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# Association between sarcopenia based on psoas muscle index and the response to nivolumab in metastatic renal cell carcinoma: A retrospective study

**Hideto Ueki[1], Takuto Hara[1], Yasuyoshi Okamura[1], Yukari Bando[1], Tomoaki Terakawa[1], Junya Furukawa[1], Kenichi Harada[2], Yuzo Nakano[1], Masato Fujisawa[1]**

*[1]Department of Urology, Kobe University Graduate School of Medicine, Kobe, [2]Department of Urology, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan*

**Purpose:** Two methods are used to identify sarcopenia by calculating skeletal muscle area on computed tomography: the skeletal muscle index (SMI) and the psoas muscle index (PMI). Programmed death (PD)-1 inhibitors are helpful in treating metastatic renal cell carcinoma (mRCC). However, there remains insufficient information regarding a clear and easy-to-use biomarker for predicting the response to PD-1 inhibitors in patients with mRCC. Therefore, we investigated the influence of sarcopenia on clinical outcomes in patients with mRCC undergoing treatment with nivolumab.

**Materials and Methods:** This study evaluated 96 patients with RCC who received nivolumab. The SMI and PMI were calculated for each patient and normalized for stature by use of the following formulas: SMI ($cm^2/m^2$)=([skeletal muscle cross-sectional area at the level of L3]/[height]$^2$) and PMI ($cm^2/m^2$) = ([left-right sum of the psoas muscle areas at the level of L3]/[height]$^2$). The relationship of the clinical variables with progression-free survival and overall survival (OS) was examined using a Cox proportional hazards model.

**Results:** According to the SMI-based definition of sarcopenia, 74.0% of patients had sarcopenia. However, according to the PMI-based definition of sarcopenia, only 34.3% of patients were diagnosed with sarcopenia. Multivariate analysis identified sarcopenia based on PMI (hazard ratio [HR], 3.85; 95% confidence interval [CI], 2.04–7.26; p<0.001) and International Metastatic RCC Database Consortium poor risk status (HR, 1.90; 95% CI, 1.03–3.50; p=0.041) as significant and independent prognostic factors of OS.

**Conclusions:** PMI-based sarcopenia is a significant prognostic factor for OS in patients with RCC who receive nivolumab therapy.

**Keywords:** Psoas muscles; Renal cell carcinoma; Sarcopenia; Skeletal muscle; Survival rate



## INTRODUCTION

Renal cell carcinoma (RCC) is a common type of kidney cancer. Approximately 20% of patients present with metastatic disease at the time of diagnosis, and one-third of patients treated for localized RCC with curative intent

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**Corresponding Author:** Hideto Ueki https://orcid.org/0000-0002-7742-4528
Department of Urology, Kobe University Graduate School of Medicine, Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan
TEL: + 81-78-382-5681, FAX: + 81-78-382-5715, E-mail: far.e.is.w@gmail.com

experience a relapse of disease at distant sites [1]. Treatment of metastatic RCC (mRCC) mainly consists of antiangiogenic drugs, sometimes preceded by debulking surgery. Five-year survival rates vary between approximately 88% (stage I) and 12% (stage IV) [2].

In the field of oncology, a meta-analysis has confirmed a significant relationship between sarcopenia and poor prognosis [3]. As a tool for diagnosing sarcopenia, the method of measuring muscle mass and density with software using axial computed tomography (CT) has been highly evaluated in terms of objectivity and reproducibility. There are two methods for calculating skeletal muscle area on CT: the skeletal muscle index (SMI) and the psoas muscle index (PMI) [4]. Previous data have suggested that sarcopenia is a significant prognostic factor in patients with mRCC [5].

Programmed death (PD)-1 inhibitors, such as nivolumab, are helpful in treating many types of advanced cancer, including mRCC. The CheckMate-025 trial data revealed that the median overall survival (OS) interval was longer for patients who received nivolumab relative to those who received everolimus (25.8 months vs. 19.7 months; $p<0.0005$) [6]. However, a long-term response to these agents is only expected in a specific subset of patients. Various biomarkers have been proposed for predicting this response, such as the PD-ligand 1 (PD-L1) and tumor mutation burden [7]; nevertheless, there remains insufficient information regarding a clear and easy-to-use biomarker for predicting the response to PD-1 inhibitors. Recent studies have indicated that nutritional parameters may predict the response to PD-1 inhibitors, such as the Eastern Cooperative Oncology Group performance status (ECOG-PS), body mass index (BMI), neutrophil-lymphocyte ratio, and sarcopenia [8]. The ECOG-PS and nutritional markers, such as hemoglobin and albumin, have also been identified as prognostic factors in patients with mRCC.

Cortellini et al. [9] reported that a low SMI is associated with shortened survival in advanced cancer patients, those with including melanoma, RCC, and lung cancer, treated with PD-1/PD-L1 checkpoint inhibitors [9]. Takenaka et al. [4] reported that poor survival and poor response in patients with sarcopenia indicate a negative association between sarcopenia and the efficacy of immune checkpoint inhibitors (ICIs) and that the predictive ability of sarcopenia is consistent across various tumor types [4]. However, there have been no reports on the relationship between sarcopenia and the therapeutic effect of nivolumab in mRCC, and it is unclear whether sarcopenia can be used as a biomarker for response to treatment with ICIs.

Therefore, this study aimed to retrospectively investigate the influence of SMI- and PMI-based sarcopenia on OS in patients receiving nivolumab for mRCC after previous treatment failure with a tyrosine kinase inhibitor (TKI).

## MATERIALS AND METHODS

### 1. Patients

This retrospective study evaluated 96 consecutive patients with RCC treated with nivolumab (240 mg/kg every 2 weeks) at Kobe University Hospital between December 2016 and October 2020. All patients underwent nivolumab therapy as a later than second-line therapy. Abdominal CT images were available for all patients. The extent of primary and metastatic lesions was determined from imaging studies, including CT, magnetic resonance imaging, and bone scintigraphy. Several variables were reviewed throughout the duration of nivolumab therapy, including age, sex, BMI, prior nephrectomy, nodal and metastasis status, histologic status, hemoglobin, corrected calcium, neutrophils, and platelets. We also collected information on the history of TKI therapy and metastasectomy after the diagnosis of mRCC. BMI was calculated as BMI ($kg/m^2$)=([weight]/[height]$^2$). Neutrophil, hemoglobin, corrected calcium, and platelet counts were categorized according to the International Metastatic RCC Database Consortium (IMDC) risk model.

### 2. Image analysis

CT images obtained at the induction of nivolumab therapy for RCC were used for the analysis. A multidetector CT scanner (Revolution CT, GE Healthcare Japan Co., Ltd., Tokyo, Japan) was used to obtain all pretreatment CT images. The technical parameters of the CT were as follows: 0.23 mm×256 rows (detector configuration), tube current modulation, 0.28 s/rotation (gantry rotation), and up to 512 slices of image data per rotation with a maximum total coverage of 160 mm in the z-direction. L3 was set as a landmark, and the cross-sectional areas of the skeletal muscle complement were identified by using attenuation thresholds of -29 to +150 HU in OsiriX Imaging Software (Pixmeo, Geneva, Switzerland). One investigator (Ueki), blinded to other clinical parameters and patient outcomes, performed all image analyses. The skeletal muscles at the L3 level included the psoas, paraspinal muscles (erector spinae and quadratus lumborum), and abdominal wall muscles (transversus abdominus, external and internal obliques, and rectus abdominus) (Fig. 1). The image was calculated for each patient and normalized for stature by using the formula SMI ($cm^2/m^2$)=([skeletal muscle cross-sectional area at the level of L3]/[height]$^2$). To calculate the PMI, the outer margin of the cross-section of the major



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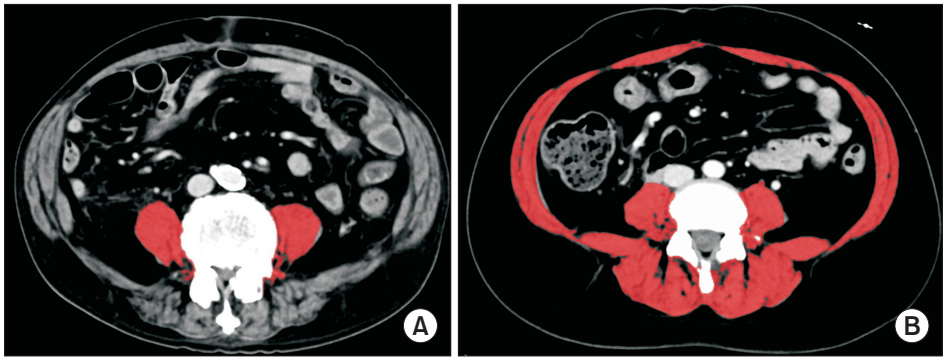


Fig. 1. Image analysis using OsiriX Imaging Software. Psoas muscle area (A) and skeletal muscle area (B) on the preoperative cross-sectional computed tomography images at the third lumbar vertebra level of patients.

psoas muscle at the level of L3 was manually traced on CT images, and the sum of the left and right cross-sectional areas was divided by the square of the height: PMI ($cm^2/m^2$)=([sum of the bilateral psoas muscle areas at the level of L3]/[height]$^2$).

### 3. Statistical analysis

This study aimed to evaluate the correlation between sarcopenia and progression-free survival (PFS) and OS. Sarcopenia was diagnosed by use of the SMI and PMI. The cutoff value of SMI for diagnosis of sarcopenia was determined by using the criteria of Martin et al. [10], defined as SMI <43 $cm^2/m^2$ for males with a BMI <25 $kg/m^2$, <53 $cm^2/m^2$ for males with BMI ≥25 $kg/m^2$, and <41 $cm^2/m^2$ for females. Our study's PMI cutoff values for sarcopenia were 6.36 $cm^2/m^2$ for males and 3.92 $cm^2/m^2$ for females, which were based on a previous report defining sarcopenia in Asian adults [11]. PFS was defined as the time between treatment initiation and disease progression or death from any cause; OS was defined as the length of time from the beginning of nivolumab treatment to the date of death or the last follow-up. Kaplan–Meier curves were constructed, and the log-rank test was used to compare PFS and OS between groups. The relationship between clinical variables, PFS, and OS was examined by using a Cox proportional hazards model. A reduced multivariate model was generated by backward elimination of the variable with the highest p-value from each iteration of the multivariate analysis. All statistical analyses were conducted using EZR (Saitama Medical Center, Jichi Medical University, Shimotsuke-shi, Tochigi-ken, Japan). Statistical significance was set at $p<0.05$.

### 4. Ethical statement

The Institutional Ethical Committee approved the current study protocol (approval no. B210259). Written informed consent was obtained from all patients.

## RESULTS

### 1. Clinical characteristics

Table 1 shows the clinicopathological characteristics of the 96 patients included in this study; 74.0% were male, and BMI was ≥25 $kg/m^2$ in 25.0% of patients. All patients were treated by nivolumab. Nivolumab was a second-line therapy in 55.2% of those patients and a third-line therapy or later in the other 44.8%. TKI had been used as a prior therapy in almost all patients. Approximately 30% of patients were ≥75 years of age. Patients had primarily intermediate (54.2%) or poor (41.7%) risk status according to the IMDC criteria. A total of 89.6% of patients had metastatic sites at baseline, with lung metastasis being the most common (64.6%). Of the 15 non–clear cell RCC cases, 7 were papillary RCC, 2 were Xp11.2 translocation RCC, 2 were spindle cell carcinoma, 1 was rhabdoid variant, 1 was granular cell carcinoma, and 2 were unclassified. In these cases, TKI was introduced as the first-line treatment, followed by nivolumab as a sequential treatment. Cabozantinib was not yet available, so no cases were treated with cabozantinib in this cohort. The PMI-based sarcopenia group included significantly more males, and it included a higher number of patients with poor IMDC risk classification. Almost all patients with M0 RCC had an inferior vena cava (IVC) tumor thrombus, and they received TKI as a presurgical therapy to reduce tumor volume. However, some cases were switched to nivolumab because of a poor response to TKI therapy, and others were introduced to nivolumab because of postoperative tumor recurrence as an IVC thrombus. These cases were therefore counted as cases with "no metastasis."

### 2. Sarcopenia

The median SMI and PMI were 40.4 $cm^2/m^2$ and 6.26 $cm^2/m^2$, respectively. When stratified by sex, the median SMI and PMI were higher in males (41.9 $cm^2/m^2$, IQR: 37.0–46.6 $cm^2/m^2$; and 6.67 $cm^2/m^2$, respectively) than in females (36.1

**Table 1.** Clinical characteristics of nivolumab-treated patients (n=96)

| Parameter | Based on SMI | | | Based on PMI | | |
|---|---|---|---|---|---|---|
| | Non-sarcopenia | Sarcopenia | p-value | Non-sarcopenia | Sarcopenia | p-value |
| Age (median, y) | | | 0.804 | | | 0.821 |
| <75 | 18 (72.0) | 47 (66.2) | | 42 (66.7) | 23 (69.7) | |
| ≥75 | 7 (28.0) | 24 (33.8) | | 21 (33.3) | 10 (30.3) | |
| Sex | | | 0.796 | | | 0.007* |
| Male | 18 (72.0) | 53 (74.6) | | 41 (65.1) | 30 (90.9) | |
| Female | 7 (28.0) | 18 (25.4) | | 22 (34.9) | 3 (9.1) | |
| BMI (kg/m$^2$) | | | 0.18 | | | 0.326 |
| <25 | 16 (64.0) | 56 (78.9) | | 45 (71.4) | 27 (81.8) | |
| ≥25 | 9 (36.0) | 15 (21.1) | | 18 (28.6) | 6 (18.2) | |
| Nephrectomy | | | 0.737 | | | >0.999 |
| No | 4 (16.0) | 9 (12.7) | | 9 (14.3) | 4 (12.1) | |
| Yes | 21 (84.0) | 62 (87.3) | | 54 (85.7) | 29 (87.9) | |
| Nodal status | | | >0.999 | | | 0.437 |
| N0 | 20 (80.0) | 55 (77.5) | | 51 (81.0) | 24 (72.7) | |
| ≥N1 | 5 (20.0) | 16 (22.5) | | 12 (19.0) | 9 (27.3) | |
| Number of metastases | | | 0.694 | | | 0.881 |
| 0 | 2 (8.0) | 8 (11.3) | | 8 (12.7) | 2 (6.1) | |
| 1 | 13 (52.0) | 36 (50.7) | | 32 (50.8) | 17 (51.5) | |
| ≥2 | 10 (40.0) | 27 (38.0) | | 23 (36.5) | 14 (42.4) | |
| Sites of metastasis | | | | | | |
| Lung | 13 (50.0) | 49 (66.2) | 0.149 | 39 (60.9) | 23 (63.9) | 0.506 |
| Liver | 3 (11.5) | 7 (9.5) | 0.717 | 4 (6.3) | 6 (16.7) | 0.088 |
| Bone | 10 (38.5) | 18 (24.3) | 0.203 | 21 (32.8) | 7 (19.4) | 0.246 |
| Metastasectomy | | | 0.446 | | | >0.999 |
| No | 24 (96.0) | 62 (87.3) | | 53 (84.1) | 33 (100.0) | |
| Yes | 1 (4.0) | 9 (12.7) | | 10 (15.9) | 0 (0.0) | |
| Histologic status | | | 0.501 | | | 0.761 |
| Clear cell | 20 (80.0) | 51 (71.8) | | 47 (74.6) | 24 (72.7) | |
| Non–clear cell | 2 (8.0) | 13 (18.3) | | 9 (14.3) | 6 (18.2) | |
| Unknown | 3 (12.0) | 7 (9.9) | | 7 (11.1) | 3 (9.1) | |
| Hemoglobin (g/dL) | | | 0.289 | | | >0.999 |
| <13.7 | 20 (80.0) | 64 (90.1) | | 55 (87.3) | 29 (87.9) | |
| ≥13.7 | 5 (20.0) | 7 (9.9) | | 8 (12.7) | 4 (12.1) | |
| Corrected calcium (mg/dL) | | | >0.999 | | | 0.069 |
| <10.0 | 22 (88.0) | 60 (84.5) | | 57 (90.5) | 25 (75.8) | |
| ≥10.0 | 3 (12.0) | 11 (15.5) | | 6 (9.5) | 8 (24.2) | |
| Neutrophil (×10$^2$/μL) | | | 0.26 | | | 0.344 |
| <70.0 | 24 (96.0) | 71 (100.0) | | 63 (100.0) | 32 (97.0) | |
| ≥70.0 | 1 (4.0) | 0 (0.0) | | 0 (0.0) | 1 (3.0) | |
| Platelet (×10$^4$/μL) | | | 0.1 | | | 0.523 |
| <24.0 | 18 (72.0) | 36 (50.7) | | 37 (58.7) | 17 (51.5) | |
| ≥24.0 | 7 (28.0) | 35 (49.3) | | 26 (41.3) | 16 (48.5) | |
| IMDC | | | 0.246 | | | 0.03* |
| Favorable | 1 (4.0) | 3 (4.2) | | 3 (4.8) | 1 (3.0) | |
| Intermediate | 11 (44.0) | 41 (57.7) | | 39 (61.9) | 13 (39.4) | |
| Poor | 13 (52.0) | 27 (38.0) | | 21 (33.3) | 19 (57.6) | |



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Table 1. Continued

| Parameter | Based on SMI | | | Based on PMI | | |
|---|---|---|---|---|---|---|
| | Non-sarcopenia | Sarcopenia | p-value | Non-sarcopenia | Sarcopenia | p-value |
| Number of previous therapies | | | 0.125 | | | 0.09 |
| 1 | 12 (48.0) | 41 (57.7) | | 40 (63.5) | 13 (39.4) | |
| 2 | 8 (32.0) | 25 (35.2) | | 18 (28.6) | 15 (45.5) | |
| ≥3 | 5 (20.0) | 5 (7.1) | | 5 (7.9) | 5 (15.2) | |

Values are presented as number (%).
IMDC, International Metastatic Renal Cell Carcinoma Database Consortium.
*Statistically significant at p<0.05.

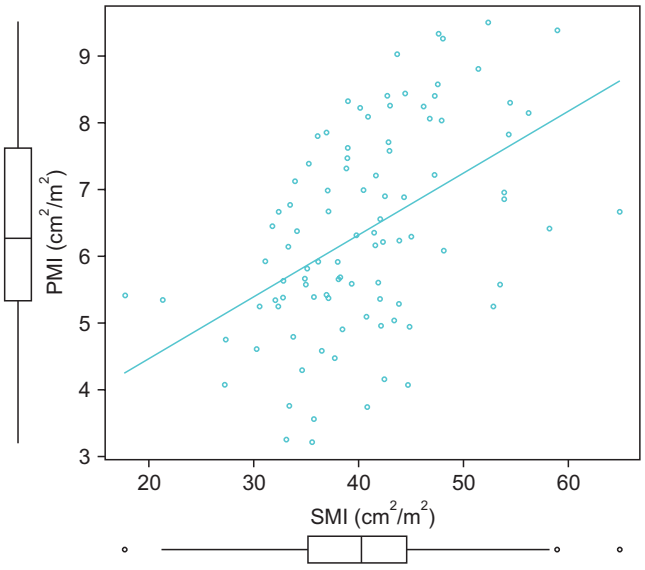


Fig. 2. Scatter plots and correlations. A moderate correlation between the skeletal muscle index (SMI) and the psoas muscle index (PMI) was found (r=0.488, 95% confidence interval: 0.319–0.627, p<0.001).

cm²/m² and 5.39 cm²/m², respectively). According to the SMI-based definition of sarcopenia, there were 71 patients (74.0%) with sarcopenia and 24 (26.0%) without sarcopenia. However, according to the PMI-based definition of sarcopenia, there were 33 patients (34.4%) with sarcopenia and 63 (65.6%) without sarcopenia (Table 1). Despite the large discrepancy in the diagnostic rate of sarcopenia, there was a moderate correlation between SMI and PMI (r=0.488; 95% confidence interval [CI], 0.319–0.627; p<0.001; Fig. 2).

Table 2 lists objective response data according to the iRECIST criteria. Although the treatment responsiveness was compared according to the presence of sarcopenia, there were no significant differences in treatment response for SMI-based and PMI-based sarcopenia.

### 3. Influence of sarcopenia on OS

A total of 46 patients (47.9%) died during follow-up (median, 9.7 months; range, 0.3–48.4 months). The median OS was 26.4 months. Patients with PMI-based sarcopenia had a significantly shorter median OS and PFS than patients without sarcopenia (10.1 months vs. 48.4 months, p<0.001; and 1.9 months vs. 8.3 months, p<0.001, respectively) (Fig. 3). As shown in Table 3, the multivariate analysis identified PMI-based sarcopenia as a significant and independent predictor of OS (hazard ratio [HR], 3.85; 95% CI, 2.04–7.26; p<0.001), along with poor IMDC risk status (HR, 1.90; 95% CI, 1.03–3.50; p=0.041). SMI-based sarcopenia was not associated with OS in this study. Multiple analyses also showed that although neither definition of sarcopenia was a significant predictor of PFS, poor IMDC risk status and histologic status were significant prognostic factors (HR, 1.86; 95% CI, 1.01–3.40; p=0.045; and HR, 2.37; 95% CI, 1.22–4.63; p=0.011, respectively).

## DISCUSSION

In the present study, we observed a significant association between PMI-based sarcopenia and a worse prognosis for patients with RCC (univariate analysis, p<0.001; multivariate analysis, p<0.001; Table 3). The most important finding in our study was that although there was a correlation between PMI and SMI, there was a large discrepancy in the proportion of patients diagnosed with sarcopenia by use of each cutoff, and SMI-based sarcopenia was not associated with prognosis. These findings emphasize the importance of using PMI as a prognostic factor in patients receiving nivolumab therapy for RCC.

In general, SMI is the most commonly used index in the literature [9,12] and is calculated as the total skeletal muscle area at the level of the third lumbar vertebra divided by height squared. This index is closely correlated with whole-body muscle mass [13] and is associated with various health-related outcomes. Although some studies have demonstrated a relationship between SMI and the total area of skeletal muscles at the level of L3 [13,14], the assessment of SMI requires dedicated specialized software because a wide variety of muscles must be measured, including the psoas, erector spinae, quadratus lumborum, transversus abdominis, rectus

**Table 2.** Differences in response to nivolumab with and without sarcopenia

| Sarcopenia | Complete response | Partial response | Stable disease | Progressive disease | p-value |
|---|---|---|---|---|---|
| Based on skeletal muscle index | | | | | |
| (-) | 1 (4.0) | 6 (24.0) | 7 (28.0) | 9 (36.0) | 0.921 |
| (+) | 4 (5.6) | 19 (26.8) | 15 (21.1) | 27 (38.0) | |
| Based on psoas muscle index | | | | | |
| (-) | 4 (6.3) | 16 (25.4) | 18 (28.6) | 20 (31.7) | 0.111 |
| (+) | 0 | 9 (27.3) | 4 (12.1) | 16 (48.5) | |

Values are presented as number (%).

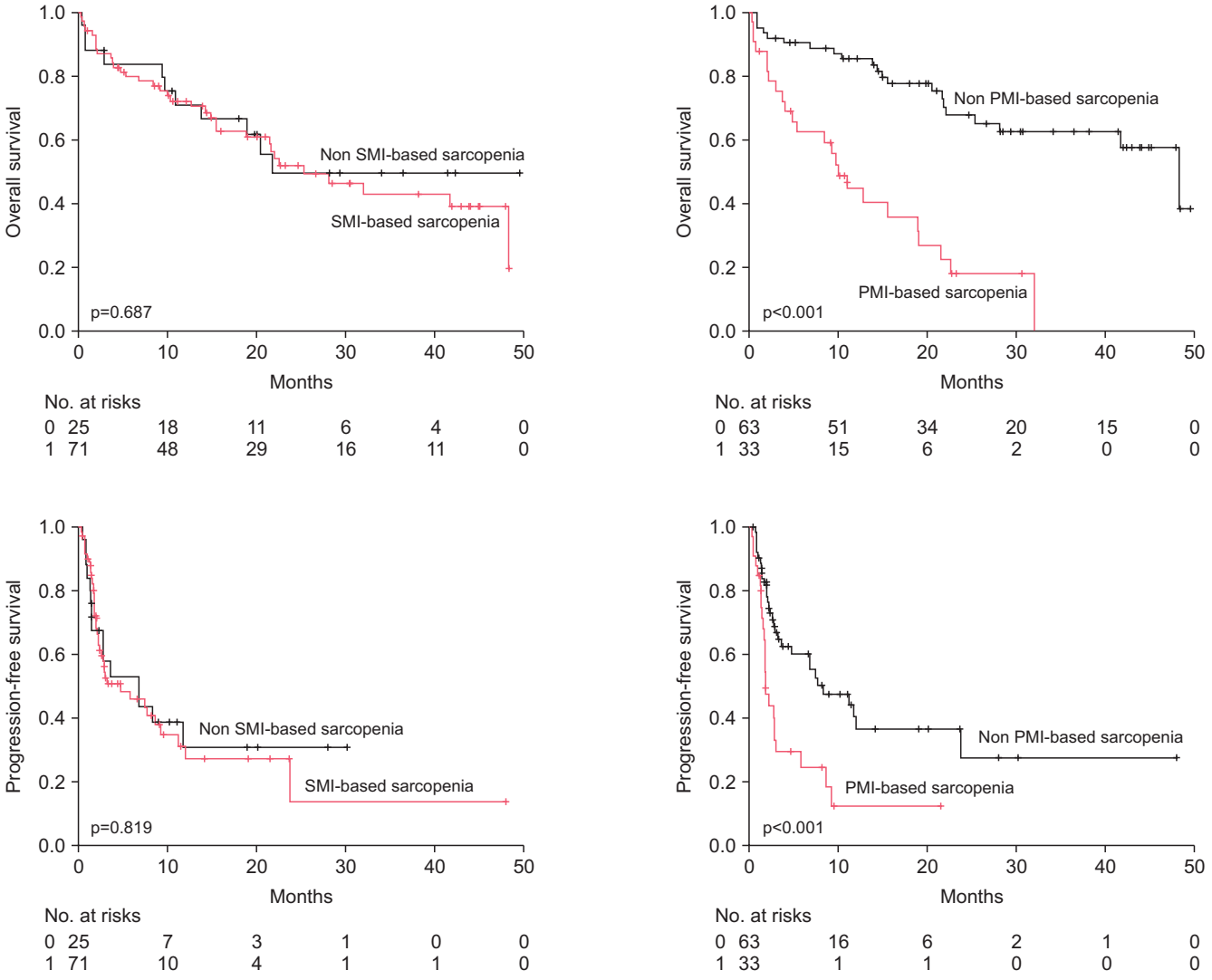


**Fig. 3.** Kaplan–Meier curves according to presence of sarcopenia. Patients with psoas muscle index (PMI)-based sarcopenia had a significantly shorter median overall survival (OS) and progression-free survival (PFS) than patients without sarcopenia. However, skeletal muscle index (SMI)-based sarcopenia was not associated with OS or PFS.

abdominis, and external and internal oblique abdominal muscles. The PMI uses the psoas central muscle area instead of the total skeletal muscle area. The PMI is calculated as the sum of the bilateral psoas muscle areas at the level of L3 divided by height squared. It is easier to calculate, and a cutoff value has been proposed for Asian adults [11]. Although some studies have suggested that PMI is not a good indicator, Yamada et al. [15] reported that PMI is an important biomarker and that measuring SMI alone is inadequate. Their report supports the results of our study, in which the results differed significantly between SMI and PMI [16]. The fact that only PMI-based sarcopenia was a prognostic factor


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**Table 3.** Cox regression analysis for overall survival and progression-free survival

| Parameter | Overall survival | | | | | | Progression-free survival | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Univariate | | | Multivariate | | | Univariate | | | Multivariate | | |
| | HR | 95% CI | p-value | HR | 95% CI | p-value | HR | 95% CI | p-value | HR | 95% CI | p-value |
| Age (<75 y vs. ≥75 y) | 0.87 | 0.46–1.62 | 0.65 | - | - | - | 0.748 | 0.42–1.34 | 0.33 | - | - | - |
| Sex (female vs. male) | 1.95 | 0.90–4.20 | 0.09 | - | - | - | 0.97 | 0.53–1.76 | 0.92 | - | - | - |
| BMI (<25 kg/m$^2$ vs. ≥25 kg/m$^2$) | 1 | 0.50–1.97 | 0.99 | - | - | - | 1.52 | 0.84–2.73 | 0.16 | - | - | - |
| Nephrectomy (no vs. yes) | 0.62 | 0.29–1.33 | 0.22 | - | - | - | 1.19 | 0.53–2.67 | 0.67 | - | - | - |
| Nodal status (N0 vs. ≥N1) | 1.2 | 0.59–2.42 | 0.62 | - | - | - | 1.01 | 0.53–1.92 | 0.98 | - | - | - |
| Metastasis status (M0 vs. M1) | 1.88 | 1.02–3.47 | 0.04* | 1.61 | 0.86–2.99 | 0.135 | 1.8 | 1.04–3.11 | 0.03* | 1.71 | 0.94–3.11 | 0.08 |
| Metastasectomy (no vs. yes) | 0.59 | 0.21–1.66 | 0.32 | - | - | - | 0.42 | 0.13–1.33 | 0.14 | - | - | - |
| Histological status (clear vs. non-clear cell) | 2.07 | 0.98–4.37 | 0.06 | - | - | - | 2.05 | 1.07–3.93 | 0.03* | 2.37 | 1.22–4.63 | 0.011* |
| IMDC status (favorable+intermediate vs. poor) | 2.62 | 1.44–4.76 | 0.002* | 1.90 | 1.03–3.50 | 0.041* | 1.9 | 1.11–3.22 | 0.02* | 1.86 | 1.01–3.40 | 0.045* |
| Number of previous therapies (1 vs. ≥2) | 1.66 | 0.92–3.00 | 0.09 | - | - | - | 1.09 | 0.64–1.84 | 0.76 | - | - | - |
| Sarcopenia based on SMI (no vs. yes) | 1.15 | 0.58–2.27 | 0.69 | - | - | - | 1.07 | 0.59–1.95 | 0.82 | - | - | - |
| Sarcopenia based on PMI (no vs. yes) | 4.53 | 2.45–8.44 | <0.001* | 3.85 | 2.04–7.26 | <0.001* | 2.45 | 1.42–4.23 | 0.001* | 1.80 | 0.98–3.29 | 0.057 |

HR, hazard ratio; CI, confidence interval; BMI, body mass index; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; SMI, skeletal muscle index; PMI, psoas muscle index.
*Statistically significant at p<0.05.

indicates the relative importance of the iliopsoas volume. As indicated in Table 1, the PMI-based sarcopenia group included significantly more patients with poor risk status according to the IMDC model, suggesting that there may be a slight relationship between PMI-based sarcopenia and IMDC risk items. We performed an additional study to determine whether there was a correlation between PMI and calcium, platelets, neutrophils, and hemoglobin. As shown in Fig. 4, there was a mild correlation for calcium and platelets; however, none of the correlation coefficient values indicated a significant correlation. PMI could be an accurate prognostic factor of the nutritional status of cancer patients because it reflects the amount of daily activity, including walking, more accurately. On the other hand, the PMI-based sarcopenia group had a higher proportion of patients with poor risk status (33.3% vs. 57.6%, p=0.03) and more than third-line treatment (7.9% vs. 15.2%, p=0.09); therefore, we need to consider the possibility that sarcopenia is the result of worsening of the disease status and performance status of patients over time. The prognostic role of PMI in the balanced patient and treatment setting should be examined further.

There have been previous reports on the relationship between prognosis and sarcopenia in patients being treated with ICIs. Martini et al. [17] focused on the fat index and reported on the prognosis of ICI-treated mRCC patients. They also calculated the SMI as in our report; however, they classified patients into body composition risk groups and examined prognosis in combination with the index calculated from the fat area. They did not examine whether SMI alone is a prognostic factor. Shiroyama et al. [18] reported that PMI-based sarcopenia at baseline is a significant predictor of worse outcomes in patients with advanced non–small cell lung carcinoma receiving PD-1 blockade. A recent meta-analysis [4] also reported a negative association between sarcopenia based on SMI and the efficacy of ICIs in solid cancers. However, it has been reported that the cutoff values associated with the same diagnostic measure vary across studies. Cutoff values of 7 and 40 have been used for PMI and SMI, respectively. We need to pay attention to this point in the diagnosis of sarcopenia. Although we used the most widely used cutoff value in this study, it is necessary to search for cutoff values optimized by race and other factors.

There are various reports on the mechanisms by which sarcopenia negatively affects the prognosis of patients with cancer. Chronic inflammation due to tumors, a significant contributor to sarcopenia, results in tumor cell immune escape through mechanisms such as T-cell exhaustion [19]. With the concept of skeletal muscle as an endocrine organ that releases cytokines, namely myokines, receiving greater

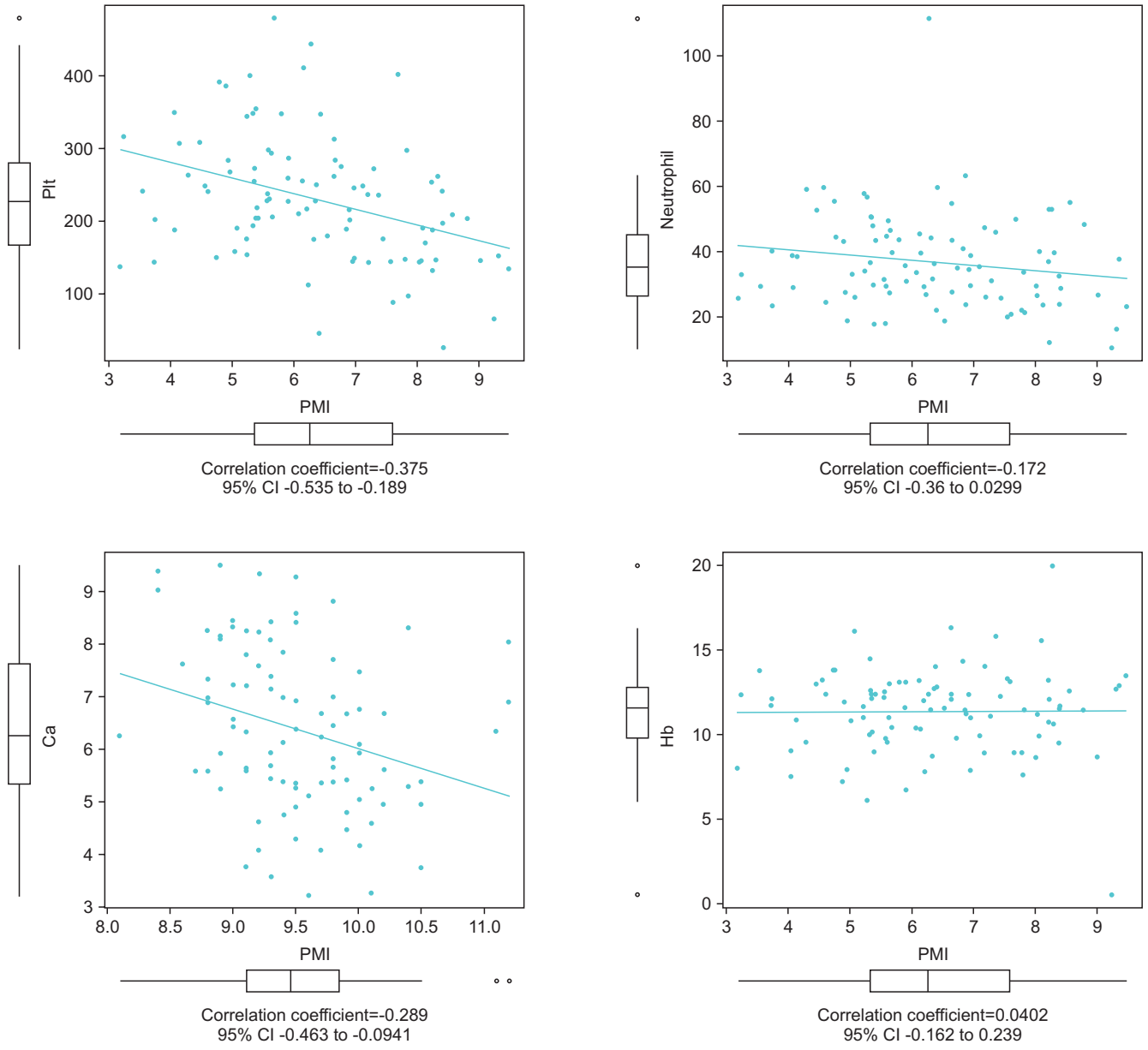


**Fig. 4.** Correlation coefficients between the psoas muscle index (PMI) and blood test items included in the IMDC risk model. There was a mild correlation between PMI and platelets (Plt) and calcium (Ca) (correlation coefficient: -0.375, 95% confidence interval [CI]: -0.535 to -0.189, and correlation coefficient: -0.289, 95% CI: -0.463 to -0.0941, respectively). However, none of the correlation coefficient values indicated a significant correlation. Hb, hemoglobin; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium.

attention [20], Okumura et al. [21] reported that decreasing muscle mass leads to lower myokine production, which causes decreased immunity. Myokines are defined as proteins, including interleukin (IL)-6, IL-8, and IL-15. Among these myokines, Waldmann et al. [22] reported that IL-15 increases the proportion of circulating natural killer cells and CD8+ T-cells. In addition, administration of IL-15 in combination with ICIs prolongs the survival of tumor-bearing mice [23]. Thus, changes in myokine levels resulting from sarcopenia may affect the efficacy of ICI treatment, indicating the predictive value of sarcopenia in immune therapy. Conversely, treatment to maintain skeletal muscle volume may be significant, as compromised immunity is likely to improve with increased skeletal muscle mass.

Many previous studies have investigated the relationship between objective factors from a single CT image and patient prognosis. In addition to skeletal muscle area and density, there are various other evaluable factors, including subcutaneous fat and visceral fat. Which part of the CT image is a better predictor could vary depending on the type of cancer and its treatment. This study was surprising in that PMI was the more significant prognostic factor, although


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SMI should reflect the whole body more than PMI. This suggests that it is not simply a matter of muscle volume but also that the quality and location of the muscle may be essential for cytokine secretion. From this point of view, myosteatosis, defined as increased fat infiltration in skeletal muscle, has recently drawn attention as a novel preoperative marker for predicting the prognosis of patients with various cancers [24]. Whether myosteatosis is less likely to occur in the iliopsoas muscle, and the specific muscles areas that are significant for ICI treatment, needs to be examined.

The present study had several limitations. This study had a retrospective design and a small sample size. Therefore, a more extensive prospective study is needed to confirm the prognostic role of sarcopenia in patients with RCC treated with nivolumab. Moreover, changes over time in skeletal muscle volume and weight after introducing ICIs, which frequently occur as a symptom of cancer cachexia, were not evaluated in the present study [25]. Finally, the cutoff values for SMI- and PMI-based sarcopenia have not been clearly defined. The volume of skeletal muscle mass differs according to ethnicity [26]. The PMI cutoff value was defined in a previous Asian study. However, the SMI cutoff we used was defined in a previous Western study. Validation studies are needed to examine whether sarcopenia based on PMI is more valuable than sarcopenia based on SMI in terms of prognosis in patients with RCC.

## CONCLUSIONS

PMI-based sarcopenia was a significant prognostic factor in patients with RCC who underwent nivolumab therapy. We hope to perform a more extensive prospective study with an evaluation of PMI and SMI to confirm our present findings and provide a helpful predictive model that includes skeletal muscle and other imaging factors, such as a fat index, in the future.

## CONFLICTS OF INTEREST

The authors have nothing to disclose.

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## AUTHORS' CONTRIBUTIONS

Research conception and design: Hideto Ueki and Takuto Hara. Data acquisition: Hideto Ueki, Takuto Hara, Yasuyoshi Okamura, Yukari Bando, Tomoaki Terakawa, Junya Furukawa, Kenichi Harada, and Yuzo Nakano. Statistical analysis: Hideto Ueki. Data analysis and interpretation: Hideto Ueki. Drafting of the manuscript: Hideto Ueki. Critical revision of the manuscript: Masato Fujisawa. Obtaining funding: none. Administrative, technical, or material support: none. Supervision: Takuto Hara, Yasuyoshi Okamura, Yukari Bando, Tomoaki Terakawa, Junya Furukawa, Kenichi Harada, Yuzo Nakano, and Masato Fujisawa. Approval of the final manuscript: all authors.

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