumab.

Methods

Study Population

We analyzed the patients treated with nivolumab with a diagnosis of mRCC between August 2013 and February 2021 retrospectively. Patients' information was collected from medical records, including data on sex, age, Eastern Cooperative Oncology Group performance status score (ECOG-PS), International metastatic RCC database consortium (IMDC) prognostic score, laboratory test results including complete blood count, pathological charactheristics, nephrectomy history, metastatic sites and detailed information on the history of previous treatments. Absolute counts of lymphocyte, platelet,and neutrophil were analyzed before first nivolumab administration. As a marker of systemic inflammation, the neutrophil-to-lymphocyte ratio (NLR) was calculated, and platelet-to-lymphocyte ratio (PLR).

Treatment and Data Collection

Nivolumab was administered intravenously at a dose of 3 mg/kg every 2 weeks until progressive disease or unacceptable toxicity developed. Safety was assessed by evaluating the incidence of immune-related adverse events (irAEs).

Treatment response was evaluated according to the response evaluation criteria in solid tumors version 1.1 (RECIST). PFS was defined as the time elapsed from the onset of nivolumab to radiological progression, drug discontinuation due to toxicity or death, and OS was defined as the time elapsed from the onset of nivolumab to death. Disease control rate (DCR) and objective response rate (ORR) were found by the best radiologic response after nivolumab administration: DCR included complete response, partial response, and stable disease; ORR included complete and partial responses, respectively.

Assessment of Low Muscle Mass

All patients underwent CT (computed tomography) examination within 30 days before receiving nivolumab administration. Total skeletal muscle area (SMA) and psoas muscle area (PMA) were measured. The cross-sectional area of the lumbar skeletal muscles at the third lumbar vertebra level (including erector spinae; psoas; quadratus lumborum; bilateral internal, external, and lateral obliques and the rectus abdominis muscles) were identified for SMA and psoas muscles for PMA. The measurements were performed with 1 to 5 mm slices.[24,27] The measurements were made automatically using attenuation thresholds as −29 Hounsfield units (HU) to +150 HU, which tissues were noticed as muscle tissue via Fujifilm Synapse 3Dand Synapse Pacs Software (Fujifilm Medical Systems, Tokyo, Japan). Henceforth, if other areas rather than muscles were involved in the calculation inaccurately, the measurements were corrected manually by the radiologist trained in this field.

The total skeletal muscle index (SMI) was defined as follows: SMI (cm^2/m^2) = cross-sectional total skeletal muscle area (cm^2)/height (m^2). Considering the various criteria cur-

rently available for sarcopenia, we used the cut-off values of 44.98 cm^2/m^2 for men and 36.05 cm^2/m^2 for women.[27] In the study of Ufuk et al. cut-off values for SMI and PMI were determined in 270 healthy kidney donors in the Turkish population. Our study was based on the cut-off values of this study for those aged 20-60 years.[27] According to another study conducted for the Turkish population, low muscle mass was not detected in our patients.[28]

The psoas muscle index (PMI) was defined as follows: PMI (cm^2/m^2)= cross-sectional area (cm^2)/height (m^2). PMI-L3 cut-off values 2.63 and 2.02 cm^2/m^2 for males and females, respectively.[27] Since there was no patient with low muscle mass according to the PMI cut-off value in the patients, participants were evaluated for median PMI separately by gender.

Statistical Analysis

Categorical variables were presented as percentages and continuous variables were expressed as mean +/- standard deviation (median and range). PFS and OS were presented as median values with a two-sided 95% confidence interval (CI). Shapiro-Wilk test was used to test normality. The baseline characteristics of patients with or without low-SMI were compared using the Pearson chi-square or Fisher's exact test for categorical variables and the Student's t-test or Mann–Whitney U test for continuous variables. Overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan–Meier method. The difference in survival was calculated using the log-rank test. The Cox proportional-hazards model was used when performing a multivariable analysis (Enter method) including the factors that showed statistical significance in univariable analysis. We evaluated the multicollinearity after calculating a variance inflation factor of < 5 for factors included in the multivariable analysis. A p-value of <0.05 was considered statistically significant. The clinical data were analyzed using IBM SPSS version 23.0.

Results

Patient Characteristics

In our study, files of 80 patients diagnosed with mRCC were scanned, and 40 of these patients were found to have received nivolumab, but only 33 patients were radiologically evaluated with CT, which were included in our study. The median patient age was 61 (range: 55-65). Males constituted (75.8%) of the study population.Considering total skeletal muscle index, low SMI was found in 10 (30.3%) patients of whom all were male. The characteristics of the participants stratified by the presence of low skeletal muscle index at lumbar 3 vertebra level including tumor-related factors and baseline laboratory test results are outlined in Table 1. All patients had been treated with tyrosine kinase inhibitör (TKI) before nivolumab. Albumin, median PMI by gender, and SMI values were statistically significantly lower in the low-SMI group compared to the normal SMI group (p<0.05) (Table 1).

Overall Survival

The median OS for all patients was 16 months (95% CI, 0-39.84) (Fig. 1). The median OS was 6.76 months (95% CI, 3.47-10.05 months) in the low SMI group and 56.26 months (95% CI, 40.76-71.76 months) in the normal SMI group, which was statistically significantly shorter(log-rank p=0.002) (Fig. 2).

The PMI median for male was found to be 7.5 cm^2/m^2. Median OS was 4.5 months (95% CI, 0-13.05 months) in individuals with PMI <7.5 for male, median OS was 61.82 months (95% CI 44.10-76.54 months) in individuals with PMI> 7.5 for male and was statistically significantly shorter (log-rank p=0.012) (Fig. 3).

The PMI median for female was found to be 6.7 cm^2/m^2. Median OS was 3.5 months (95% CI, 1.12-5.88 months) in individuals with PMI <6.7 for female, median OS was 64.83 months (95% CI 50.24-79.41 months) in individuals with PMI> 6.7 for male and was statistically significantly shorter (log-rank p=0.001) (Fig. 3).

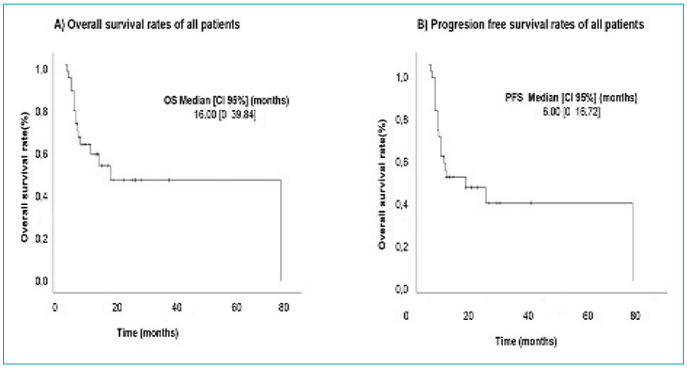

Figure 1. Kaplan-Meier curves were used to estimate survival, and log-rank tests were used for comparison.

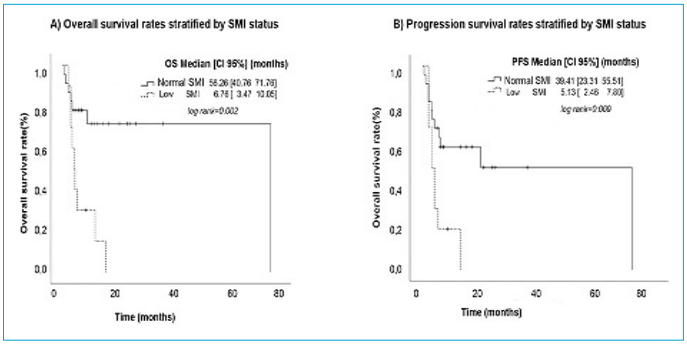

Figure 2. Kaplan-Meier curves were used to estimate survival, and log-rank tests were used for comparison.

Table 1. Patient characteristics stratified by the presence of low skeletal muscle index at lumbar 3 vertebra level

	Low SMI (n, 10)	Normal SMI (n, 23)	Total (n, 33)	
Age- mean [IQR]				
Sex	62.5 [54-67]	61 [56-64]	61 [55-65]	0.527
Female n (%)	0 (0)	8 (34.8)	8 (24.2)	0.032
Male	10 (100)	15 (65.2)	25 (75.8)	
BMI	26 [25-26]	26 [23-29]	26 [25-27]	0.393
IMDC score n (%)				
Favourable	0 (0)	7 (0.4)	7 (21.2)	0.139
İntermediate	7 (70)	12 (52.2)	19 (57.6)	
Poor	3 (30)	4 (17.4)	7 (21,2)	
Male median PMI<7.5	9 (90)	3 (20)	12 (48)	0.001
Female median PMI<6.7	0 (0)	4 (50)	4 (50)	
SMI	40.2 [39.6-42.9]	53.2 [48.4-58.6]	49.8 [41.6-54.5]	0.001
Nephrectomy n (%)	7 (70)	18 (78.3)	25 (75.8)	0.611
Histological type n (%)				
Clear cell	8 (80)	21 (91.3)	29 (87.9)	0.299
Papillary	1 (10)	2 (8.7)	3 (9.1)	
Chromophobe	1 (10)	0 (0)	1 (3)	
Fuhrman Grade n (%)				
2	1 (10)	5 (22.7)	6 (18.8)	0.309
3	7 (70)	9 (40.9)	16 (50)	
4	2 (20)	8 (36.4)	10 (31.3)	
Sarcomatoid differantiation	0 (0)	4 (17.4)	4 (12.1)	0.159
Previous treatment				
TKI	8 (80)	20 (87)	28 (84.8)	0.609
IFN+TKI	2 (20)	3 (13)	5 (15.2)	
ECOG				
0	1 (10)	0 (0)	1 (3)	0.193
1	6 (60)	19 (82.6)	25 (75.8)	
2				
Site of metastasis	3 (30)	4 (17.4)	7 (21.2)	
Brain	2 (20)	3 (13)	5 (15.2)	0.609
Lung	8 (80)	21 (91.3)	29 (87.9)	0.391
Liver	2 (20)	5 (21.7)	7 (1.2)	0.911
Metastatic site number	2.5 [2-3]	3 [2-4]	3 [2-3]	0.550
Albumin	27.5 [26-35]	36 [34-38]	35 [31-38]	0.003
NLR	2.69 [1.5 3.6]	2.48 [1.69-3.28]	2.48 [1.69-3.44]	0.751
PLR	0.01 [0 0.01]	0.01 [0 0.01]	0.01 [0 0.01]	0.089
Line of nivolumab				
2	5 (50)	17 (73.9)	22 (66.7)	0.353
3	4 (40)	4 (17.4)	8 (24.2)	
4	1 (10)	2 (8.7)	3 (9.1)	
Radiologic response of nivolumab				
PR	4 (40)	9 (39.1)	13 (39.4)	0.532
SD	1 (10)	6 (26.1)	7 (21.2)	
PD	5 (50)	8 (34.8)	13 (39.4)	
Progression	9 (90)	11 (47.8)	20 (60.6)	0.023
Exitus	9 (90)	7 (30.4)	16 (48.5)	0.002

Quantitative variables, M [IQR], M median, IQR:Q1 Q3, qualitative variables n(%) withpresented; BMI: Body massindex, IMDC: International metastatic RCC data base consortium, PMI: Psoas muscle index, SMI: Total skeletal muscle index, IFN: Interferon, TKI: Tyrosine kinase inhibitor, ECOG-PS: Eastern Cooperative Oncology Group-Performance score, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, RECIST: Response evaluation criteria in solid tumors version, PR: Partial response, SD: Stable disease, PD: Progressivedisease.

Clinical parameters thought to affect overall survival were analyzed with in the univariate-multivariate analysis and the results were presented in Table 2. In the univariate analysis, ıt were observed that SMI, ECOG, IMDC, PLR, median PMI by gender, parameters had a statistically significant relationship with OS ($p<0.05$). In the multivariate analysis, ECOG-PS significant association of variables on OS was found ($p<0.05$) (Table 2).

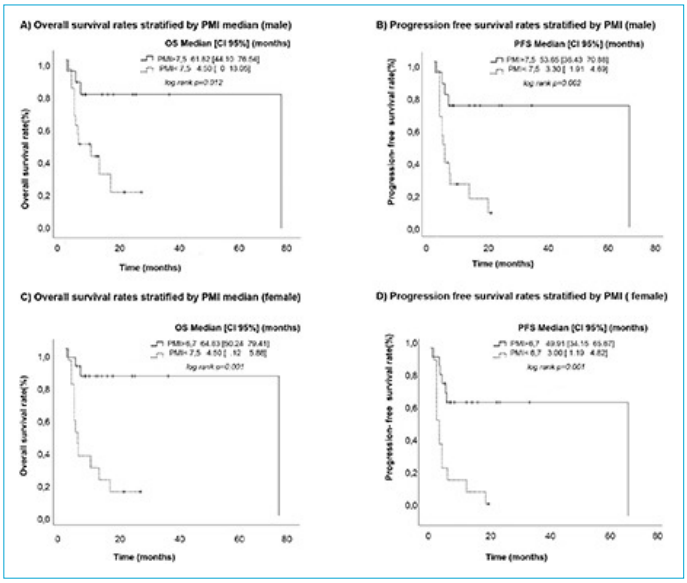

Figure 3. Kaplan-Meier curves were used to estimate survival, and log-rank tests were used for comparison.

Progression-Free Survival

The median PFS for all patients was 6 months (95% CI, 0-16.72) (Fig. 1). Median PFS was 5.13 months (95% CI 2.46-7.80 months) in the low SMI group and 39.41 months (95% CI, 23.32-55.51 months) in the group with normal SMI, and this was statistically significantly shorter (log-rank p=0.009) (Fig. 2).

Median PFS was 3.3 months (95% CI, 1.91-4.69 months) in individuals with PMI <7.5 for male, median PFS was 53.65 months (95% CI 36.43-70.88 months) in individuals with PMI> 7.5 for male and was statistically significantly shorter (log-rank p=0.002) (Fig. 3).

The PMI median for female was found to be 6.7 cm^2/m^2. Median PFS was 3 months (95% CI, 1.19-4.82 months) in individuals with PMI <6.7 for female, median PFS was 49.91 months (95% CI 34.15-65.67 months) in individuals with PMI> 6.7 for male and was statistically significantly shorter (log-rank p=0.001) (Fig. 3).

Table 2. Univariate and multivariate analyses for prognostic factors on overall survival

	Univariate		Multivariate	
Variable	**Hazard ratio (95%CI)**	**p**	**Hazard ratio (95%CI)**	**p**
Age (≥60 years old)	1.29 (0.46-3.65)	0.631		
Male	2.50 (0.56-11.14)	0.230		
BMI	0.89 (0.76-1.05)	0.462		
Low SMI	4.52 (1.58-12.94)	0.005	1.88 (0.52-6.80)	0.335
ECOG-PS	3.46 (1.08-11.10)	0.037	3.45 (1.10-10.85)	0.034
Histological type n(%)				
(ref: clear cell)		0.433		
Papillary	0.27 (0.03-2.18)	0.218		
Chromophobe	0.40 (0.04-4.64)	0.464		
Stage at diagnosis (%) (ref:1)		0.250		
2	2.37 (0.25-22.95)	0.456		
3	1.36 (0.12-15.27)	0.803		
4	4.60 (0.57-37.32)	0.153		
Fuhrman Grade (ref:2)		0.166		
3	3.39 (0.42-27.19)	0.251		
4	6.65 (0.79-56.05)	0.082		
Sarcomatoid differantiation	1.48 (0.33-6.57)	0.610		
Nephrectomy	0.53 (0.16-1.74)	0.294		
IMDC score (ref: favourable)		0.045		0.650
Intermediate	0.12 (0.0-0.998)	0.048	2.06 (0.21-20.18)	0.534
Poor	0.24 (0.17-1.55)	0.236	3.10 (0.25-37.96)	0.377
Site of metastasis (multiple)	4.65 (0.59-36.40)	0.144		
Previous treatment (IFN+TKI)	0.69 (0.15-3.06)	0.622		
Line of nivolumab (ref:2)		0.780		
3	1.71 (0.22-13.55)	0.612		
4	2.12 (0.25-18.16)	0.494		
SMI	0.94 (0.88-1.01)	0.065		
Male median PMI(<7.5 vs>7.5)	4.36 (1.22 -5.57)	0.023	0 (0-460000,00)	0.927
Female median PMI(<6.7 vs >6.7)	7.36 (2.06-26.26)	0.002	36155.15 (0-626000.00)	0.907
NLR	1.21 (0.95-1.53)	0.122		
PLR	1.01 (1.01-1.02)	0.013	0 (0-8830000.00)	0.415

BMI: Body mass index, SMI: Total skeletal muscle index, ECOG-PS: Eastern Cooperative Oncology Group-Performance score, IMDC: International metastatic RCC data base consortium, IFN: Interferon, TKI: Tyrosine kinase inhibitor, PMI: Psoas muscle index, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio.

Clinical parameters thought to affect progression-free survival were analyzed with in the univariate-multivariate analysis and the results are presented in Table 3. A statistically significant relationship was found between SMI, Fuhrman grade, IMDC, median PMI by gender, and PFS (p<0.05). In the multivariate analysis, higher Furhman grade was found to be associated with shorter PFS (p<0.05) (Table 3).

Tumor Response

When treatment responses were evaluated according to RECIST criteria in the group with low SMI, 4 out of 10 patients had a partial response (PR), one patient had stable disease (SD), five patients had progressive disease (PD), and ORR was 40%. During the follow-up period, 9 of the patients in this group died due to disease progression. In the normal-SMI group, 9 (39%) of 23 patients had PR, 6 (26%) had SD, 8 (34%) had PD, and ORR was 39%. In this group, progression developed in 11 (47%) patients during follow-up, and 7 (30%) patients died due to progression. In the follow-up of the patients, progression and death rates due to progression were found to be significantly higher in the low-SMI group (p<0.05) (Table 1).

Toxicity

During nivolumab treatment, grade 2 hypothyroidism developed in two patients, elevated grade 1 transaminases

Table 3. Univariate and multivariate analyses for prognostic factors on progression-free survival

	Univariate		Multivariate	
Variable	**Hazard ratio (95%CI)**	**p**	**Hazard ratio (95%CI)**	**p**
Age (≥60 yearsold)	1.01 (0.41-2.51)	0.978		
Male	1.05 (0.38-2.93)	0.924		
BMI	0,89 (0.77-1.02)	0.096		
Low SMI	3.19 (1.24-8.24)	0.016	1.64 (0.58-4.65)	0.353
ECOG-PS (ref:0)	2.66 (0.98-7.20)	0.055		
Histological type				
(ref: clear cell)		0.369		
Papillary	1.79 (0.52-6.19)	0.361		
Chromophobe	3.41 (0.43-27.15)	0.247		
Stage of diagnosis (%) (ref:1)		0.218		
2	2.99 (0.31-29.32)	0.347		
3	2.78 (0.30-25.49)	0.366		
4	6.10 (0.76-48.97)	0.089		
Fuhrman Grade (ref:2)		0.045	0.017	
3	4.54 (0.58-35.60)	0.150	2.46 (0.22-27.04)	0.463
4	8.72 (1.08-70.41)	0.042	12.18 (1.17-126.74)	0.036
Sarcomatoid differantiation	1.15 (0.26-5.01)	0.852		
Nephrectomy	0.43 (0.16-1.18)	0.103		
IMDC (ref: favourable)		0.049	0.452	
Intermediate	5.83 (0.75-45.20)	0.091	3.92 (0.41-38.02)	0.238
Poor	12.18 (1.44-102.93)	0.022	4.82 (0.40-57.73)	0.214
Site of metastasis (multiple)	2.36 (0.53-10.47)	0.259		
Previous treatment (IFN+TKI)	0.60 (0.14-2.58)	0.488		
Line of nivolumab (ref:2)		0.680		
3	0.96 (0.34-2.69)	0.933		
4	0.40 (0.05-3.08)	0.380		
SMI	0.95 (0.90-1.01)	0.092		
Male median PMI (<7.5 vs>7.5)	4.83 (1.58-14.74)	0.006	1.90 (0.15-24.14)	0.619
Female median PMI (<6.7 vs >6.7)	4.54 (1.71-12.09)	0.002	2.45 (0.38-15.66)	0.343
NLR	1.10 (0.87-1.39)	0.428		
PLR	1.01 (0.99-1.01)	0.068		

BMI: Body mass index, SMI: Total skeletal muscle index, ECOG-PS: Eastern Cooperative Oncology Group-Performance score, IMDC: International metastatic RCC data base consortium, IFN: Interferon, TKI: Tyrosine kinase inhibitor, PMI: Psoas muscle index, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio.

in three patients, grade 2 lichen planus in one patient, and hypophysitis in one patient. Treatment was continued with hormone replacement in patients who developed hypothyroidism and hypophysitis. Elevated grade 1 transaminase devoleped in one patient in the low SMI group, and other advers events were observed in the normal SMI group. There were no patients who discontinued the drug due to side effects or underwent dose modifications.

Discussion

In this study, we found that in mRCC patients treated with nivolumab, those with low SMI had shorter OS and PFS than their normal counterparts.Male and females with low median PMI also found significantly shorter OS and PFS. Two studies suggested cut-off values for PMI and SMI at the L3 vertebra level in the Turkish population with minor differences in between.Ideally, the cutoff values in these two studies are used. Low muscle mass (LMM) was not detected in our study compared to the lower cut-off values in the study of Bahat et al. Therefore, we determined our study cut-offs according to the Ufuk et al study, although the number of patients was lower.[27,28]

Many prognostic markers have been identified for RCC, including systemic inflammatory indices.A meta-analysis observed that NLR, PLR, and CRP, known as systemic inflammatory markers, significantly affected OS and PFS in metastatic RCC patients receiving TKI.[4] In phase 1 clinical study, shorter survival was found in patients with sarcopenia and high systemic inflammatory indices such as PLR and NLR in cancer patients treated with ICI.[29] In our study, a significantly shorter OS was found in patients with high PLR, but no significant relationship was shown between NLR and survival.

Serum albumin is a marker that is synthesized in the liver, shows the protein level in the blood and is used in the assessment of nutritional status, and is also a negative acute phase reactant. The relationship between hypoalbuminemia and poor survival outcomes has been investigated for many types of cancer in the literature. The relationship between albumin and RCC prognosis in previous studies may be low albumin as an indirect indicator of sarcopenia.[22] In our study, we found significantly lower albumin levels in the low-SMI group.

Sarcopenia has been reported as a condition associated with an increased catabolic process, fatigue, inadequate treatment response, and short survival time.[30] The muscles in our skeletal system act as a secretory organ that can secrete some cytokines such as interleukin-6 (IL-6), IL-8, and peptide structures such as leukemia inhibitory factor.[31] These cytokines contribute to the development of sarcopenia, and when sarcopenia develops, protein synthesis decreases, and the catabolic process begins, systemic inflammation increases and ATP synthesis decreases by activating oxidative pathways. After a decrease in systemic immune response occurs, treatment response and tolerance are also affected.[32] In patients with sarcopenia, a decrease in treatment response, an increase in toxicity and postoperative complications, and a related shortening in survival have been reported.[33] In the presence of sarcopenia in melanoma patients treated with ICI, drug-related toxicity was found to be higher.[34]

In RCC patients; it is known that IMDC prognostic scoring system, Furhman nuclear grade system, and ECOG-PS are important prognostic factors for survival.[35,36] Furhman nuclear grade was also higher in RCC patients with sarcopenia.[12] In our study, some differences were observed between groups due to low muscle mass. Significantly, in patients with low SMI group compared to normal SMI group; ECOG-PS was worse, albumin was lower, IMDC prognostic score was higher, and Furhman nuclear grade was also higher.

Sarcopenia may be an important prognostic marker in patients receiving ICI.Studies with preclinical tumor models have shown suppression of the immune system due to cachexia and tumor induction, which may explain the decrease in immunotherapy treatment efficacy in patients with cachexia.[37] Studies with some solid tumors such as malignant melanoma and lung cancer have shown shorter survival times in patients treated with ICI due to sarcopenia and increased inflammation.[38,39] In the study of Kim et al. sarcopenic patients among HCC patients who treated with Nivolumab were evaluated according to SMI, and shorter OS was observed in these patients.[40] In another study, shorter OS and PFS were observed in the group defined as sarcopenic according to SMI in 142 patients with NSCL who received ICI.[41] In another study on NSCL, both OS and PFS were significantly shorter in the group with psoas muscle mass loss in patients who received Nivolumab.[42]

Different results have been observed in studies on the prognostic significance of sarcopenia in RCC patients.[12-14,22] In some studies, shorter OS was found in patients with low SMI, while some studies did not find a significant effect on OS.[13,14,43,44] In a meta-analysis, no significant difference was found between RCC patients with and without sarcopenia in PFS.[45] In another study, shorter PFS was found in RCC patients with sarcopenia.[22] This may be related to the differences in the patient populations in the studies and the different methods used for the sarcopenia marker.In addition, in previous studies, patients had received TKI and IFN therapy for mRCC treatment but in our study, patients who received nivolumab were evaluated. Previous studies

investigating the relationship between mRCC and sarcopenia included patients using TKI and IFN, but in our study, mRCC patients receiving nivolumab were evaluated.[22,23] In our study, significantly shorter OS and PFS were found in the low SMI group.

Our study has some limitations and strengths. To our knowledge, our study is the first to show the relationship between low muscle mass, a marker of sarcopenia, and survival in mRCC patients receiving nivolumab. In our study; a retrospective analysis method with potential bias was used in patient selection andpatients from only one center were evaluated,and the number of patients was limited compared to previous studies.[13,14]

In conclusion, sarcopenia may be a prognostic marker in mRCC patients treated with nivolumab, but future prospective randomized studies with higher number of participants are required to clarify the potential association of low muscle mass with survival in RCC patients receiving nivolumab.

Disclosures

Ethics Committee Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – S.Y.T., M.Y., G.B.; Design – S.Y.T., D.T., M.Y., G.B.; Supervision – S.Y.T., G.B., I.G.; Materials – S.Y.T., I.G., M.O.N.; Data collection &/or processing – S.Y.T., I.G., E.I., M.O.N.; Analysis and/or interpretation – S.Y.T., G.B., M.Y., D.T.; Literature search – S.Y.T., G.B.; Writing – S.Y.T., M.Y., G.B.; Critical review – S.Y.T., G.B., M.Y.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424. [CrossRef]
2. Ljungberg B, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M, et al. EAU guidelines on renal cell carcinoma: 2014 update. Eur Urol 2015;67:913–24. [CrossRef]
3. Brookman-May SD, May M, Shariat SF, Novara G, Zigeuner R, Cindolo L, et al; Members of the CORONA-Project; Members of the SATURN-Project; Young Academic Urologists Renal Cancer Group. Time to recurrence is a significant predictor of cancer-specific survival after recurrence in patients with recurrent renal cell carcinoma--results from a comprehensive multi-centre database (CORONA/SATURN-Project). BJU Int 2013;112:909–16. [CrossRef]
4. Semeniuk-Wojtaś A, Lubas A, Stec R, Syryło T, Niemczyk S, Szczylik C. Neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and C-reactive protein as new and simple prognostic factors in patients with metastatic renal cell cancer treated with tyrosine kinase inhibitors: a systemic review and meta-analysis. Clin Genitourin Cancer 2018;16:685–93. [CrossRef]
5. 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;35:771–80. [CrossRef]
6. Yilmaz M. Is there predictive significance of HALP score in metastatic RCC patients treated with nivolumab? EJMI 2021;5:33–8. [CrossRef]
7. Blum D, Stene GB, Solheim TS, Fayers P, Hjermstad MJ, Baracos VE, et al. Validation of the consensus-definition for cancer cachexia and evaluation of a classification model--a study based on data from an international multicentre project (EPCRC-CSA). Ann Oncol 2014;25:1635–42. [CrossRef]
8. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, 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;31:1539–47.
9. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al; Writing group for the european working group on sarcopenia in older people 2 (ewgsop2), and the extended group for EWGSOP2. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019;48:16–31.
10. Marzetti E, Calvani R, Tosato M, Cesari M, Di Bari M, Cherubini A, et al; SPRINTT Consortium. Sarcopenia: an overview. Aging Clin Exp Res 2017;29:11–7. [CrossRef]
11. Shachar SS, Williams GR, Muss HB, Nishijima TF. Prognostic value of sarcopenia in adults with solid tumours: A meta-analysis and systematic review. Eur J Cancer 2016;57:58–67. [CrossRef]
12. Psutka SP, Boorjian SA, Moynagh MR, Schmit GD, Costello BA, Thompson RH, 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;195:270–6.
13. Sharma P, Zargar-Shoshtari K, Caracciolo JT, Fishman M, Poch MA, Pow-Sang J, et al. Sarcopenia as a predictor of overall survival after cytoreductive nephrectomy for metastatic renal cell carcinoma. Urol Oncol 2015;33:339.e17–23. [CrossRef]
14. Taguchi S, Nakagawa T. Re: Prognostic Significance of Sarcopenia in Patients with Metastatic Renal Cell Carcinoma: H. Fukushima, Y. Nakanishi, M. Kataoka, K. Tobisu and F. Koga J Urol 2016;195:26–32. J Urol 2016;195:1951–2. [CrossRef]
15. Higgins MI, Martini DJ, Patil DH, Nabavizadeh R, Steele S, Williams M, et al. Sarcopenia and modified Glasgow Prognostic Score predict postsurgical outcomes in localized renal cell carcinoma. Cancer 2021;127:1974–83. [CrossRef]
16. Motzer RJ, Rini BI, McDermott DF, Redman BG, Kuzel TM, Harrison MR, et al. Nivolumab for metastatic renal cell carcinoma: results of a randomized phase II trial. J Clin Oncol 2015;33:1430–7.

17. Yilmaz M. Atypical response patterns in metastatic melanoma and renal cell carcinoma patients treated with nivolumab: A single center experience. J Oncol Pharm Pract 2021;27:1106–11.
18. Budui SL, Rossi AP, Zamboni M. The pathogenetic bases of sarcopenia. Clin Cases Miner Bone Metab 2015;12:22–6. [CrossRef]
19. Mariathasan S, Turley SJ, Nickles D, Castiglioni A, Yuen K, Wang Y, et al. TGFβ attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells. Nature 2018;554:544–8.
20. Tsukamoto H, Fujieda K, Miyashita A, Fukushima S, Ikeda T, Kubo Y, et al. Combined blockade of IL6 and PD-1/PD-L1 signaling abrogates mutual regulation of their immunosuppressive effects in the tumor microenvironment. Cancer Res 2018;78:5011–22. [CrossRef]
21. Nelke C, Dziewas R, Minnerup J, Meuth SG, Ruck T. Skeletal muscle as potential central link between sarcopenia and immune senescence. EBioMedicine 2019;49:381–8. [CrossRef]
22. Ishihara H, Kondo T, Omae K, Takagi T, Iizuka J, Kobayashi H, et al. Sarcopenia and the modified glasgow prognostic score are significant predictors of survival among patients with metastatic renal cell carcinoma who are receiving first-line sunitinib treatment. Target Oncol 2016;11:605–17. [CrossRef]
23. 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.
24. van der Werf A, Langius JAE, de van der Schueren MAE, Nurmohamed SA, van der Pant KAMI, Blauwhoff-Buskermolen S, et al. Percentiles for skeletal muscle index, area and radiation attenuation based on computed tomography imaging in a healthy Caucasian population. Eur J Clin Nutr 2018;72:288–96.
25. Derstine BA, Holcombe SA, Ross BE, Wang NC, Su GL, Wang SC. Skeletal muscle cutoff values for sarcopenia diagnosis using T10 to L5 measurements in a healthy US population. Sci Rep 2018;8:11369. [CrossRef]
26. Hamaguchi Y, Kaido T, Okumura S, Kobayashi A, Shirai H, Yao S, et al. Proposal for new selection criteria considering pre-transplant muscularity and visceral adiposity in living donor liver transplantation. J Cachexia Sarcopenia Muscle 2018;9:246–54.
27. Ufuk F, Herek D. Reference skeletal muscle mass values at L3 Vertebrae level based on computed tomography in healthy Turkish adults. Int J Gerontol 2019;13:221e225.
28. Bahat G, Turkmen BO, Aliyev S, Catikkas NM, Bakir B, Karan MA. Cut-off values of skeletal muscle index and psoas muscle index at L3 vertebra level by computerized tomography to assess low muscle mass. Clin Nutr 2021;40:4360–5. [CrossRef]
29. Bilen MA, Martini DJ, Liu Y, Shabto JM, Brown JT, Williams M, et al. Combined effect of sarcopenia and systemic inflammation on survival in patients with advanced stage cancer treated with immunotherapy. Oncologist 2020;25:528–35. [CrossRef]
30. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 2011;12:489–95.
31. Pratesi A, Tarantini F, Di Bari M. Skeletal muscle: an endocrine organ. Clin Cases Miner Bone Metab 2013;10:11–4. [CrossRef]
32. Wherry EJ, Kurachi M. Molecular and cellular insights into T cell exhaustion. Nat Rev Immunol 2015;15:486–99. [CrossRef]
33. Kazemi-Bajestani SM, Mazurak VC, Baracos V. Computed tomography-defined muscle and fat wasting are associated with cancer clinical outcomes. Semin Cell Dev Biol 2016;54:2–10.
34. Daly LE, Power DG, O'Reilly Á, Donnellan P, Cushen SJ, O'Sullivan K, et al. The impact of body composition parameters on ipilimumab toxicity and survival in patients with metastatic melanoma. Br J Cancer 2017;116:310–7. [CrossRef]
35. Klatte T, Rossi SH, Stewart GD. Prognostic factors and prognostic models for renal cell carcinoma: a literature review. World J Urol 2018;36:1943–52. [CrossRef]
36. Fuhrman SA, Lasky LC, Limas C. Prognostic significance of morphologic parameters in renal cell carcinoma. Am J Surg Pathol 1982;6:655–63. [CrossRef]
37. Flint TR, Fearon DT, Janowitz T. Connecting the metabolic and immune responses to cancer. Trends Mol Med 2017;23:451–64.
38. Cortellini A, Bozzetti F, Palumbo P, Brocco D, Di Marino P, Tinari N, et al. Weighing the role of skeletal muscle mass and muscle density in cancer patients receiving PD-1/PD-L1 checkpoint inhibitors: a multicenter real-life study. Sci Rep 2020;10:1456.
39. Cortellini A, Verna L, Porzio G, Bozzetti F, Palumbo P, Masciocchi C, et al. Predictive value of skeletal muscle mass for immunotherapy with nivolumab in non-small cell lung cancer patients: A "hypothesis-generator" preliminary report. Thorac Cancer 2019;10:347–51. [CrossRef]
40. Kim N, Yu JI, Park HC, Yoo GS, Choi C, Hong JY, et al. Incorporating sarcopenia and inflammation with radiation therapy in patients with hepatocellular carcinoma treated with nivolumab. Cancer Immunol Immunother 2021;70:1593–603.
41. Roch B, Coffy A, Jean-Baptiste S, Palaysi E, Daures JP, Pujol JL, et al. Cachexia - sarcopenia as a determinant of disease control rate and survival in non-small lung cancer patients receiving immune-checkpoint inhibitors. Lung Cancer 2020;143:19–26.
42. Tsukagoshi M, Yokobori T, Yajima T, Maeno T, Shimizu K, Mogi A, et al. Skeletal muscle mass predicts the outcome of nivolumab treatment for non-small cell lung cancer. Medicine (Baltimore) 2020;99:e19059. [CrossRef]
43. Antoun S, Lanoy E, Iacovelli R, Albiges-Sauvin L, Loriot Y, Merad-Taoufik M, et al. Skeletal muscle density predicts prognosis in patients with metastatic renal cell carcinoma treated with targeted therapies. Cancer 2013;119:3377–84. [CrossRef]
44. Gu W, Zhu Y, Wang H, Zhang H, Shi G, Liu X, et al. Prognostic value of components of body composition in patients treated with targeted therapy for advanced renal cell carcinoma: a retrospective case series. PLoS One 2015;10:e0118022.
45. Hu X, Liao DW, Yang ZQ, Yang WX, Xiong SC, Li X. Sarcopenia predicts prognosis of patients with renal cell carcinoma: A systematic review and meta-analysis. Int Braz J Urol 2020;46:705–15.