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Research Article

Prognostic Effect of Psoas Muscle Index, a Parameter of Sarcopenia, in Solid Cancer Patients Receiving Immunotherapy

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Abstract

Objectives: In this study, our objective was to evaluate the prognostic feature of sarcopenia and prognostic laboratory markers, defined by using PMI measurement in patients with kidney cancer and malignant melanoma, receiving immunotherapy.

Methods: Diagnosed with and followed up for kidney cancer (RCC) and malignant melanoma (MM) and received Nivolumab immunotherapy in the Oncology Clinic, were retrospectively analyzed. Laboratory examinations and CT images used for staging in the diagnosis were retrospectively used for psoas muscle measurements.

Results: We investigated the effect of pretreatment PMI on survival and response to treatment. For this purpose, 93 patients with malignant melanoma (n=45) and kidney cancer (n=48) were included in the study. Among female patients with and without sarcopenia at baseline, median progression-free survival was 30.2 and 50.1 months (p=0.769), respectively, while in men, conversely, 54.8 and 34.3 months (p=0.307), respectively. Median overall survival was 31.0 and 51.7 months (p=0.763) in female patients with and without sarcopenia, respectively, and 62.9 and 52.4 months in males with and without sarcopenia (p=0.906).

Conclusion: This result may suggest that sarcopenia has a negative effect on the immune response. It should be considered that sarcopenia may affect the clinical outcomes of immunotherapy. Further studies are needed.

Keywords: PMI, sarcopenia, metabolic index, solid cancer, immunotherapy

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The term sarcopenia, defined as a gradual decrease in muscle strength and mass with age, and firstly defined by Dr. Irwin Rosenberg in the 1980s, is a condition that increasingly progresses after the fourth decade of life.[1,2] Baumgartner et al. used x-ray absorptiometry to predict age-related sarcopenia, which is a public health problem, in comparison with younger people.[3]

Initially associated with age, sarcopenia has also been associated with adverse outcomes in many chronic diseases. Sarcopenia is quite common in the oncological patient group. Previous results in studies of sarcopenia in oncology suggest that the prevalence in adults with cancer ranges from 11% to 74%, depending on the method used and the study population involved.[4] In addition, the incidence of

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sarcopenia is high in studies conducted with more specific patient groups with solid cancer. This rate was detected as 43% in patients with non-small cell lung cancer (NSCLC), 52% in patients with small cell lung cancer (SCLC),[5] 57% in patients with gastric cancer,[6] and 29% in patients with metastatic renal cell carcinoma.[7]

Recently, the effect of sarcopenia in oncology has attracted attention. The increase in research on sarcopenia may be largely due to the prevalence of computed tomography (CT) used in staging as a part of routine care in oncology, and therefore its use in retrospective studies. Although studies related to body weight and body mass index (BMI) have been conducted in cancer patients, these parameters are often inaccurate and are not sufficient to distinguish between different tissue components of the body.[8] Numerous techniques and methodologies are now available to assess body composition, ranging from simple anthropometric measurements to more advanced magnetic resonance imaging (MRI).[9] CT, an important imaging method, is usually a measurement based on a single section at the level of the L3 vertebra to estimate body composition for the diagnosis of sarcopenia. This can be advantageous not only in determining the amount of muscle mass, but also in providing information about skeletal muscle density.[10]

Retrospective studies on sarcopenia may not be sufficient to evaluate every factor that may cause sarcopenia. Because there are many different causes that can be associated with sarcopenia in cancer patients. For example, major factors such as cachexia caused by the cancer itself, the effect of the treatments and age will affect the results.[11] In this respect, it seems that it is quite difficult to accurately determine the causes of changes in muscle mass measurements.

Hamaguchi et al. reported a strong and significant relationship between psoas muscle mass and all skeletal muscle mass measured by bio-impedance analysis.[12] Based on these data, it has been suggested that psoas muscle mass can be used as a parameter to evaluate skeletal muscle mass of the whole body. It has been previously reported that psoas muscle mass index (PMI) is a prognostic factor in patients with various types of cancer (gastrointestinal, liver, pancreatic, urological cancer, etc.).[13-18]

Immune check-point inhibitors (ICI) have shown to be a more effective treatment option than chemotherapy treatment, which is used very frequently and is now a historical treatment in solid cancer patients.[19,20] Although this treatment is a revolutionary treatment option, the search for parameters that will show which patients will respond positively or negatively to this treatment continues.[21,22] Recently, several studies have shown the adverse effect of sarcopenia on patients receiving ICI therapy, such as lung cancer, melanoma, gastrointestinal tract, urothelial carcinoma.[23-25] However, it is unclear whether sarcopenia is a predictive factor for clinical outcomes in patients with malignancy receiving ICI. A meta-analysis demonstrated the association between sarcopenia and immunotherapy, especially in patients with non-small cell lung cancer.[26] In our study, patients with kidney cancer and malignant melanoma who received Nivolumab immunotherapy were examined in order to examine the effect of sarcopenia on the immune treatment response. In these patients, sarcopenia was defined by retrospective measuring of muscle masses from routine CT images taken for diagnosis and staging, and the aim was to investigate the relationship of sarcopenia with immunotherapy efficacy and prognostic markers.

Methods

Between 31.01.2013 and 09.01.2022, 93 patients who were diagnosed with and followed up for kidney cancer (RCC) and malignant melanoma (MM) and received Nivolumab immunotherapy in the Oncology Clinic of Antalya Training and Research Hospital, were retrospectively analyzed. Patients receiving Nivolumab were grouped according to these two diseases.

After institutional ethics review approval, general and demographic information of patients from electronic medical records and oncology archive files (age, gender, height-weight, smoking history and performance information) were collected. Apart from this information of the patient, diagnosis, date of diagnosis, stage at diagnosis, histological subtypes, metastasis sites and laboratory results were recorded. Evaluation in terms of sarcopenia was obtained by making measurements from CTs taken at the time of diagnosis. In addition, the progression of the disease (if any), the last control date and survival were noted. The patients were classified as local (Stage 1-2), locally advanced (Stage 3) and advanced (Stage 4) at the time of diagnosis.

The results of the patients whose caliper measurements from the triceps skinfold were recorded during their nutritional assessment were analyzed. The caliper instrument, which is generally used as one of the anthropometric measurements of nutritional assessment, is an instrument used to measure skinfold thickness that allows the evaluation of the thickness of the subcutaneous adipose tissue.[27]

From the laboratory examinations of the patients at the time of diagnosis, Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR) and lymphocyte/monocyte ratio (LMR), Systemic Inflammatory Index (SII), Prognostic Nutritional Index (PNI), Pan-immune Inflammation Value (PIV), Hemoglobin-Albumin - Lymphocyte-Platelet (HALP) scores and LIPI: Lung Immune Prognostic Index, known as prognostic and inflammatory indices, were calculated by using hemogram, LDH, albumin and calcium values.

These indicators were SII = platelet count (10^9/L) x neutrophil count/lymphocyte count (10^9/L); NLR = neutrophil

count (10^9/L)/lymphocyte count (10^9/L); PLR = platelet count (10^9/L)/ lymphocyte count (10^9/L);[19] PIV = neutrophil count (10^9/L) × platelet count (10^9/L) × monocyte count (10^9/L)/lymphocyte count (10^9/L), and HALP score = hemoglobin (g/L) × albumin (g/L) × lymphocytes (/L)/platelets (/L). The relationship of these scores with the muscle measurements described below and their effect on treatment responses were examined.

Evaluation of Sarcopenia

CT images used for staging in the diagnosis were retrospectively used for psoas muscle measurements. A radiologist measured the cross-sectional areas of the bilateral psoas muscles by manually measuring CT images of the mid-level of the third lumbar vertebra using a software program (Sectra Workstation IDS7 Version: 21.2.9.6220 #2019 Sectra AB). Consistent with the literature, measured PMI (mm^2/m^2) was calculated by normalizing the psoas muscle area for height in square meters.

The cut-off points for PMI found in the literature were used to evaluate the sarcopenic status of the patients. Due to differences in PMI values between male and female patients, separate cut-off points were used for survival for males and females. In the literature, cut-off values of <6.36 cm^2/m^2 for men and <3.92 cm^2/m^2 for women in this study by Shiroyama et al.[28] were also used in our study.

Using these gender-specific cut-off points for PMI, patients were divided into two groups: "sarcopenic" and "non-sarcopenic". The effect of pre-treatment PMI on survival and response to treatment was investigated. Parameters associated with overall survival (OS) were also investigated in univariate and multivariate analyses. In addition, the relationship of sarcopenia with inflammatory, prognostic and immunological indices and scores were examined.

Definitions

Lung Immune Prognostic Index (LIPI): It is divided into three subsets of scores based on the relationship between the derived neutrophil-to-lymphocyte ratio (dNLR) [neutrophils/ (leukocytes - neutrophils)] and the blood lactate dehydrogenase (LDH) level: Good, moderate, and poor LIPI, according to cut-off values:

dNLR ≤3 and LDH ≤ upper limit normal (ULN)

dNLR >3 or LDH > (ULN)

dNLR >3 and LDH > (ULN)

Diagnosis-treatment interval: Time from diagnosis to initiation of treatment (days).

Caliper measurement: Triceps skinfold thickness measurement, used in nutritional research.

Follow-up period: Time from the diagnosis of cancer to the date of the last control (months).

Inclusion Criteria

Patients over 18 years of age with a diagnosis of RCC and MM, active treatment and follow-up in our clinic, and who received Nivolumab treatment as immunotherapy were included in the study.

Exclusion Criteria

Patients under the age of 18, with a second active cancer, who received combination therapy, and whose patient information and follow-up results could not be reached were not included in the study.

Statistical Analysis

Statistical analysis was performed by using "IBM SPSS Statistics for Windows. Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA)". Descriptive statistics are presented as n and % for categorical variables, and Mean±SD, median (min-max) for continuous variables. When the data of the study were analyzed in terms of normality assumptions, Kolmogorov-Smirnov values were examined and Parametric tests, Independent t test and Mann Whitney U test, were applied to determine whether there was a significant difference between the determined continuous variables and the groups. Chi Square test was used to compare categorical variables. Kaplan Meier method was used to compare survival times between various variables. $p<0.05$ was considered statistically significant.

Results

110 patients who received nivolumab therapy were screened. From this patient group, 17 patients whose treatment and follow-up results could not be reached were excluded from the study. A total of 93 patients (67 men; 26 women) were included in the analysis. The patients were examined in two groups as sarcopenic (n=46) and non-sarcopenic (n=47).

Accordingly, it was observed that the gender distribution between the groups was balanced. When the groups were examined in terms of age, the mean age was found to be higher in those with sarcopenia (60.38±13.43 vs 65.93±10.38, p=0.028). There was no difference between the groups in terms of performance score (PS). The rate of smoking was found to be higher in the non-sarcopenic group (p=0.037).

While 48 (51.6%) of the patients were RCC, 45 (48.4%) were MM. While 57 (61.3%) of the patients were in the early stage (stage 1-2-3); 36 (38.7%) were at advanced stage (stage 4). There was no significant difference in the distribution of cancer type and stage between sarcopenic and non-sarco-

penic groups. Diagnosis interval was found to be shorter in patients with sarcopenia (p=0.046). There was no significant difference between the groups with and without sarcopenia in terms of BMI, caliper measurement, follow-up time, laboratory parameters and immune-inflammatory prognostic scores. The general demographic and clinical characteristics of the patients and their distribution by sarcopenia groups are shown in Table 1.

Table 1. General demographic and clinical characteristics

	Total n (%)	Non-sarcopenic	Sarcopenic	p
Gender				
Female	26 (28.0)	9 (19.1)	17 (37.0)	0.056[a]
Male	67 (72.0)	38 (80.9)	29 (63.0)	
Age	63.13±12.27	60.38±13.43	65.93±10.38	0.028[d]
PS				
0	4 (4.3)	3 (6.4)	1 (2.2)	0.272[b]
1	59 (63.4)	32 (68.1)	27 (58.7)	
2	30 (32.3)	12 (25.5)	18 (39.1)	
Smoking				
No	29 (31.2)	10 (21.3)	19 (41.3)	0.037[a]
Yes	64 (68.8)	37 (78.7)	27 (58.7)	
Smoking time	20 (0-50)	20 (0-45)	20 (0-44)	0.884[c]
Diagnosis				
RCC	48 (51.6)	24 (51.1)	24 (52.2)	0.915[a]
MM	45 (48.4)	23 (48.9)	22 (47.8)	
Staging at Diagnosis				
1	2 (2.2)	2 (4.3)	0 (0)	0.160[b]
2	29 (31.2)	15 (31.9)	14 (30.4)	
3	26 (28.0)	16 (34.0)	10 (21.7)	
4	36 (38.7)	14 (29.8)	22 (47.8)	
Diagnosis - treatment interval (days)	481.9±631.8	610.9±745	350.1±462.1	0.046[d]
BMI				
Normal	38 (40.9)	19 (40.4)	19 (41.3)	0.509[a]
Overweight	41 (44.1)	19 (40.4)	22 (47.8)	
Obese	14 (15.1)	9 (19.1)	5 (10.9)	
BMI	25.68±3.90	26.33±4.08	25.03±3.65	0.109[d]
Caliper measurement				
None	59 (63.4)	31 (66.0)	28 (60.9)	0.610[a]
Available	34 (36.6)	16 (34.0)	18 (39.1)	
Caliper measurement	9.96±0.87	9.83±0.91	10.08±0.84	0.419[d]
Follow-up time	54.29±26.80	43.55±31.46	39.48±26.14	0.500[d]
LDH (U/L)	257 (150-615)	249 (150-503)	262 (164-615)	0.792[c]
Hemoglobin (g/dL)	10.66±1.08	10.85±1.1	10.48±1.05	0.097[d]
WBC (10^3/mm^3)	8.57±0.87	8.54±0.83	8.61±0.93	0.730[d]
Neutrophils (10^3/mm^3)	3.98±0.59	3.97±0.57	4±0.63	0.810[d]
Lymphocytes (10^3/mm^3)	2.50±0.42	2.51±0.38	2.5±0.46	0.991[d]
Monocytes (10^3/mm^3)	0.68±0.18	0.66±0.17	0.7±0.19	0.361[d]
PLT (10^3/mm^3)	358.62±309.15	389.64±422.81	326.93±103.08	0.331[d]
Calcium (mg/dL)	8.65±0.72	8.76±0.73	8.56±0.7	0.181[d]
CRP (mg/dL)	47.12±26.61	45.87±29.62	48.39±23.42	0.651[d]
ALP (U/L)	130.41±90.81	130.66±92.76	130.15±89.8	0.979[d]
Albumin (g/L)	3.40 (2.4-4.0)	3.60 (3-4)	3.30 (2.40-3.90)	0.860[c]
NLR	1.60±0.19	1.6±0.2	1.62±0.18	0.699[d]
PLR	145.32±121.68	157.58±166.08	132.8±41.93	0.329[d]
LMR	4.13±1.89	4.15±1.66	4.13±2.12	0.959[d]
PIV	393.35±380.97	425.67±517.73	360.34±143.26	0.411[d]
SII	572.70±475.98	619.54±649.11	524.86±166.89	0.340[d]
PNI	15.77±2.20	15.86±2.01	15.7±2.41	0.727[d]
HALP	28.96±11.96	29.46±11.8	28.45±12.23	0.685[d]
LIPI	1.90±0.94	1.85±0.96	1.96±0.94	0.593[d]

a=Chi Square test, b=Fisher's Exact test, d=Independent t test, c=Mann Whitney U test, p<0.05 statistically significant.

PS: Performance score, RCC: Renal Cell Carcinoma, MM: Malignant Melanoma, BMI: Body mass index, LDH: Lactate dehydrogenase, WBC: White blood cell, PLT: Platelet, CRP: C-reactive protein, ALP: Alkaline phosphatase, NLR: Neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, LMR: lymphocyte/monocyte ratio, PIV: Pan-immune Inflammation Value, SII: Systemic Inflammatory Index, PNI: Prognostic Nutritional Index, HALP: Hemoglobin-Albumin-Lymphocyte-Platelet, LIPI: Lung Immune Prognostic Index.

Diagnostic groups of the patients were grouped as RCC (n=48) and MM (n=45). There was no statistically significant difference between various clinical and laboratory variables according to these groups (p>0.05). Comparison of various clinical and laboratory variables according to diagnosis groups is shown in Table 2.

Table 2. Comparison of diagnostic groups and various clinical variables

	Diagnosis		
	RCC	MM	p
Lung met, n (%)			
None	15 (31.3)	15 (33.3)	0.830[a]
Present	33 (68.8)	30 (66.7)	
Lymph node met, n (%)			
None	8 (16.7)	3 (6.7)	0.136[a]
Present	40 (83.3)	42 (93.3)	
Liver met, n (%)			
None	35 (72.9)	37 (82.2)	0.283[a]
Present	13 (27,1)	8 (17.8)	
Bone met, n (%)			
None	28 (58.3)	32 (71.1)	0.198[a]
Present	20 (41.7)	13 (28.9)	
Brain met, n (%)			
None	43 (89.6)	38 (84.4)	0.450[a]
Present	5 (10.4)	7 (15.6)	
Bone marrow met, n (%)			
None	48 (100)	44 (97.8)	0.484[b]
Present	0 (0)	1 (2.2)	
Spleen met, n (%)			
None	47 (97.9)	44 (97.8)	1.000[b]
Present	1 (2.1)	1 (2.2)	
ALP, n (%)			
Low	29 (60.4)	27 (60)	0.967[a]
High	19 (39.6)	18 (40)	
Albumin, n (%)			
Normal	9 (18.8)	14 (31.1)	0.167[a]
Above normal	39 (81.3)	31 (68.9)	
LDH, n (%)			
Normal	8 (16.7)	15 (33.3)	0.063[a]
Above normal	40 (83.3)	30 (66.7)	
Calcium, n (%)			
Normal	46 (95.8)	44 (97.8)	0.1000[b]
Above normal	2 (4.2)	1 (2.2)	
LIPI, n (%)			
0	2 (4.2)	8 (17.8)	0.095[a]
1	8 (16.7)	8 (17.8)	
2	38 (79.2)	29 (64.4)	

a=Chi Square test, b=Fisher's Exact test, p<0.05 statistically significant. Met: Metastasis, ALP: Alkaline phosphatase, LDH: Lactate dehydrogenase, LIPI: Lung Immune Prognostic Index.

In our study, triceps skinfold thickness measurement could be performed with caliper in 35 patients. The mean triceps skinfold thickness was found to be 0.99 cm. It was found to be 0.98 cm (range 0.85-1.20) in men and 1.04 cm (range 0.95-1.26) in women. The relationship of caliper measurement, which can be measured in some of the patients, with body mass index and scores was examined. Accordingly, no statistically significant relationship was found between the caliper measurement and the variables PMI (r=-0.60 p=0.367), BMI (r=0.055 p=0.758), NLR (r=-0.110 p=0.535), PLR (r=-0.086 p=0.629), LMR (r=0.012 p=0.945), PIV (r=-0.092 p=0.607), SII (r=-0.116 p=0.513), PNI (r=-0.043 p=0.808) and HALP (r=0.111 p=0.533). The relationship of caliper measurement with Body mass index and laboratory parameters is shown in Table 3.

The effects of these recorded and calculated parameters of the patients on survival outcomes were analyzed. As seen in Table 4, the overall median overall survival (months) (mOS) was 46.56 (95%CI: 24.27-68.86) while 2-year survival was 68.2%, while 5-year survival was 45.4% (Fig. 1). Median OS did not show a statistically significant difference according to BMI groups (p=0.499). While 2-year survival was 65.4% in the normal group, 5-year survival was 39.1%. In the overweight group, 2-year survival was 70.4%, while 5-year survival was 52.6%. In the obese group, 2-year survival was 69.2%, while 5-year survival was 28.7%.

The mOS durations (months) did not show a statistically significant difference according to the diagnostic groups (p=0.299). While 2-year survival was 72.9% in the RCC group, 5-year survival was 51.2%. 2-year survival in the M. Melanoma group was 62.9%, while 5-year survival was 38.7% (Fig. 2).

There was no statistically significant difference in median overall survival time (mOS) (months) in female patients according to Sarcopenia groups (p=0.763). 2-year survival was 66.7% in non-sarcopenia group, while 5-year survival was 37.0%. 2-year survival in sarcopenia group was 62.7%, while 5-year survival was 26.4%.

There was also no statistically significant difference in mOS in male patients according to Sarcopenia groups (p=0.906). In the non-sarcopenia group, 2-year survival was 64.7%, while 5-year survival was 46.4%. 2-year survival in the sarcopenia group was 75.9%, while 5-year survival was 57.0%. The factors affecting survival are shown in Table 4.

The mOS in female RCC patients according to the Sarcopenia groups did not show a statistically significant difference

Table 3. Correlation results of the relationship between caliper measurement and scores

	1	2	3	4	5	6	7	8	9	10
1-Caliper Measurement Result										
r	1									
p										
2-PMI										
r	-0.160	1								
p	0.367									
3-BMI										
r	0.055	0.062	1							
p	0.758	0.553								
4-NLR										
r	-0.110	-0.137	-0.120	1						
p	0.535	0.191	0.251							
5-PLR										
r	-0.086	0.071	-0.032	0.025	1					
p	0.629	0.497	0.759	0.815						
6-LMR										
r	0.012	0.110	0.062	-.337**	-0.123	1				
p	0.945	0.292	0.556	0.001	0.241					
7-PIV										
r	-0.092	0.043	-0.053	0.128	.966**	-.267**	1			
p	0.607	0.682	0.612	0.222	<0.001	0.010				
8-SII										
r	-0.116	0.068	-0.051	0.069	.985**	-0.038	.963**	1		
p	0.513	0.516	0.628	0.508	<0.001	0.721	<0.001			
9-PNİ										
r	-0.043	0.123	0.059	-.493**	-0.094	.692**	-0.101	0.019	1	
p	0.808	0.241	0.572	<0.001	0.370	<0.001	0.335	0.855		
10-HALP										
r	0.111	0.154	0.118	-0.201	-.497**	0.203	-.454**	-.470**	.413**	1
p	0.533	0.140	0.261	0.053	<0.001	0.051	<0.001	<0.001	<0.001	

*Correlation is significant at 0.05 level (Pearson correlation test), ** Correlation is significant at 0.01 level (Pearson correlation test).

(p=0.914). In the non-sarcopenia group, 2-year survival was 87.5%, while 5-year survival was 33.3%. 2-year survival was 60%, while 5-year survival was 30.0% in the sarcopenia group.

The mOS in RCC male patients according to the Sarcopenia groups did not show a statistically significant difference (p=0.127). In the non-sarcopenia group, 2-year survival was 73.7%, while 5-year survival was 63.2%. 2-year survival was 68.8%, while 5-year survival was 53.5% in the sarcopenia group.

The mOS in female patients with melanoma according to the Sarcopenia groups did not show a statistically significant difference (p=0.522). In the non-sarcopenia group, 2-year survival was 75%, while 5-year survival was 50.0%. In the sarcopenia group, 2-year survival was 38.1%, while 5-year survival was 19.0%.

The mOS in male patients with melanoma according to the Sarcopenia groups did not show a statistically significant difference (p=0.107). In the non-sarcopenia group, 2-year survival was 55.1%, while 5-year survival was 27.6%. 2-year survival in the sarcopenia group was 84.6%, while 5-year survival was 59.8%.

As seen in Table 5, overall progression-free survival times (PFS) (months) was 36.86 (95%CI: 27.53-46.19), and 2-year PFS was 66.6%, while 5-year PFS was 39.5% (Fig. 3).

The median PFS were not statistically significantly different according to the BMI groups (p=0.925). While 2-year PFS was 67.8% in the normal group, 5-year PFS was 48.7%. In the overweight group, 2-year PFS was 67.1%, while 5-year PFS was 40.9%. In the obese group, 2-year PFS was 69.2%, while 5-year PFS was 34.6%.

Table 4. OS comparisons of patients

Overall Survival (months)	Median (95% CI)	p
General	46.56 (24.27-68.86)	
BMI		
Normal	39.66 (19.88-59.44)	0.499
Overweight	71.60 (13.00-130.20)	
Obese	50.40 (29.11-71.68)	
Diagnosis		
RCC	62.93 (31.87-94.67)	0.299
M. Melanoma	35.40 (24.24-46.55)	
Sarcopenia - Female		
Non-sarcopenic	51.76 (4.33-99.19)	0.763
Sarcopenic	31.03 (20.37-41.69)	
Sarcopenia – Male		
Non-sarcopenic	50.40 (13.79-87.01)	0.906
Sarcopenic	62.93 (23.17-102.69)	
RCC sarcopenia - Female		
Non-sarcopenic	51.76 (0.00-116.91)	0.914
Sarcopenic	31.03 (13.54-48.52)	
RCC sarcopenia – Male		
Non-sarcopenic	82.50 (43.77-121.22)	0.127
Sarcopenic	62.93 (28.25-97.61)	
Melanoma sarcopenia – Female		
Non-sarcopenic	27.83 (0.00-56.03)	0.522
Sarcopenic	21.63 (9.05-34.21)	
Melanoma sarcopenia - Male		
Non-sarcopenic	31.73 (1.74-61.71)	0.107
Sarcopenic	-(-)	

Kaplan Meier curve, Long rank test, p<0.05 statistically significant, RCC: Renal Cell Carcinoma, MM: Malign melanoma.

Table 5. PFS comparisons of patients

PFS (months)	Median (95% CI)	p
General	36.86 (27.53-46.19)	
BMI		
Normal	37.16 (19.07-65.25)	0.925
Overweight	30.96 (19.30-42.63)	
Obese	36.86 (32.49-41.24)	
Diagnosis		
RCC	42.16 (22.22-62.11)	0.513
M. Melanoma	34.73 (25.50-43.96)	
Sarcopenia - Female		
Non-sarcopenic	50.16 (0.00-127.67)	0.769
Sarcopenic	30.26 (0.00-62.26)	
Sarcopenia - Male		
Non-sarcopenic	34.30 (26.00-42.59)	0.307
Sarcopenic	54.86 (19.84-89.88)	
RCC sarcopenia - Female		
Non-sarcopenic	51.16 (0.00-115.74)	0.746
Sarcopenic	30.26 (-)	
RCC sarcopenia - Male		
Non-sarcopenic	42.16 (22.59-61.73)	0.725
Sarcopenic	39.26 (16.48-62.05)	
Melanoma sarcopenia - Female		
Non-sarcopenic	60.43 (-)	0.471
Sarcopenic	13.70 (9.05-34.21)	
Melanoma sarcopenia - Male		
Non-sarcopenic	30.30 (4.20-64.39)	0.066
Sarcopenic	-(-)	

Kaplan Meier curve, Long rank test, p<0.05 statistically significant.

The median PFS did not show a statistically significant difference according to the diagnostic groups (p=0.513). While 2-year PFS was 70.3% in the RCC group, 5-year PFS was 41.8%, and 2-year PFS was 62.5% in the M. Melanoma group, while 5-year PFS was 37% (Fig. 4).

There was no statistically significant difference in the median PFS in male patients compared to the Sarcopenia groups (p=0.307). While 2-year PFS was 64.2% in the non-

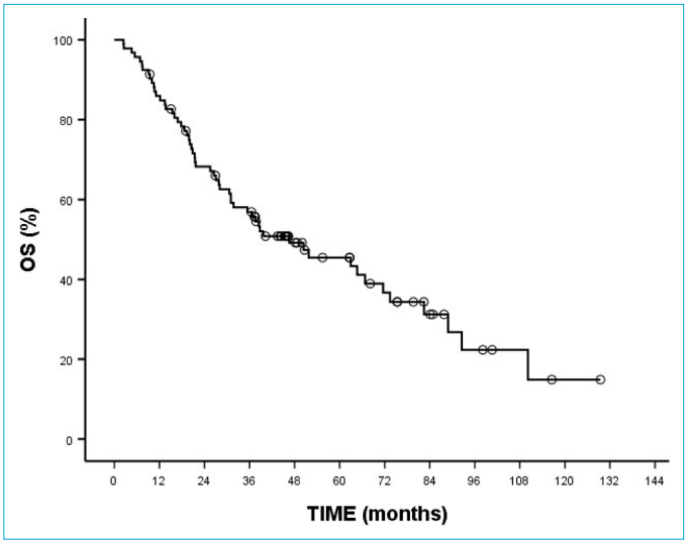

Figure 1. Overall Survival.

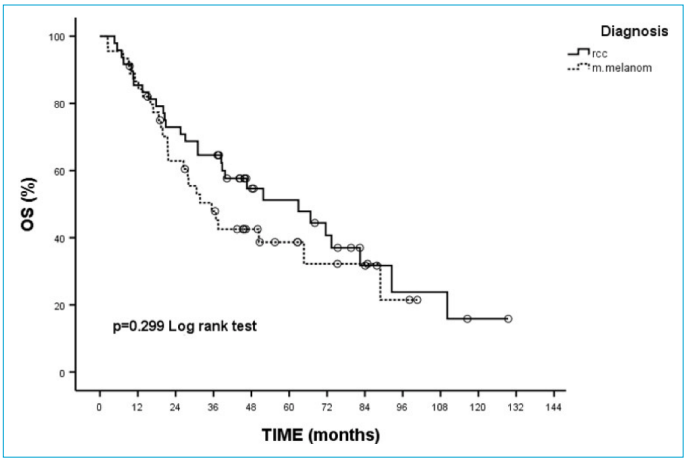

Figure 2. OS diffrences RCC and MM.

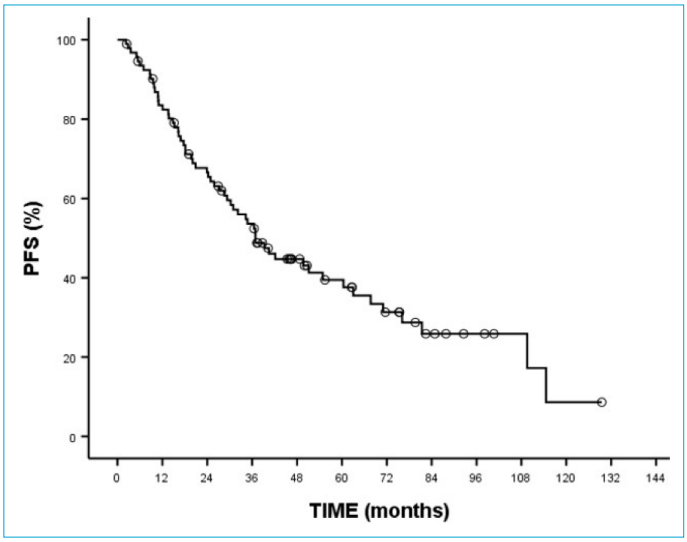

Figure 3. Progression Free Survival.

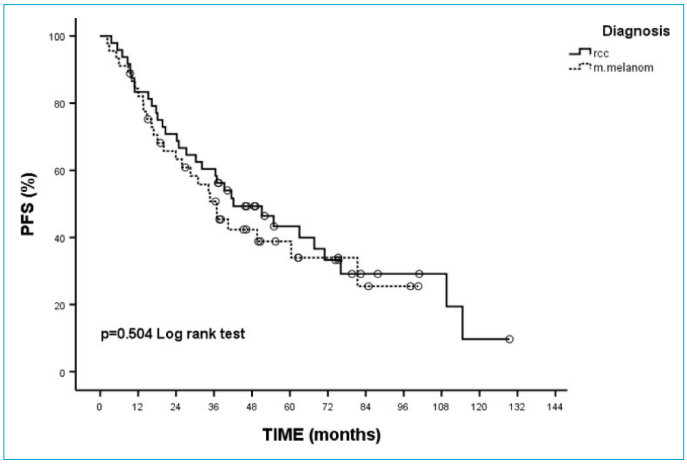

Figure 4. PFS diffrences RCC and MM.

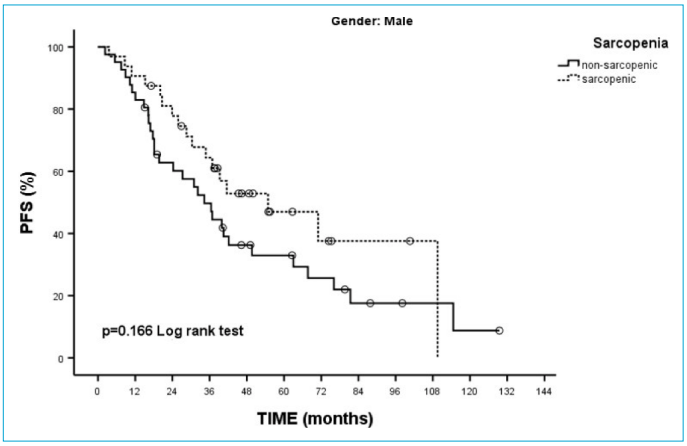

Figure 5. PFS differences between sarcopenic and non sarcopenic male patient.

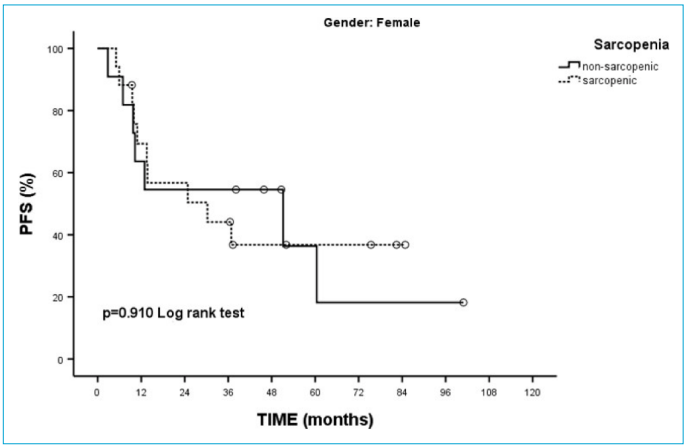

Figure 6. PFS differences between sarcopenic and non sarcopenic female patient.

sarcopenia group, 5-year PFS was 34.1%. In the sarcopenia group, 2-year PFS was 75.0%, while 5-year survival was 45.5% (Fig. 5).

There was no statistically significant difference in median PFS in female patients according to Sarcopenia groups (p=0.769). In the non-sarcopenia group, 2-year PFS was 66.7%, while 5-year PFS was 44.4%, and 2-year PFS was 56.7% in the sarcopenia group, while 5-year survival was 36.8% (Fig. 6).

The median PFS in RCC female patients did not show a statistically significant difference according to the Sarcopenia groups (p=0.746). In the non-sarcopenia group, 2-year PFS was 60%, while 5-year PFS was 30%. In the sarcopenia group, 2-year PFS was 75%, while 5-year survival was 50%.

The median PFS in RCC male patients did not show a statistically significant difference according to the Sarcopenia groups (p=0.725). While 2-year PFS was 72.4% in the non-sarcopenia group, 5-year PFS was 43.9%. In the sarcopenia group, 2-year PFS was 68.8%, while 5-year survival was 36.2%.

The median PFS in female patients with melanoma did not show a statistically significant difference according to the Sarcopenia groups (p=0.471). While 2-year PFS was 75% in the non-sarcopenia group, 5-year PFS was 75%. In the sarcopenia group, 2-year PFS was 38.9%, while 5-year survival was 19.4%.

The median PFS in male patients with melanoma did not show a statistically significant difference according to the Sarcopenia groups (p=0.066). While 2-year PFS was 56.7% in the non-sarcopenia group, 5-year PFS was 23.6%. In the sarcopenia group, 2-year PFS was 83.3%, while 5-year survival was 56.3%.

Discussion

Sarcopenia, defined as loss of skeletal muscle mass and function, is a common problem among cancer patients, but it is often difficult to diagnose with clinical findings.

Recently, with increasing frequency, sarcopenia has been used in various studies on solid cancer patients.[13-18]

These studies have been studied in bladder, hepatocellular cancer, upper urinary tract, pancreatic, esophageal and lung squamous cell cancers, respectively, and it has been reported to have the ability to independently predict disease outcomes. In a comprehensive meta-analysis of 7843 solid cancer patients showing that sarcopenia is associated with adverse survival outcomes in cancer patients, low muscle mass has been associated with poorer survival overall (OS; HR 1.44, 95% CI [1.32, 1.56]; p<0.001).[4]

In patients who received chemotherapy or were operated, included in cancer and sarcopenia studies, although sarcopenia has been shown to be associated with increased chemotherapeutic toxicity and postoperative complications, the effect of sarcopenia on the outcome of immunotherapy still remains unclear.[29-31] However, in a study, it was shown that sarcopenia causes a negative effect on immunity by affecting the immune system.[32] From this perspective, sarcopenia was thought to have a detrimental effect on the antitumor response of immunotherapy. Most studies have reported that sarcopenia is associated with worse treatment response and shorter survival in patients with NSCLC treated with immunotherapy.[26] This analysis was mainly based on lung cancer data and did not include other types of cancer. Other studies have also shown that sarcopenia has a negative effect on clinical outcomes in patients with melanoma and urothelial carcinoma.[25,33,34] However, some studies have reported that sarcopenia has no effect on the outcome of malignancies.[35,36]

Most of these studies described sarcopenia by measurement of psoas muscle mass. We also used psoas muscle mass as a measurement in our study. We examined the effect of sarcopenia in patients with malignant melanoma (MM) and kidney cancer (RCC) receiving nivolumab immunotherapy.

First of all, the time between diagnosis and treatment interval was found to be shorter in patients with sarcopenia in both cancers. This result encouraged us as a prognostic marker because the short interval between diagnosis and treatment, which is one of the criteria of the International Metastatic Renal Cell Carcinoma Database Consortium used to predict the prognosis in kidney cancer, is similar to the poor prognostic feature.[37] Although it was initially thought that sarcopenia might have an effect on the poor prognosis caused by the faster progression of cancer or the earlier need for treatment, our final result was that we could not find a significant relationship between survival outcomes and sarcopenia, suggesting that the relationship between this time from diagnosis to treatment and sarcopenia might be coincidental.

Secondly, a statistically significant difference was found between age and sarcopenia group. The mean age was found to be higher in those with sarcopenia. This situation was found in line with the results in the literature, in accordance with the definition of sarcopenia, which is also included in the onset definitions of sarcopenia, and which, unlike cachexia, is expected to develop with age without any underlying disease. In one study, it was detected that 53% to 57% of men and 43 to 60% of women over the age of 80 had sarcopenia.[38] In our study, the mean age was found to be 5.5 years more in those with sarcopenia than in those without.

In our study, when the results of triceps skinfold thickness measured with a caliper during the nutritional evaluations of some of the patients were assessed, as expected, the average skin thickness of women was higher than that of men. Triceps skinfold thickness results are one of the anthropometric measurements used to estimate body fat percentage and therefore body composition, which gives indirect information in terms of body composition. In this way, a local fat tissue measurement with calipers can give an idea about its distribution from the total fat mass in the body. While there is loss of muscle mass in sarcopenic patients, an increase in adipose tissue can be expected. The concept of sarcopenic obesity stands as an important confounding factor in this respect. These people have both low muscle mass and high body fat, and the risk of metabolic disease is higher than those who are only sarcopenic or obese.[39] Studies examining direct sarcopenia and triceps skin fold are not clear in the literature. In a study that examined the correlation between fat measurements obtained in body fat composition imaging methods and skin fold thickness measurement, it was found that the measurement values of subcutaneous adipose tissue showed a significant positive correlation.[40] However, the correlation coefficient values differed depending on the measurement site. Despite the significant differences between the values obtained, the greatest correlation between them was observed for the triceps skinfold (r=0.7) and the calf skinfold (r=0.6). Although no correlation was found with sarcopenic and non-sarcopenic conditions in our study, it was thought that this situation was not sufficient to show this correlation, since only one-third of the patients included in the study were examined.

In our study, no relationship was found between survival outcomes and sarcopenia status. The relationship between sarcopenia and survival outcomes in patients receiving chemotherapy in the literature could not be demonstrated in RCC and MM cancers, which are immune active tumors and receiving immunotherapy, in our study. In a study ex-

amining the relationship between immunotherapy and sarcopenia,[28] the PMI cut-off values used in the assessment of sarcopenia were used in our study, and accordingly, they were divided as sarcopenia present/absent. However, in our study population, contrary to this study, although we evaluated sarcopenia separately according to gender, no relationship was found with survival outcomes. The fact that this immunotherapy study was performed only in patients with lung cancer may have caused these different results.[35] However, in another lung cancer study, similar to our study, no significant correlation was found between sarcopenia and survival outcomes.[36]

Interestingly, although there was no statistically significant difference, the survival time was longer in non-sarcopenic patients in women, while a numerically longer survival time was found in male patients with sarcopenia as an unexpected result. In the literature, in the study on the relationship between sarcopenia and survival after bile duct cancer surgery, the opposite of our finding, the effect of sarcopenia on survival was shown in men, but no relationship was found in women.[41] In the subgroup analysis of these results, when both cancers were analyzed separately by gender and sarcopenia, both median survival outcomes and two- and five-year survival rates were higher in the group without sarcopenia than in the group with sarcopenia, except for male patients with sarcopenic malignant melanoma who could not reach the median. In the initial general analysis, the effect of sarcopenia on survival outcomes differed depending on whether they were men or women may be due to the unbalanced distribution of gender and sarcopenia in diseases, and the presence of malignant melanoma patients with a much lower median survival compared to RCC in our study, and the cases that did not reach the median survival in sarcopenic male malignant melanoma patients.

In conclusion, in our study, we could not show the survival relationship between muscle mass measurements obtained in retrospective measurements from current imaging in patients with kidney cancer and melanoma, two important immune-active cancers. And again, although the level of inflammation markers of the patients and a limited number of patients were examined, a relationship could not be shown with the caliper triceps measurements.

Our study is important in terms of evaluating a single immunotherapy treatment in kidney cancer and melanoma patients with known immune-active tumors in oncology. Although the PMI cut-off point was not found to be significant depending on the number of our patients, this relationship could not be shown when we evaluated in our own patient population the cut-off points that were measured similarly in the literature and used for the differentiation of sarcopenia and found to be significant.

The retrospective design and the relatively small number of patients are limitations of our study. Numerical differences that were not statistically significant were thought to gain statistical significance in studies involving more patients. Apart from this, although sarcopenia was evaluated separately according to gender, it was thought that the significant difference in the number of male and female patients in the study may have affected the results. Therefore, prospective studies, designed with a larger patient population and equal distribution in terms of gender, are needed.

Disclosures

Ethics Committee Approval: This study was approved by the institutional review board of the Antalya Education and Research Hospital ethics committee.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – A.H.Ö., İ.B.; Design – A.H.Ö.; Supervision – A.H.Ö., İ.B.; Materials – A.H.Ö., Y.K.S.; Data collection &/or processing – A.H.Ö., Y.K.S.; Analysis and/or interpretation – A.H.Ö., İ.B.; Literature search –A.H.Ö.; Writing – A.H.Ö., Y.K.S.; Critical review – A.H.Ö., İ.B., Y.K.S.

References

1. Rosenberg IH. Sarcopenia: origins and clinical relevance. J Nutr. 1997;127(5 Suppl):990-991.
2. Rolland Y, Czerwinski S, Abellan Van Kan G, Morley JE, Cesari M, Onder G, et al. Sarcopenia: its assessment, etiology, pathogenesis, consequences and future perspectives. J Nutr Health Aging, 2008;12(7):433-50.
3. Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol. 1998;147(8):755-63..
4. 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.
5. Yang M, Shen Y, Tan L, Li W. Prognostic Value of Sarcopenia in Lung Cancer: A Systematic Review and Meta-Analysis. Chest. 2019;156:101–11.
6. Tegels JJ, van Vugt JL, Reisinger KW, Hulsewé KW, Hoofwijk AG, Derikx JP, et al. Sarcopenia is Highly Prevalent in Patients Undergoing Surgery for Gastric Cancer But Not Associated With Worse Outcomes. J Surg Oncol. 2015;112:403–7.
7. 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):e317–323.
8. Shachar SS, Williams GR. The Obesity Paradox in Cancer-Moving beyond BMI-Response. Cancer Epidemiol Biomarkers

Prev. 2017;26(6):981.
9. Rubbieri G, Mossello E, Di Bari M. Techniques for the diagnosis of sarcopenia. Clin Cases Miner Bone Metab. 2014 Sep;11(3):181-4. PMID: 25568650; PMCID: PMC4269140.
10. Aubrey J, Esfandiari N, Baracos VE, Buteau FA, Frenette J, Putman CT, et al. Measurement of skeletal muscle radiation attenuation and basis of its biological variation. Acta Physiol (Oxf). 2014 Mar;210(3):489-97.
11. Williams GR, Deal AM, Muss HB, Weinberg MS, Sanoff HK, Guerard EJ, et al. Frailty and skeletal muscle in older adults with cancer. J Geriatr Oncol. 2018; 9(1):68-73.
12. Hamaguchi Y, Kaido T, Okumura S, Kobayashi A, Hammad A, Tamai Y, et al. Proposal for new diagnostic criteria for low skeletal muscle mass based on computed tomography imaging in Asian adults. Nutrition. 2016;32(11-12):1200–1205.
13. Kasahara R, Kawahara T, Ohtake S, Saitoh Y, Tsutsumi S, Teranishi JI, et al. A low psoas muscle index before treatment can predict a poorer prognosis in advanced bladder cancer patients who receive gemcitabine and nedaplatin therapy. Biomed Res Int. 2017; 1–4.
14. Yuri Y, Nishikawa H, Enomoto H, Ishii A, Iwata Y, Miyamoto Y, et al. Implication of psoas muscle index on survival for hepatocellular carcinoma undergoing radiofrequency ablation therapy. J Cancer. 2017;8(9):1507–1516.
15. Tsutsumi S, Kawahara T, Teranishi JI, Yao M, Uemura H. A low psoas muscle volume predicts longer hospitalization and cancer recurrence in upper urinary tract urothelial carcinoma. Mol Clin Oncol. 2018;8(2):320–322.
16. Ishii N, Iwata Y, Nishikawa H, Enomoto H, Aizawa N, Ishii A,et al. Effect of pretreatment psoas muscle mass on survival for patients with unresectable pancreatic cancer undergoing systemic chemotherapy. Oncol Lett. 2017;14(5):6059–6065.
17. Ozawa Y, Nakano T, Taniyama Y, Sakurai T, Onodera Y, Kamiya K,et al. Evaluation of the impact of psoas muscle index, a parameter of sarcopenia, in patients with esophageal squamous cell carcinoma receiving neoadjuvant therapy. Esophagus. 2019;16(4):345–351.
18. Ozeki N, Kawaguchi K, Fukui T, Nakamura S, Hakiri S, Mori S, et al. Psoas muscle mass in patients undergoing lung cancer surgery: a prognostic difference between squamous cell carcinoma and adenocarcinoma. Int J Clin Oncol. 2020; 25(5):876–884.
19. Doroshow DB, Sanmamed MF, Hastings K, Politi K, Rimm DL, Chen L, et al. Immunotherapy in Non-Small Cell Lung Cancer: Facts and Hopes. Clin Cancer Res. 2019; 25:4592–602.
20. Wolchok JD, Hodi FS, Weber JS, Allison JP, Urba WJ, Robert C, et al. Development of Ipilimumab: A Novel Immunotherapeutic Approach for the Treatment of Advanced Melanoma. Ann N Y Acad Sci. 2013; 1291:1–13.
21. Wei Y, Du Q, Jiang X, Li L, Li T, Li M, et al. Efficacy and Safety of Combination Immunotherapy for Malignant Solid Tumors: A Systematic Review and Meta-Analysis. Crit Rev Oncol Hematol. 2019; 138:178–89.
22. Gibney GT, Weiner LM, Atkins MB. Predictive Biomarkers for Checkpoint Inhibitor-Based Immunotherapy. Lancet Oncol. 2016; 7:e542–51.
23. Khaddour K, Gomez-Perez SL, Jain N, Patel JD, Boumber Y. Obesity, Sarcopenia, and Outcomes in Non-Small Cell Lung Cancer Patients Treated With Immune Checkpoint Inhibitors and Tyrosine Kinase Inhibitors. Front Oncol. 2020;10:576314.
24. Young AC, Quach HT, Song H, Davis EJ, Moslehi JJ, Ye F, et al. Impact of Body Composition on Outcomes From Anti-PD1 +/- Anti-CTLA-4 Treatment in Melanoma. J Immunother Cancer. 2020; 8(2):e000821.
25. Shimizu T, Miyake M, Hori S, Ichikawa K, Omori C, Iemura Y, et al. Clinical Impact of Sarcopenia and Inflammatory/Nutritional Markers in Patients with Unresectable Metastatic Urothelial Carcinoma Treated with Pembrolizumab. Diagnostics (Basel). 2020;10(5):310.
26. Wang J, Cao L, Xu S. Sarcopenia affects clinical efficacy of immune checkpoint inhibitors in non-small cell lung cancer patients: A systematic review and meta-analysis. Int Immunopharmacol. 2020; 88:106907.
27. Malinowski A, Bożiłow W. Podstawy Antropometrii-Metody, Techniki, Normy.1st ed.(Warszawa/Poland): Wydawnictwo Naukowe PWN; 1997; ISBN 83-01-12338-9.
28. Shiroyama T, Nagatomo I, Koyama S, Hirata H, Nishida S, Miyake K, et al. Impact of sarcopenia in patients with advanced non-small cell lung cancer treated with PD-1 inhibitors: A preliminary retrospective study. Sci Rep. 2019; 21;9(1):2447.
29. Rinninella E, Cintoni M, Raoul P, Pozzo C, Strippoli A, Bria E, et al. Muscle mass, assessed at diagnosis by L3-CT scan as a prognostic marker of clinical outcomes in patients with gastric cancer: A systematic review and meta-analysis. Clin Nutr. 2020;39(7):2045-2054.
30. Buentzel J, Heinz J, Bleckmann A, Bauer C, Röver C, Bohnenberger H, et al. Sarcopenia as Prognostic Factor in Lung Cancer Patients: A Systematic Review and Meta-analysis. Anticancer Res. 2019 ;39(9):4603-4612.
31. Deng HY, Hou L, Zha P, Huang KL, Peng L. Sarcopenia is an Independent Unfavorable Prognostic Factor of non-Small Cell Lung Cancer After Surgical Resection: A Comprehensive Systematic Review and Meta-Analysis. Eur J Surg Oncol. 2019; 45:728–35.
32. 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.
33. Chu MP, Li Y, Ghosh S, Sass S, Smylie M, Walker J, et al. Body Composition is Prognostic and Predictive of Ipilimumab Activity in Metastatic Melanoma. J Cachexia Sarcopenia Muscle. 2020; 11:748–55.
34. Loosen SH, van den Bosch V, Gorgulho J, Schulze-Hagen M,

Kandler J, Jördens MS, et al. Progressive Sarcopenia Correlates With Poor Response and Outcome to Immune Checkpoint Inhibitor Therapy. J Clin Med. 2021; 10(7):1361.
35. 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.
36. 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.
37. Heng DY, Xie W, Regan MM, Harshman LC, Bjarnason GA, Vaishampayan UN, 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.
38. Lindle RS, Metter EJ, Lynch NA, Fleg JL, Fozard JL, Tobin J, et al. Age and gender comparisons of muscle strength in 654 women and men aged 20-93 yr. J Appl Physiol. 1997; 83:1581.
39. Hsu KJ, Liao CD, Tsai MW, Chen CN. Effects of Exercise and Nutritional Intervention on Body Composition, Metabolic Health, and Physical Performance in Adults with Sarcopenic Obesity: A Meta-Analysis. Nutrients. 2019;11(9):2163.
40. Lewandowski Z, Dychała E, Pisula-Lewandowska A, Danel DP. Comparison of Skinfold Thickness Measured by Caliper and Ultrasound Scanner in Normative Weight Women. International Journal of Environmental Research and Public Health. 2022; 19(23):16230.
41. Jördens MS, Heinrichs L, Loosen SH, Wittig L, Keitel V, Schöler D, et al. Sarcopenia Predicts Cancer Mortality in Male but Not in Female Patients Undergoing Surgery for Cholangiocellular Carcinoma. Cancers. 2021; 13(21):5359.