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The relationship between medical therapy and sarcopenia in advanced non-small cell lung cancer patients

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ABSTRACT

Aims: Sarcopenia, characterized by loss of skeletal muscle mass and function, is associated with worse clinical outcomes in patients with cancer. This study aims to determine the prevalence of sarcopenia before and after chemotherapy in advanced non-small cell lung cancer (NSCLC) patients and to evaluate its effect on treatment response.

Methods: Between October 13, 2022, and February 13, 2023, 38 patients over 18 years of age with advanced NSCLC who were admitted to the medical oncology department outpatient clinic were included in the study. Bioelectrical impedance analysis (BIA) and anthropometric measurements (hand grip strength and walking speed) were performed for all patients according to European Working Group on Sarcopenia in the Elderly (EWGSOP) criteria.

Results: Before treatment, 23.7% of patients had probable sarcopenia, 10.5% had sarcopenia, and 15.8% had severe sarcopenia. Sarcopenia developed in 21.1% of patients without sarcopenia before treatment, while 21.1% of patients with possible sarcopenia developed severe sarcopenia after treatment. Thirty percent of patients with pre-treatment sarcopenia died after treatment, and progression was detected in all remaining patients after treatment. Progression of sarcopenia was not significantly associated with BIA parameters but was associated with worse ECOG scores, lower oxygen saturation, decreased lean body mass and lower vitamin D levels. Adenocarcinoma subtype, stage 4, and platinum-based chemotherapy were associated with an increase in the post-treatment sarcopenia score.

Conclusion: The prevalence of sarcopenia in patients with NSCLC is approximately 50%, and disease stage, type, and treatment regimen play an important role in the development of sarcopenia. The presence of sarcopenia before treatment may have an impact on treatment response and increase the risk of chemotherapy-related toxicity and mortality.

Keywords: Lung cancer, bioelectrical impedance, advanced cancer, chemotherapy, sarcopenia

INTRODUCTION

Lung cancer originates from respiratory epithelial cells and is the leading cause of cancer incidence and mortality worldwide.[1] Malignant diseases cause significant loss of skeletal muscle mass, quality, and function.[2] This is associated with malnutrition, lipolysis, inflammation, and vicious metabolic cycles. Fat and muscle loss in cancer patients may be attributed to a "metabolic parasite" effect due to the tumor's appetite for glucose and glutamine. These relationships promote the occurrence of cachexia, which is an important cause of mortality in patients with advanced cancer and is observed in approximately 50% of patients.[3]

Cancer treatment can cause skeletal muscle changes in a variety of ways. Surgery radiotherapy, chemotherapy, and hormone therapy cause systemic loss of muscle mass.[4] Sarcopenia is associated with shorter disease-free survival and worse overall survival in advanced lung cancer.[5] Furthermore, skeletal muscle loss has been shown to negatively affect treatment outcomes in patients with cancer.[6] However sarcopenia before or after treatment is associated with decreased disease control.[7] Although it has been suggested that platinum-based chemotherapy drugs are distributed in lean body-mass, it is thought that sarcopenic

patients may be at a greater risk of toxicity.[8] However, although chemotherapy has been shown to improve quality of life and survival in patients with advanced cancer, there are limited data on the relationship between changes in muscle mass and function during chemotherapy and response to treatment and survival. Given the increasing incidence of cancer and an aging population, early detection of sarcopenia may play a prognostic role. The development of treatment strategies aimed at reversing or preventing metabolic changes that promote cancer progression or recurrence and improving quality of life is important for the early prevention of tissue loss.

The aim of this study was to determine the frequency of sarcopenia in patients with newly diagnosed advanced non-small cell lung cancer (NSCLC) patients according to the European Working Group on Sarcopenia in Older People (EWGSOP) criteria, to detect new sarcopenia after standard chemotherapy protocol, and to determine the effect of sarcopenia on response to treatment. The aim of this study was to improve the survival and treatment complications of the disease with early detection of sarcopenia and to contribute to future studies.

METHODS

Ethics

This study was a prospective cross-sectional study and the protocol of the study was approved by the Kırıkkale University Clinical Researches Ethics Committee (Date: 13.10.2020, Decision No: 09/01). In 2013, the updated Declaration of Helsinki in Brazil was planned in accordance with the updated Declaration of Helsinki resolutions, patient rights regulations, and the Good Clinical Practice Rules.

Research Population

This prospective cross-sectional study was conducted in the outpatient clinic of the Department of Internal Medicine, Division of Medical Oncology, Kırıkkale University Faculty of Medicine. Between October 13, 2022, and February 13, 2023, 38 patients over 18 years of age with advanced NSCLC who were admitted to the medical oncology department outpatient clinic were included in the study. The sample size for the study was calculated as at least 28 patients with a 5% probability of error and 80% sampling power. Patients with advanced NSCLC who had no history of limb amputation that could interfere with bioelectrical impedance analysis (BIA), no cognitive impairment that might affect muscle measurement, and no signs of malnutrition were eligible for inclusion. Patients were excluded if they had acute decompensated heart failure, COPD exacerbation, malnutrition, or immobility, as well as those with implanted metal devices such as permanent pacemakers. Additionally, individuals with comorbidities that could affect the accuracy of muscle mass measurements using BIA, including prosthetic limbs, severe pretibial edema, mechanical heart valves, or pacemakers, were not included in the study.

Demographic characteristics, smoking history, cancer stage, chemotherapy regimen to be used, performance status, anthropometric measurements, biochemical parameters, and sarcopenia status were recorded on the patient follow-up form. Patients were categorized into three groups according to the presence or absence of sarcopenia: those without sarcopenia, those with possible sarcopenia, and those with sarcopenia.

Anthropometric Measurements

Anthropometric measurements included height, body weight, waist circumference, hip circumference, calf circumference, and upper middle arm circumference. BMI was calculated by dividing weight (kg) by the square of height (m^2). Waist circumference was measured at the midpoint of the distance between the iliac crest and the lower rib; hip circumference was measured at the widest part of the hip; calf circumference was measured at the thickest part of the calf when the knee joint was flexed 90 degrees in the sitting position; and upper mid-arm circumference was measured with a tape measure at the midpoint of the upper extremity between the humeral head and the olecranon process.

Evaluation of Sarcopenia

Sarcopenia was diagnosed based on the criteria of the EWGSOP working group. According to these criteria, sarcopenia is defined as a decrease in skeletal muscle mass accompanied by a decrease in muscle strength and/or muscle function. Skeletal muscle mass was assessed with a BIA device (Bodystat QuadScan4000, Appendix 5). After entering the patient's age, gender, height, and body weight into the device, measurement was performed at a frequency of 50 kHz. The resistance value measured during the analysis was used to calculate the skeletal muscle mass using the formula proposed by Jannsen et al.[9] The formula is as follows: [(height2/resistance value in BIA device measurement ×0.401)+(sex×3.825)+(age×0.071)]+5.102

For the variables used in the formula, height is calculated in meters, resistance is calculated in ohms, and sex is coded as 1 for males and 0 for females. The value obtained with this formula was divided by the square of the height of the patients in meters, and the absolute skeletal muscle mass was obtained. An absolute skeletal muscle mass value of <6.42 kg/m^2 in women and <8.87 kg/m^2 in men indicates decreased skeletal muscle mass.[10]

Muscle strength and hand squeeze strength were evaluated using an electronic hand dynomemeter, with results recorded in kilograms. Low muscle strength for men and women was determined according to the cut-off points given in the EWGSOP consensus based on body-mass index (BMI). Muscle performance was assessed based on walking speed, measured over a 4-meter track using an electronic stopwatch, and walking speed was calculated in m/sec using the formula 4 m/walking time (sec). Walking speed <0.8 m/sec was evaluated in favor of decreased muscle performance.[10]

Statistical Analysis

Statistical evaluation Statistical Package for Social Sciences (SPSS) for Windows 23 (IBM SPSS Inc., Chicago, IL) program was used. The normal distribution of the data was evaluated by the Kolmogorov-Smirnov test. Normally distributed numerical data were expressed as mean±standard deviation, and non-normally distributed numerical data were expressed as median (min-max). Qualitative data were expressed as numbers and percentages. The Chi-square test was used for the comparison of qualitative data, and the Fisher-exact

test was used if the expected frequencies were not met. Independent samples The T-test was used for comparison of normally distributed numerical data between two groups, and the Mann-Whitney U test was used for comparison of non-normally distributed numerical variables between groups. The ANOVA test (post hoc Bonferroni test) was used for comparison of numerical variables with a normal distribution between more than 2 groups, and the Kruskall-Wallis H test (post hoc Dunn's test) was used for comparison of numerical variables without a normal distribution. Changes before and after treatment were evaluated by paired samples T test or Wilcoxon sign test according to normality distribution. Post-treatment changes in categorical variables were evaluated by the McNemar test or the marginal homogeneity test. A value of $p<0.05$ was considered significant in statistical analyses.

RESULTS

The study included 38 patients, 32 (84.2%) males and 6 (15.8%) females, aged between 46 and 83 years (mean age: 66.4±8.6 years). Demographic data are shown in **Table 1**. Before treatment, 23.7% (n=9) had probable sarcopenia, 10.5% (n=4) had sarcopenia, and 15.8% (n=6) had severe sarcopenia. Anthropometric measurements and sarcopenia-related parameters of the patients are shown in the **Supplementary Table 1**. 63.2% (n=18) of the patients were stage 4 and had metastasis. When the post-treatment changes were analyzed, a significant decrease in mean walking speed (0.8±0.2 m/s vs. 0.7±0.4 m/s; p=0.031) was found after treatment. Of 19 patients without sarcopenia before treatment, 4 (21.1%) developed probable sarcopenia after treatment, and 4 (21.1%) developed severe sarcopenia after treatment (p<0.001).

Table 1. Demographic characteristics of patients

Variables	All patients n=38
Gender, n (%)	
Female	6 (15.8)
Male	32 (84.2)
Smoking, n (%)	
None	9 (23.7)
Active	12 (31.6)
Quit	17 (44.7)
Smoking, package/year	50 (7-120)
Profession, n (%)	
Worker	18 (47.4)
Public servant	8 (21.1)
Housewife	6 (15.8)
Self-employment	4 (10.5)
Farmer	2 (5.3)
Cancer type, n(%)	
Adenocarcinoma	18 (47.4)
SCC	15 (39.5)
NOS	5 (13.2)
Treatment, n (%)	
Platinum-based chemotherapy	30 (78.9)
Immunotherapy	8 (21.1)

Data were presented as mean±standard deviation, median (min-max) and number (%). Abbreviations: SCC: Squamous cell carcinoma, NOS: Non-small cell lung cancer unclassified type

Supplementary Table 1. Anthropometric measurements and distribution of parameters associated with sarcopenia

Variables	All patients n=38
Boy, cm	168.4±8.2
Weight , kg	75.0±18.2
Waist circumference, cm	102.0±12.6
Hip circumference, cm	104.9±11.2
Waist/hip ratio	0.9±0.1
Fat mass, %	32.6±8.6
Fat mass, kg	21.9 (8.6-62.1)
Fat-free weight, kg	48.9±13.5
Total body weight, kg	75.0±18.0
Dry fat-free weight, kg	11 (1.6-20.8)
Total body fluid, %	54.2±9.2
Total body fluid, kg	39.2±7.3
ECW, %	23.2±5.0
ECW, kg	17.0±3.8
ICW, %	32.0±9.7
ICW, kg	23.6±9.1
Body cell mass	31.4±6.9
Third cavity fluid	0.5 [(-0.5)-3.2]
Nutrition score	0.44 (0.17-0.70)
Disease score	0.8±0.3
BMR	1512.9±279.0
BMR/BW ratio	20.7±2.6
EAR	2301.3±513.2
VKI	26.4±6.2
BFMI	7.7 (2.9-25.8)
FFMI	17.5±3.3
Impedance 50	527 (384-1547)
Resistance 50	525 (383-1059)
Reactance 50	51.3 (16.2-11.27)
Phase Angle	5.3 (1.8-46.8)
Grip strength	23.4±10.1
Walking speed	0.8±0.2
Muscle mass	8.7±1.7
Sarcopenia, n (%)	
None	19 (50.0)
Possible	9 (23.7)
Sarcopenia	4 (10.5)
Severe	6 (15.8)

Data are presented as mean±standard deviation, median (min-max) and number (%). Abbreviations: BMR: Basal metabolic rate, BMR/BW: Basal metabolic rate/body weight, EAR: Average caloric requirement, ECW: Extracellular body fluid, ICW: Intracellular body fluid, BMI: Body-mass index, BFMI: Fat mass index, FFMI: Fat-free mass index

Mean lean, median dry lean weight, total body weight (kg), extracellular body fluid (ECW) (kg), mean disease score, mean basal metabolic rate (BMR), mean average caloric requirement (EAR), and mean BMI were lower, while median impedance 50, median resistance 50, and median reactance 50 levels were higher in patients with sarcopenia before treatment (**Table 2**).

There was a significant increase in saturation percentage after treatment in patients without sarcopenia before treatment

Table 2. Anthropometric measurements associated with sarcopenia

Variables	Sarcopenia			p
	None n=19	Possible n=9	Exist n=10	
Height, cm	170.3±9	164.7±7.5	168.3±6.3	0.235
Weight, kg	83.5±19.2	68.4±11.7	65.0±12.8	0.007*
Waist circumference, cm	103.8±14.7	103.9±8.3	96.8±11.1	0.328
Hip circumference, cm	106.3±10.6	107.7±10.5	100.0±12.4	0.260
Waist–hip ratio	1.0±0.1	1.0±0.1	0.9±0.2	0.309
Fat mass, %	32.4±8.2	29.5±7.9	35.7±9.9	0.304
Fat mass, kg	23.6 (8.6-62.1)	20.3 (11.1-27.6)	20.6 (10.6-47.1)	0.244
Fat-free weight, kg	55.7±9.9	49.2±10.1	35.5±13.0	<0.001*
Total body weight, kg	83.4±19	70.4±11.7	63.1±12.7	0.007*
Dry fat-free weight, kg	12.5 (0.8-20.8)	11 (1.3-17.3)	8.2 [(-1.6)-12.7]	0.021*
Total body fluid, %	53.0±10.3	56.7±7.9	54.1±8.7	0.618
Total body fluid, kg	42.8±6.4	39.5±5.9	32.0±4.4	<0.001*
ECW, %	23.7±5.6	24.8±3.1	20.8±4.7	0.194
ECW, kg	19.1±3.2	17.2±2.2	12.9±2.5	<0.001*
ICW, %	32.0±13.1	30.6±4.0	33.1±5.1	0.866
ICW, kg	26.2±8.1	21.4±3.8	20.4±2.0	0.190
Body cell mass	33.0±8.6	30.6±5.4	29.1±3.0	0.334
Third cavity fluid	0.4 [(-3.8)-3.2]	0.5 [(0.1)-2.4]	0.3 [(-5.0)-1.8]	0.094
Nutrition score	0.4±0.1	0.5±0.1	0.4±0.1	0.105
Disease score	0.8±0.3	0.8±0.1	0.6±0.2	0.027*
BMR	1655.1±245.0	1505.9±233.5	1249.1±177.5	<0.001*
BMR/BW ratio	20.4±2.8	22.0±2.4	20.1±2.4	0.246
EAR	2592.3±490.7	2226.1±262.3	1815.9±306.2	<0.001*
BMI	28.7±6.4	26.5±4.1	22.0±5.7	0.029*
BFMI	8.2 (2.9-25.8)	7.8 (4.0-11.5)	7.3 (5.0-19.6)	0.598
FFMI	19.1±2.3	18.2±3.0	13.7±2.6	<0.001*
Impedance 50	506 (384-1042)	508 (404-590)	675 (542-1547)	0.001*
Resistance 50	503 (383-903)	507 (402-589)	665.5 (541-1059)	<0.001*
Reactance 50	42.9 (16.2-678)	43 (28.5-169)	111.5 (33.1-1127)	0.210
Phase Angle	5 (1.8-29.9)	4.4 (2.4-8.3)	9.7 (3.2-46.8)	0.010*
Grip strength	31.5±6.5	14.0±3.6	16.6±6.9	<0.001*
Walking speed	0.9±0.1	0.7±0.2	0.7±0.3	<0.001*
Muscle mass	9.4±1.3	9.3±1.5	6.9±1.3	<0.001*

Data are shown as mean±standard deviation and median (min-max). *p<0.05 indicates statistical significance. Abbreviations: BMR: Basal metabolic rate, BMR/BW: Basal metabolic rate/body weight, EAR: Average caloric requirement, ECW: Extracellular body fluid, ICW: Intracellular body fluid, BMI: Body-mass index, BFMI: Fat mass index, FFMI: Fat-free mass index

(94.7±2.6 versus 92.5±5.2; p=0.035), whereas saturation level did not change after treatment in patients with possible sarcopenia or sarcopenia. In patients with sarcopenia, the median ECOG performance score decreased significantly after treatment (p<0.05).

Sarcopenia was observed after treatment in 11 patients without sarcopenia at baseline and in 11 patients with possible sarcopenia (Table 3). Those with an increased sarcopenia score had higher pre-treatment median fat mass (21 kg vs. 28 kg; p=0.050) and mean BMI (25.8±4.3 vs. 30.4±7.6; p=0.037), lower median impedance 50 (538 vs. 506; p=0.050), and lower median resistance 50 (534 vs. 503; p=0.041). Other anthropometric characteristics did not differ significantly between the groups.

Post-treatment saturation percentage decreased significantly in those with an increased sarcopenia score compared to pretreatment (92.7±2.6 versus 89.8±4.5; p=0.041), and the ECOG performance score increased (1 versus 1.5; p=0.003). In patients whose sarcopenia score did not change, saturation and ECOG performance score did not change significantly, but 25-OH vitamin D level increased significantly after treatment (20 versus 30; p=0.001). It was found to decrease significantly in those with an increased sarcopenia score (25 versus 12; p=0.020). There was no significant difference in other laboratory findings (Table 4).

Anthropometric characteristics did not differ significantly after treatment in patients with an unchanged sarcopenia score. In patients whose sarcopenia score increased, weight, waist circumference, BMI, lean weight, total body weight, dry lean weight, ECW, intracellular fluid content (ICW), body mass cell, BMR, mean caloric requirement, and lean mass index decreased significantly (Table 5).

Table 3. The relationship between the change in sarcopenia score and pretreatment anthropometric characteristics

Laboratory findings	Sarcopenia			p
	None n=19	Possible n=9	Exist n=10	
Hemoglobin, gr/dl	12.6±1.9	11.5±1.6	11.6±1.9	0.218
WBC, x10^9/L	7.6 (3.3-23.0)	7.1 (2.6-16.1)	11 (6.6-20.5)	0.137
Platelets, x10^9/L	239 (163-568)	351 (145-575)	310 (146-448)	0.505
Neutrophil, x10^9/L	4.7 (1.8-17.8)	5.9 (1.6-14.6)	8 (5.0-19.5)	0.074
ALT, u/l	22 (6-93)	11 (6-94)	13 (5-77)	0.849
AST, u/l	19 (9-31)	13 (9-25)	15.5 (14-33)	0.878
UREA, mg/dl	38 (19-61)	30 (16-73)	38.5 (12-78)	0.678
Creatinine, mg/dl	1±0.4	0.7±0.2	0.9±0.4	0.089
GFR, ml/dk	82.2±25.8	99±19.9	80.4±23.4	0.175
Sodium, mmol/l	138.6±4.3	137.4±2.5	139.3±2.2	0.505
Potassium, mmol/l	4.6±0.6	4.4±0.3	4.5±0.3	0.439
Magnesium, mg/dl	2.1±0.4	2±0.4	15.6±42.6	0.823
Calcium, mg/dl	9.6±1	9.1±0.4	9.2±0.7	0.371
Phosphorus, mg/dl	3.3±1.1	3.9±1	3.2±0.8	0.244
Total protein, gr/dl	7±0.7	6.8±1	7.1±0.5	0.669
Albumin, gr/dl	4±0.6	3.6±0.6	3.7±0.7	0.197
25-OH vitamin D, ng/dl	20 (11-46)	25 (15-49)	19 (15-25)	0.315
Sedimentation, mm/s	38 (5-120)	49 (17-88)	85.5 (1-135)	0.192
CRP, mg/dl	16.8 (0.1-99.0)	26.2 (0.2-132)	30.7 (2.0-195)	0.092

Data are shown as mean±standard deviation and median (min-max). Abbreviations: ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, GFR: Glomerular filtration rate, WBC: White blood cells

Table 4. Changes in clinical findings according to the change in sarcopenia score

Variables	Sarcopenia score after treatment					
	Not changed		p	Increased		p
	Pre-treatment	Post-treatment		Pre-treatment	Post-treatment	
Saturation, %	93.6±3.7	94.8±3.3	0.298	92.7±2.6	89.8±4.5	0.041*
ECOG PS	1 (0-2)	0 (0-3)	0.649	1 (0-1)	1.5 (0-4)	0.003*
Hemoglobin, gr/dl	12.4±2.1	11.9±1.8	0.206	11.9±1.8	10.8±1.8	0.050*
WBC, x10^9/L	8.7 (2.6-23)	7.6 (2.1-19.6)	0.282	6.3 (4.6-15.1)	9.5 (3.8-12.9)	0.731
Platelets, x10^9/L	242 (145-575)	246 (144-487)	0.185	311 (167-536)	193 (1358-491)	0.056
Neutrophil, x10^9/L	6.2 (1.6-17.8)	5.2 (2.7-12.5)	0.242	3.9 (0.7-15.1)	6.3 (2.5-12.1)	0.748
ALT, u/l	16 (6-93)	16 (6-48)	0.162	20 (6-94)	12 (5-34)	0.056
AST, u/l	18 (8-98)	16 (9-30)	0.188	19 (8-57)	17 (9-31)	0.181
Ure, mg/dl	37 (17-60)	31 (10-49)	0.478	33 (16-61)	41 (20-75)	0.565
Creatinine, mg/dl	0.8±0.3	0.9±0.3	0.135	1.0±0.4	0.9±0.4	0.271
GFR, ml/dk	90.4±24.2	85.2±20.4	0.104	77.5±28.8	84.1±26	0.395
Sodium, mmol/l	138.4±3.2	138.7±3.9	0.692	138.7±4.4	139.8±1.5	0.483
Potassium, mmol/l	4.6±0.4	4.6±0.5	0.705	4.4±0.7	4.2±0.5	0.139
Magnesium, mg/dl	2.1±0.3	2.1±0.4	0.630	2±0.4	2.1±0.3	0.363
Calcium, mg/dl	9.3±0.6	9.5±0.5	0.413	9.6±1.2	8.7±1.1	0.111
Phosphorus, mg/dl	3.3±1.0	3.5±0.8	0.592	3.7±1.0	3.2±0.5	0.075
Total protein, gr/dl	7.1±0.6	7.1±0.6	0.466	6.9±0.7	6.6±1.1	0.241
Albumin, gr/dl	4.1±0.5	4.3±0.3	0.229	3.7±0.6	3.7±0.9	0.914
25-OH vitamin D, ng/dl	20 (12-40)	30 (15-53)	0.001*	25 (11-49)	12 (7-30)	0.020*
Sedimentation, mm/s	39 (5-135)	42 (15-117)	0.428	54 (9-117)	75 (10-127)	0.096
CRP, mg/dl	12.9 (0.1-154)	8.2 (0.1-84)	0.347	35.5 (3-99)	9 (2.2-185)	0.818

Data are shown as mean±standard deviation and median (min-max). *p<0.05 indicates statistical significance. Abbreviations: ECOG PS: Eastern cooperative oncology group performance score, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, GFR: Glomerular filtration rate, WBC: White blood cells

Table 5. Changes in anthropometric findings according to the change in sarcopenia score

Variables	Sarcopenia score after treatment					
	Not changed		p	Increased		p
	Pre-treatment	Post-treatment		Pre-treatment	Post-treatment	
Weight, kg	73.5±13.3	75.1±15.0	0.565	86.4±22.4	75.1±15.9	0.003*
Waist circumference, cm	101.4±10.3	100.8±13.1	0.930	106.5±15.8	104.7±16.1	0.043*
Hip circumference, cm	106.2±9.7	105.4±10.9	0.795	107.8±12	106.3±14.2	0.428
Waist/hip ratio	0.9±0.1	0.9±0.1	0.686	1.0±0.1	1.0±0.1	0.911
Fat mass, %	30.3±8.2	30.4±9.4	0.985	35.5±8.9	34.5±11.0	0.644
Fat mass, kg	21 (11-47)	20.5 (8-55)	0.844	28 (9-62)	23 (12-46)	0.169
Fat-free weight, kg	48.6±13.8	51.8±9.4	0.266	55.0±11.8	48.6±10.9	0.001*
Total body weight, kg	73.5±13.3	75±15	0.517	86.1±22.1	75.1±15.9	0.004*
Dry fat-free weight, kg	11.8 (1.3-19)	12 (1.1-20.3)	0.731	12.5 (0.8-20.8)	9 (1.5-21.5)	0.027*
Total body fluid, %	54.9±7.4	55±9.5	0.944	52.1±11.6	52.8±12.6	0.767
Total body fluid, kg	39.0±6.2	40.3±5.8	0.137	43.2±7.1	38.4±7.1	0.004*
ECW, %	23.7±5.0	23.5±4.2	0.800	22.8±4.8	22.7±5.9	0.919
ECW, kg	17.2±3.4	17.1±2	0.994	18.9±2.9	16.5±3.5	0.010*
ICW, %	32.7±12.3	30.6±3.9	0.444	28.9±5.0	30.2±4.6	0.196
ICW, kg	24.2±11.9	22.7±4.1	0.539	23.9±4.0	22.1±3.9	0.007*
Body cell mass	30.1±7.4	32.3±5.7	0.164	34.9±6.5	31.5±5.6	0.003*
Third cavity fluid	0.5 [(-3.4)-2.4]	0.9 [(-4.7)-3.8]	0.076	0.4 [(-3.8)-3.2]	1 [(-6.3)-2.8]	0.912
Nutrition score	0.4±0.1	0.7±0.3	0.322	0.4±0.01	0.4±0.1	0.436
Disease score	0.8±0.3	0.8±0.1	0.918	0.8±0.1	0.7±0.2	0.298
BMR	1526.7±225.2	1564.8±223.1	0.226	1648.8±286.5	1491.9±257.7	0.001*
BMR/BW	21.3±2.5	21.2±2.7	0.940	19.7±3.1	20.2±2.9	0.460
EAR	2392.8±439.8	2357.1±386.3	0.568	2453.4±518.1	2188.7±423.0	0.003*
BMI	25.8±4.3	26.3±4.9	0.497	30.4±7.6	26.5±5.6	0.003*
BFMI	7.2 (4-19.6)	6.7 (2.9-23.0)	0.909	10.3 (2.9-26.0)	7.3 (4.1-19.0)	0.163
FFMI	17.6±2.5	18±2.2	0.273	19.2±2.7	17.0±2.8	<0.01*
Impedance 50	538 (404-1042)	522 (386-734)	0.177	506 (384-560)	510 (386-711)	0.852
Resistance 50	534 (402-903)	514 (385-720)	0.195	503 (383-559)	523 (388-1899)	0.175
Reactance 50	58 (29-678)	41.6 (13-498)	0.059	37.8 (16-678)	33.1 (13-675)	0.340
Phase Angle	5.4 (3.2-30)	4.5 (2-17)	0.234	4.4 (1.8-7.4)	3.7 (1.8-37)	0.259
Grip strength	25.8±9.7	25.6±9.5	0.802	24.4±9.4	17.2±6.2	0.029*
Walking speed	0.8±0.3	0.8±0.4	0.933	0.9±0.1	0.6±0.3	0.004*
Muscle mass	8.7±1.6	9±1.6	0.164	9.4±1.1	7.8±1.9	0.017*

Data are shown as mean±standard deviation and median (min-max). *p<0.05 indicates statistical significance. Abbreviations: BMR: Basal metabolic rate, BMR/BW: Basal metabolic rate/body weight, EAR: Average caloric requirement, ECW: Extracellular body fluid, ICW: Intracellular body fluid, BMI: Body-mass index, BFMI: Fat mass index, FFMI: Fat-free mass index

In patients with the adenocarcinoma subtype, there was a significant decrease in mean handgrip strength and mean walking speed and an increase in the sarcopenia score after medical treatment. Patients with the SSC subtype had a significant decrease in mean walking speed and median phase angel score after medical treatment. In patients with the NOS subtype, there was a significant increase in vitamin D levels and a significant decrease in mean urea value after treatment. No significant change was observed in other measurements (**Supplementary Table 2**).

In patients with stage 3 at baseline, there were significant decreases in mean waist and hip circumference, mean fat mass, and mean fat mass index; increases in mean total body fluid and mean basal metabolic rate/body weight (BMR/BW) ratio; and no significant change in sarcopenia score after treatment. In patients with stage 4 NSCLC, an increase in sarcopenia score was observed after treatment, while a significant decrease was observed in walking speed, albumin level, platelet count, and ECW (%) (**Table 4**). Thrombocytopenia (platelet level below 150×109) was detected in 25% of patients with stage 4 NSCLC after treatment (**Supplementary Table 3**).

Patients who received platinum-based therapy at baseline showed a significant increase in sarcopenia score after treatment, while hip circumference, handgrip strength, walking speed, and platelet count decreased significantly (**Supplementary Table 4**). In patients receiving immunotherapy, no significant change was observed after treatment. Thrombocytopenia was detected in 25% of patients receiving platinum-based therapy.

A significant increase in sarcopenia score was observed in patients whose vitamin D level decreased after treatment, while a significant decrease was observed in muscle mass,

Supplementary Table 2. Symptoms associated with the type of disease

Variables		Findings	p
Adenocarcinoma			
Grip strength, kg	Pre-treatment	20.4±7.4	0.044 *
	Post-treatment	17.7±6.5	
Walking speed, m/s	Pre-treatment	0.7±0.3	0.043*
	Post-treatment	0.6±0.4	
Sarcopenia score	Pre-treatment	1 (0-3)	0.026 *
	Post-treatment	2 (0-3)	
SSC			
Walking speed, m/s	Pre-treatment	0.9±0.1	0.049*
	Post-treatment	0.7±0.3	
Sarcopenia score	Pre-treatment	0 (0-3)	0.301
	Post-treatment	1 (0-3)	
Fat mass, %	Pre-treatment	28.5±5.5	0.029
	Post-treatment	25.5±3.9	
Phase Angle	Pre-treatment	5.0 (3-8.7)	0.050*
	Post-treatment	4.4 (1.8-5.7)	
NOS			
Urea, mg/dl	Pre-treatment	40 (21-60)	0.043*
	Post-treatment	31 (10-43)	
Vitamin D, ng/dl	Pre-treatment	19 (15-25)	0.050*
	Post-treatment	30 (15-40)	
Sarcopenia score	Pre-treatment	0 (0-2)	0.999
	Post-treatment	0 (0-2)	

Data are shown as mean±standard deviation and median (min-max). *p<0.05 indicates statistical significance. SCC: Squamous cell carcinoma, NOS: Non-small cell lung cancer unclassified type

Supplementary Table 3. Findings associated with the stage of the disease

Variables		Findings	p
Phase 3			
Waist circumference (cm)	Pre-treatment	101.9±13.5	0.046*
	Post-treatment	99.9±14.2	
Hip circumference (cm)	Pre-treatment	105.1±11	0.027*
	Post-treatment	103.5±10.8	
Sarcopenia score	Pre-treatment	0 (0-2)	0.194
	Post-treatment	0.5 (0-3)	
Fat mass, %	Pre-treatment	31.6±9.7	0.012*
	Post-treatment	27.9±7.5	
Fat mass, kg	Pre-treatment	21 (11-62)	0.013*
	Post-treatment	17 (8.3-46)	
Total body fluid, %	Pre-treatment	54.7±10.9	0.030*
	Post-treatment	58.9±9.0	
ECW, %	Pre-treatment	23.5±4.2	0.017*
	Post-treatment	25.6±3.4	
Third cavity fluid	Pre-treatment	0.8 [(-3.8)-2.4]	0.023*
	Post-treatment	1.0 [(-2.0)-3.8]	
BMR/BW ratio	Pre-treatment	20.7±3.1	0.007*
	Post-treatment	21.9±2.4	
BFMI	Pre-treatment	7.2 (4.0-25.8)	0.013*
	Post-treatment	6.2 (2.9-19.0)	
Phase 4			
Platelets	Pre-treatment	241 (145-457)	0.020*
	Post-treatment	188 (147-366)	
Albumin	Pre-treatment	3.8±0.5	0.038*
	Post-treatment	4.1±0.6	
Walking speed	Pre-treatment	0.8±0.3	0.009*
	Post-treatment	0.6±0.4	
Sarcopenia score	Pre-treatment	1 (0-3)	0.048*
	Post-treatment	1.5 (0-3)	
ECW, %	Pre-treatment	22.5±4.1	0.019*
	Post-treatment	21.3±5.2	
ECW, kg	Pre-treatment	17.4±3.3	0.049*
	Post-treatment	15.9±2.6	

Data are shown as mean±standard deviation and median (min-max). *p<0.05 indicates statistical significance. Abbreviations: BMR: Basal metabolic rate, BMR/BW: Basal metabolic rate/body weight ratio, ECW: Extracellular body fluid, BFMI: Fat mass index

Supplementary Table 4. Findings related to the treatment regimen

Variables		Findings	p
Platinum-based chemotherapy			
Hip circumference, cm	Pre-treatment	107.1±11.0	0.046*
	Post-treatment	105.0±11.5	
Platelets, x10^9/L	Pre-treatment	275 (145-575)	0.007*
	Post-treatment	217 (147-491)	
Grip strength, kg	Pre-treatment	25.2±10.3	0.052
	Post-treatment	22.0±9.0	
Walking speed, m/s	Pre-treatment	0.8±0.2	0.029*
	Post-treatment	0.7±0.3	
Sarcopenia score	Pre-treatment	0 (0-3)	0.046*
	Post-treatment	1 (0-3)	

Data are shown as mean±standard deviation and median (IQR). *p<0.05 indicates statistical significance

walking speed, the patient's performance level, and saturation measurement. Significant differences were also found in anthropometric findings (**Supplementary Table 5**). In patients who were found to have progression on thoracic tomography after medical treatment, significant differences were found in anthropometric measurements, but a significant decrease was observed in saturation measurements and walking speed, a worsening of performance status was detected, and an increase in the sarcopenia score was determined (**Table 6**).

DISCUSSION

Sarcopenia is defined as a loss in skeletal muscle mass, quality, and function associated with malnutrition, aging, a sedentary lifestyle, and chronic diseases, especially COPD and malignancies.[2] Sarcopenia in cancer patients is associated with malnutrition, lipolysis, inflammatory status, and vicious metabolic cycles. This relationship promotes the occurrence of cachexia, which is considered a major cause of mortality in advanced cancer patients. Cachexia is an exhaustion syndrome that affects approximately 50% of patients with lung cancer, occurring even in the presence of adequate caloric intake.[11,12] Therefore, the development of therapeutic strategies aimed at reversing or at least counteracting the metabolic changes that promote cancer progression or recurrence and improving quality of life is important for the early prevention of tissue loss.[13]

Skeletal muscle loss in NSCLC has been shown to negatively affect treatment outcomes.[6] In our study, approximately

Supplementary Table 5. Associated findings in patients with decreased vitamin D levels after treatment

Variables		Findings	p
Weight (kg)	Pre-treatment	76.6±18.5	0.019*
	Post-treatment	69.5±14.6	
Saturation	Pre-treatment	93.1±2.9	0.041*
	Post-treatment	90.1±5.2	
ECOG PS	Pre-treatment	1 (0-1)	0.023 *
	Post-treatment	1 (0-4)	
Sedimentation, mm/s	Pre-treatment	43 (14-86)	0.029*
	Post-treatment	75 (10-104)	
Grip strength, kg	Pre-treatment	23.0±9.2	0.197
	Post-treatment	18.7±9.8	
Walking speed, m/s	Pre-treatment	0.9±0.2	0.003*
	Post-treatment	0.6±0.3	
Muscle mass, kg	Pre-treatment	9.6±1.3	0.014*
	Post-treatment	8.5±1.6	
Sarcopenia score	Pre-treatment	0 (0-1)	0.011*
	Post-treatment	2 (0-3)	
Fat-free weight, kg	Pre-treatment	52.6±10.7	0.002*
	Post-treatment	48.0±11.7	
Total body weight, kg	Pre-treatment	76.6±18.5	0.019*
	Post-treatment	69.5±14.5	
Dry fat-free weight, kg	Pre-treatment	12.5 (0.8-17.8)	0.016*
	Post-treatment	7.9 (1.5-18.1)	
Total body fluid, kg	Pre-treatment	42.0±6.7	0.009*
	Post-treatment	39.1±7.3	
ECW, kg	Pre-treatment	18.1±2.8	0.032*
	Post-treatment	16.8±3.3	
ICW, kg	Pre-treatment	22.9±3.4	0.019*
	Post-treatment	21.5±3.4	
Body cell mass	Pre-treatment	33.4±5.9	0.010*
	Post-treatment	30.7±4.9	
BMR	Pre-treatment	1584.4±261.1	0.002*
	Post-treatment	1471.4±281.7	
EAR	Pre-treatment	2344.5±398.4	0.010*
	Post-treatment	2139.6±416.9	
BMI	Pre-treatment	27.3±5.4	0.014*
	Post-treatment	24.8±4.2	
FFMI	Pre-treatment	18.7±2.6	0.002*
	Post-treatment	17.0±2.9	
Resistance 50	Pre-treatment	519 (383-586)	0.050*
	Post-treatment	523 (388-710)	

Data are shown as mean±standard deviation and median (min-max). *p<0.05 indicates statistical significance. Abbreviations: BMR: Basal metabolic rate, EAR: Estimated average calorie requirement, ECW: Extracellular body fluid, ICW: Intracellular body fluid, BMI: Body-mass index, FFMI: Fat-free mass index

Table 6. Associated findings in patients with progression after medical treatment

Variables		Findings	p
Weight, kg	Pre-treatment	86.6±22.0	0.024*
	Post-treatment	76.3±16.2	
Waist circumference, cm	Pre-treatment	104.0±17.1	0.039*
	Post-treatment	101.3±17.7	
Saturation, %	Pre-treatment	94.1±2.8	0.005*
	Post-treatment	89.8±5.4	
ECOG PS	Pre-treatment	1 (0-1)	0.014*
	Post-treatment	3 (0-4)	
Hemoglobin, gr/dl	Pre-treatment	11.9±1.7	0.030*
	Post-treatment	10.6±1.8	
Sedimentation, mm/s	Pre-treatment	39 (15-117)	0.043*
	Post-treatment	73 (10-109)	
Walking speed, m/s	Pre-treatment	0.9±0.2	0.016*
	Post-treatment	0.5±0.3	
Muscle mass, kg	Pre-treatment	9.7±1.0	0.050*
	Post-treatment	8.1±2.2	
Sarcopenia score	Pre-treatment	0 (0-1)	0.023*
	Post-treatment	1 (0-3)	
Fat-free weight, kg	Pre-treatment	58.7±10.6	0.010*
	Post-treatment	52.6±11.0	
Total body weight, kg	Pre-treatment	86.2±21.6	0.029*
	Post-treatment	76.3±16.2	
Total body fluid, kg	Pre-treatment	45.3±6.2	0.037*
	Post-treatment	40.9±7.0	
ECW, kg	Pre-treatment	20.5±3.4	0.032*
	Post-treatment	17.3±3.3	
BMR	Pre-treatment	1734±265.7	0.010*
	Post-treatment	1583.3±267.7	
EAR	Pre-treatment	2631.3±500.6	0.003*
	Post-treatment	2327.4±437.0	
BMI	Pre-treatment	28.6±6.5	0.028*
	Post-treatment	25.3±4.6	
FFMI	Pre-treatment	19.5±2.6	0.001*
	Post-treatment	17.4±2.9	

Data are shown as mean±standard deviation and median (min-max) *p<0.05 indicates statistical significance. Abbreviations: BMR: Basal metabolic rate, EAR: Average calorie requirement, ECW: Extracellular body fluid, BMI: Body-mass index, FFMI: Fat-free mass index

80% of the patients received platinum-based chemotherapy, and the remaining patients received immunochemotherapy. Furthermore, the treatment distribution was similar in patients with and without sarcopenia at baseline, but sarcopenia developed after treatment in a large portion of patients who did not have sarcopenia or who had possible sarcopenia. On the other hand, 70% of the patients with pre-treatment sarcopenia showed regression in CT findings after treatment, while this rate was 42% in patients without pre-treatment sarcopenia. The disease control rate defines the proportion of patients with a reduced or stable disease burden during the study period.[14] In our study, we found that patients with sarcopenia exhibited a worse disease control rate. In a previous study, the presence of sarcopenia before treatment and worsening sarcopenic status after starting treatments were shown to be associated with a decreased disease control rate.[7]

The relationship between sarcopenia and stage in NSCLC may also play an important role in response to treatment. In the literature, the relationship between cancer stage and sarcopenia presents conflicting results. Some previous studies did not report a significant association between sarcopenia and cancer stage.[15,16] A study by Kinsey et al.[17] reported that patients with stage 4 NSCLC were more likely to experience a decrease in lean weight levels during treatment. Thrombocytopenia was also observed in 25% of patients with stage 4 NSCLC, which constituted the majority of our study,

while no significant difference was found in post-treatment platelet levels in stage 3 patients. However, a 0.5 increase in sarcopenia scores was observed in both stages. However, the sarcopenia score tended to be higher, and ECW levels significantly decreased in stage 4 patients both before and after treatment.

Weight loss has been shown to be a negative prognostic factor in patients with lung cancer.[18] While weight and BMI levels were significantly lower in patients with sarcopenia at baseline, there was no significant change in weight or BMI levels in these patients after treatment. On the other hand, patients without sarcopenia had higher weight and BMI levels at baseline, whereas a significant decrease in weight and BMI levels was observed after treatment. Although there was no post-treatment death in these patients, progression was detected on a post-treatment CT scan in 42% of them. Therefore, a loss in weight and BMI levels may lead to a worsening prognosis. In patients whose sarcopenia score increased after treatment, weight and BMI levels decreased, saturation levels decreased, and the ECOG performance score increased, while handshake strength, walking speed, and muscle mass decreased. The decrease in muscle mass is driven by a variable combination of reduced caloric/protein intake, metabolic changes, and inflammation.[19] This was consistent with decreased levels of LBM, BCM, and FFMI. A reduced lean mass index has been shown to be an independent predictor of reduced quality of life and mortality.[20,21] It has also been reported that low FFMI is more common in patients at risk of malnutrition and in patients with high levels of inflammatory biomarkers.[16] Among patients with weight loss, a higher incidence of mortality has been reported in those with low FFMI compared to those with a normal lean mass index.[18] A consequence of low lean mass may result in a low volume of distribution of cytotoxic chemotherapy drugs. In a previous study, low lean body weight was shown to be a significant predictor of toxicity in patients administered 5-FU using the dosing rule per unit of body surface area.[22]

It has been suggested that vitamin D deficiency may play an important role in the development of sarcopenia during chemotherapy, targeted therapy, and immunotherapy.[23] Increased levels of proinflammatory and anti-inflammatory cytokines (such as TNF-α, IFN-γ, and IL-6) due to vitamin D deficiency may result in increased muscle catabolism and decreased muscle protein synthesis.[24] In our study, no significant correlation was observed between pre-treatment sarcopenia and vitamin D levels. However, an increase in post-treatment vitamin D levels was observed in patients whose sarcopenia score did not change after treatment, while a decrease in post-treatment vitamin D levels was observed in patients whose sarcopenia score increased after treatment. Also, in patients whose vitamin D levels dropped after treatment, their saturation percentage and ECOG performance score got worse. There was also more inflammation and lower BMI measurements like walking speed, muscle mass, body cell mass, BMR, and lean mass index. These variables did not differ significantly in patients with unchanged or increased vitamin D levels after treatment compared to pretreatment. All these findings support the idea that decreased vitamin D levels, especially after treatment, increase the risk of sarcopenia, in accordance with the literature.

Limitations

This study has some important limitations. First, although this study had a prospective design, it was single-centered and had a small sample size. The small sample size may affect the statistical significance of differences in subgroup analyses. However, the large sample size could partially compensate for this limitation. Second, CT is considered the gold standard for measuring body composition, but we did not assess body composition by CT in our study. However, BIA measurement is a feasible, non-invasive, low-cost measurement and is widely used in clinical research settings. Finally, the limited number of patients receiving immunotherapy may have limited the significance of changes in BIA parameters.

CONCLUSION

Approximately half of NSCLC patients have sarcopenia before treatment, and this rate increases after treatment. In addition, it was observed that the risk of sarcopenia increased after treatment in patients without sarcopenia before treatment, and the severity of sarcopenia increased in patients with sarcopenia. Sarcopenia was found to be associated with body weight, BMI, waist circumference, and hip circumference. Therefore, anthropometric measurements and sarcopenia findings should be regularly screened in NSCLC patients before and after treatment.

Platinum-based chemotherapy may cause significant differences in the BIA parameters associated with sarcopenia. In addition, vitamin D deficiency may play an important role in the development of sarcopenia. Although a decrease in vitamin D levels is expected in patients with advanced NSCLC, vitamin D replacement may both reduce the risk of sarcopenia and improve the prognosis. Therefore, control of vitamin D levels may be important in the follow-up of NSCLC patients. The findings of this study will guide future research in the prevention and treatment of sarcopenia in patients suffering from NSCLC.

ETHICAL DECLARATIONS

Ethics Committee Approval

The protocol of the study was approved by the Kırıkkale University Clinical Research Ethics Committee (Date: 13.10.2020, Decision No: 09/01).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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