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Original Article

Sarcopenia Detected in Aged Patients in Intensive Care Units is Associated with Poor Prognosis

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ABSTRACT

Background/Purpose: Sarcopenia is a syndrome characterised by progressive and generalised loss of skeletal muscle mass. The aim of this study was to evaluate effects of sarcopenia on the prognosis of the critical aged patients admitted to intensive care unit (ICU).

Methods: The study was planned as a retrospective and observational study and performed after the approval from the ethics committee (approval number is E. Kurul-E-18-1928). Patients older than 40 years of age having abdominal tomography and admitted to the ICU were included. All patients were divided into two groups as sarcopenic and non-sarcopenic by muscle mass measuring by abdominal tomography. We compared the prognosis and clinical features of the patients with and without sarcopenia.

Results: A total of 105 patients were included in the study. Fifty five (59%) of the patients were found as sarcopenic and 70.8% over 70 years of age. The length of stay in ICU and in hospital were 27.8±29.7 and 33.0±31.2 days in sarcopenic patients, 15.1±17 and 23.8±21.3 days in nonsarcopenic patients respectively (p <0.05). Thirty day mortality was found 49.1% in sarcopenic patients (p <0.05).

Conclusion: The presence of sarcopenia in critically aged patients is important because it is associated with increased 30-day mortality, prolonged ICU and hospital stay.

1. INTRODUCTION

Sarcopenia was first described by Irwin Rosenberg in 1989, who defined sarcopenia as a condition of age-related loss of muscle mass.[1] In 2009 The European Sarcopenia Study Group (EWGSOP) defined sarcopenia as "a syndrome characterised by progressive and generalised loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death".[2] In the fourth decade of life, muscle mass and appendicular skeletal muscle strength begin to decrease.[3] A reduction of 3% or more in the functional capacity of the muscle from the age of sixth decade and a loss of more than 50% muscle mass from the eighth decade.[4] The prevalence of sarcopenia has been reported as 5-13% and 11-50%

for 60-70 years and over 80 years of age respectively.[5] In a study using abdominal computed tomography (CT) in intensive care unit (ICU), the frequency of sarcopenia was found to be 15-50 % in cancer patients[6], 30-45 % in patients with liver failure[7] and 60-70 % in critically ill patients.[8] It is expected that it will affect 1.2 million people in 2025 and 2 million people in 2050.[9]

The distinctions of 'primary sarcopenia' and 'secondary sarcopenia' have been proposed by EWGSOP. Primary sarcopenia indicates muscle wasting related to aging, while secondary sarcopenia, refers to muscle loss related to inflammation or malnutrition. Because it is mostly due to multiple reasons, classification as primary or secondary may not always be reasonable.[2] Considering that the muscle mass is approximately 60% of the body weight, the pathological changes due to the excessive losses may have very large clinical consequences, especially in an aged population.[10] Intensive care unit-acquired weakness (ICU-AW) may be considered as one of the types of secondary sarcopenia. ICU-AW, which is defined as bilateral symmetrical limb weakness. is a result of axonal polyneuropathy (critical illness polyneuropathy), myopathy (critical illness myopathy) or frequently a combination of both (critical illness neuromyopathy). It primarily affects the lower limbs and may extend to a tetraplegia in more severe cases. It is associated with respiratory muscle weakness, delaying of weaning from mechanical ventilation, prolonged ICU and hospital stay and mortality.[11]

EWSGOP reported that a hand grip strength of less than 20 kg in women, less than 30 kg in men and a walking speed of less than 0.8 m/sec in clinical examination can be used for the diagnosis of sarcopenia.[2] Sarcopenia in trunk muscles is a dominant risk factor that adversely affects prognosis. However, it is not possible for every patient to be diagnosed with clinical examination in ICU patients. Since radiological examinations show the relationship between total body fat and muscle mass, they can be used in the diagnosis of sarcopenia.[12] Abdominal CT is accepted as the gold standard methods for diagnosing sarcopenia by fully evaluating fat tissue and muscle mass.[13] In the abdominal CT, L3 vertebra region is correlated with the muscle mass in the whole body.[5] Therefore, the cross-sectional total area (with adipose tissue and skeletal muscle) is evaluated in abdominal CT including psoas, paraspinal muscles (erector spinae, quadratus lumborum) and abdominal wall muscles (transversus abdominis, external and internal obliques, rectus abdominus) at the level of L3 vertebra. In order to normalize the skeletal muscle index (SMI) according to the height, the total muscle area is divided by the square of the height and is defined in unit of cm^2/m^2.[2] Similarly, the evaluation of the thickness of the psoas muscle in the lumbar 3rd or 4th vertebra may help in determining mortality after major surgery.[14] The measurement of the anterior-posterior diameter of the transverse psoas muscle at the umbilical level and the normalization by dividing the height is another radiological parameter used in the diagnosis.[15]

Sarcopenia may not be considered in patients when first admission to ICU. It is important to predict mortality and stratify the risk of death in ICUs. There are few studies evaluating the frequency of sarcopenia and its relation with mortality in the ICU. Although there are articles about the relationship between sarcopenia and mortality.[16] There are also articles reporting that there is no relationship.[17] The aim of this study was to evaluate the diagnosis of sarcopenia by abdominal CT, the prevelance of it among the critical aged patients and the effects of it on the prognosis of the critical patients admitted to ICU.

2. METHODS

2.1. Study Design

The study was planned as a retrospective and observational study and performed after the approval from the ethics committee of Health Sciences University Ankara Numune Training and Research Hospital (approval number is E. Kurul-E-18-1928).

2.2. Participants

Among all patients hospitalized in a tertiary general ICU between 1 May 2017 and 30 April 2018, patients over the age of 40 who underwent abdominal CT during their follow-up in the ICU were included in the study. Informed and written consent was obtained from all study participants. This study was conducted in accordance with the ethical principles of the Helsinki Declaration-2013 and followed good clinical practice guidelines. Medical records of these patients were reviewed. Patients with missing data and without abdominal CT were not included in the study.

2.3. Outcome and Measures and Procedures

Radiological evaluation of the patients with abdominal CT was performed by the same experienced radiologist using standard anatomical landmarks. During abdominal CT the muscles at the level of L3 vertebra were determined and the psoas, paraspinal muscles (erector spinae, quadratus lumborum) and abdominal wall muscles (transverse abdominus, external and internal obliques, rectus abdominus) were marked. The muscle cross-sectional area at the level of L3 was used as it was linearly associated with whole-body muscle mass, and by dividing this value by the square of the height the skeletal muscle index was calculated for each patient in cm^2/m^2. CT scan with 64-detector (Aquilion 64, Toshiba Medical Systems, Tochigi, Japan, 2011) was used in abdominal CT. Two mm section thickness, 64 x 0.5 collimation, 0.5 seconds rotation time, 120 kV and 300 mA were used in CT investigations. The evaluation

of the images was done on the OsiriX (10.0, 64 bit, Switzerland) workstation. The evaluation was performed at L3 vertebral level, in the axial section in which both transverse projections were observed. Skeletal muscle area was measured by 2D/3D segmentation tool at this level. In skeletal muscle area measurements, pixels in the range of -30, +150 Hounsfield Unit (HU) density were marked by automatic segmentation.[18] The necessary adjustments in the marked contours of the fields have been made manually.

The cut off value for L3 skeletal muscle index was accepted as 38.5 cm^2/m^2 in women and 52.4 cm^2/m^2 in men.[18] According to these threshold values, patients were divided into two groups as sarcopenic and non-sarcopenic patients. The demographic data of patients, primary diagnosis at admission to ICU (respiratory failure, sepsis, cardiovascular failure, neurological, gastrointestinal symptoms, multi-trauma, surgical, cancer, drug overdose), comorbidities, body mass index (BMI), APACHE II (Acute Physiology and Chronic Health Evaluation) and SOFA (Sequential Organ Failure Assesment) scores, blood prealbumin, albumin, Vitamin D, urea and creatinine level, nutrition status (total parenteral or enteral nutrition), duration of ventilation, length of stay in ICU and hospital, and prognosis in the ICU (alive or death) were recorded.

SPSS Statistics for Windows v.21.0 (IBM Corp., Armonk, NY) was used. Descriptive statistics were expressed as mean, median, standard deviation, minimum-maximum for numerical variables and as number and percentage for categorical variables. The assumption of normality was examined with the Kolmogorov-Smirnov test, which failed to meet the assumption. Kruskal-Wallis test was used to determine whether there was a difference between groups. In the case of differences between the groups, paired comparison tests were used to determine the group that drove the difference. The differences between categorical variables were examined by chi-square test. For an effect size of 0.35 was calculated the minimum effective sample size as 79 for double-sided hypothesis testing (2x2 contingency table using 2 degrees of freedom). In this calculation, the PASS package program was used, with a minimum statistical power of 80% and a significance (alpha-type I error) level of 0.05.

3. RESULTS

Among the 445 patients admitted to the tertiary general ICU, 105 patients were found to meet the study inclusion criteria. Twelve patients with incomplete data were excluded from the study. Data of the remaining 93 patients were analyzed (Figure 1). There was no statistically difference between men and women in terms of the frequency of sarcopenia (p >0.05). BMI was higher in nonsarcopenic patients than sarcopenic patients (25.6±3.5 vs 24.2±4.8, p <0.05). Fifty five (59%) of all patients were found as sarcopenic (p <0.05). The characteristics of the patients, reasons for admission to the ICU and comorbidities were similar between goups (p >0.05) (Table 1). The presence of sarcopenia, and APACHE

Figure 1. Consort diagram

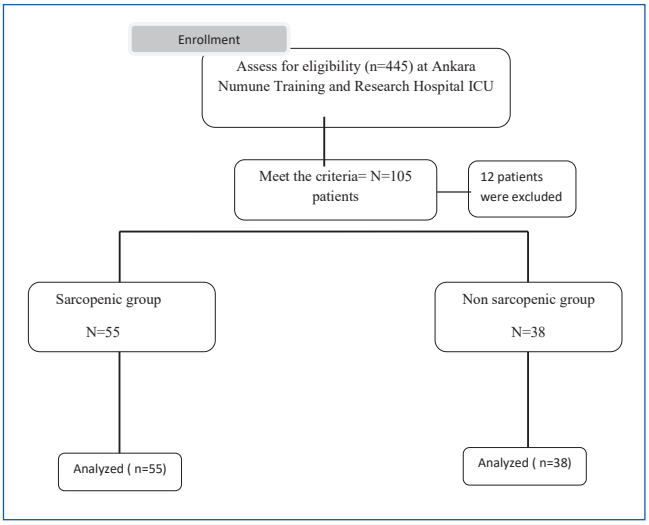

Table 1. Demographic characteristics of the groups

Parametres		N (%)	Sarcopenic Group	Non-sarcopenic Group	p value
Age (Years)	41-50	25 (26.9%)	9 (33.3%)	16 (66.7%)	0.001
	51-60	10 (20.0%)	8 (80.0%)	2 (20.0%)	
	61-70	17 (18.3%)	10 (58.8%)	7 (41.2%)	
	70<	41 (34.8%)	28 (70.8%)	13 (29.2%)	
Sex	Female	37 (40.0%)	21 (38.2%)	16 (42.1%)	0.86
	Male	56 (60.0%)	34 (61.8%)	22 (57.9%)	
BMI (kg/m^2)			24.2±4.8	25.6±3.5	0.04
Prevalence			55 (59.0%)	38 (41.0%)	0.03
Primary diagnosis					
Neurological disease			13 (61.9%)	8 (38.1%)	0.96
Respiratory			7 (63.6%)	4 (36.3%)	0.90
Cardiovascular			2 (66.6%)	1 (33.4%)	0.21
Gastrointestinal			7 (63.6%)	4 (36.3%)	0.90
Cancer			6 (66.6%)	3 (33.3%)	0.15
Sepsis			4 (66.6%)	2 (3.3%)	0.16
Multi-trauma			11 (52.4%)	10 (47.6%)	0.61
Postoperative			3 (75.0%)	1 (25.0%)	0.49
Drug overdose, suicide			3 (50.0%)	3 (50.0%)	0.51
Comorbidities					
DM			6 (42.9%)	8 (57.1%)	0.36
HT			15 (55.5%)	12 (41.4%)	0.91
CAD			14 (58.3%)	10 (41.6)	0.90
Stroke			6 (42.9%)	8 (57.1%)	0.10
COPD			5 (62.5%)	3 (37.5%)	0.73
Malignity			14 (58.3%)	10 (41.6%)	0.18
Demans			3 (50.0%)	3 (50.0%)	0.41
Chronic renal disease			5 (62.5%)	3 (37.5%)	0.61
Hepatic failure			3 (50.0%)	3 (50.0%)	0.88

Note: Results are demonstrated as mean±*SD* or n (%)
BMI: Body mass index, DM: Diabetes Mellitus, HT: Hypertension, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease

II and SOFA scores were similar between groups (p> 0.05). Prealbumin levels were significantly lower in the sarcopenic group (p <0.001). Vit D, albumin, urea, creatinine, nutrition status and mechanical ventilation time were not different between the groups (p> 0.05). The length of stay in ICU and in hospital were 27.8±29.7 and 33.0±31.2 days in sarcopenic patients, 15.1±17 and 23.8±21.3 days in nonsarcopenic patients respectively (p <0.05). Mortality was found to be 49.1% in patients with sarcopenia, and this value was found to 23 % in non-sarcopenic patients (Table 2). SMI was lower in patients over the age of 70 compared to those older than 40 (p <0.05) (Table 3).

Table 2. Comparison of patients admission characteristics of sarcopenic and non-sarcopenic groups

Parametres		Sarcopenic	Non-sarcopenic	*p* value
APACHE II		21.2±9.2	18.1±9.7	0.1
SOFA		6.5±3.2	6.0±3.7	0.3
Prealbumin		0.08±0.05	0.1±0.05	0.006
Albumin		2.7±0.8	3.0±0.08	0.1
Vitamin D		9.7±10.6	7.3±4.5	0.7
BUN		8.01±1.04	7.6±0.9	0.2
Creatinin		1.7±1.5	1.5±1.3	0.7
GFR		63.4±36.2	67.9±35.7	0.6
Nutrition	TPN	18 (32.7%)	9 (23%)	0.5
	EN	37 (67.3%)	29 (76.3%)	
Mechanical ventilation	Yes	39 (70.9%)	22 (57.9%)	0.3
	No	16 (29.1%)	16 (42.1%)	
Length of stay ICU (day)		27.8±29.7	15.1±17	0.001
Length of stay in hospital (day)		33.0±31.2	23.8±21.3	0.04
Outcome	Death	27 (49.1%)	9 (23%)	0.02
	Alive	28 (50.9%)	29 (76%)	

Note: Results are demonstrated as mean±*SD* or n (%)
APACHE II: Acute physiology and Chronic Health Evaluation II, SOFA: Sequential Organ Failure Assessment Score, BUN: Blood urea nitrogen, GFR: Glomerulary filtration rate, TPN: Total parenteral nutrition, EN: Enteral nutrition, ICU: Intensive care unit

Table 3. Comparison of skeletal mass index between sarcopenic and non-sarcopenic groups

Age (Years)		Mean Difference	Standard Error	*p* value
41-50	51-60	22.02	9.66	0.377
	61-70	20.65	8.61	0.279
	71 <	27.29*	8.13	0.018
51-60	41-50	-22.02	9.66	0.37
	61-70	-1.364906	8.613395	1.000
	71 <	5.277508	8.134873	1.000
61-70	41-50	-20.655494	8.613395	0.279
	51-60	1.364906	8.613395	1.000
	71<	6.642414	6.851392	1.000
71<	41-50	-27.297908*	8.134873	0.018
	51-60	-5.277508	8.134873	1.000
	61-70	-6.642414	6.851392	1.000

When we reached the analysis results of the study, the post-hoc power we obtained according to the distribution of mortality, which is our primary outcome variable, in groups with and without sarcopenia was found to be 0.84. For this power, according to the results observed in the 2-degrees-of-freedom chi-square table (Chi-Square: 10,75 and df:2), an effect size of 0.34 was calculated with 93 people at significance level of 0.05.

4. DISCUSSION

In this study the prevalance of sarcopenia was found to be 59% in the patients admitted to general ICU in a one-year period and most common in patients over 70 years of age. Sarcopenia was associated with an increase in mortality and a prolongation in the lenght of stay at hospital and ICU.

EWGSOP reported the incidence of sarcopenia as 5.8-14.9% in the normal population, 4.1% in men and 16.6% in women.[19] On the other hand, they reported that the incidence in the elderly was between 1-29%. Moisey et al, found this figure to be 71% in aged trauma patients.[9] However, the number of studies investigating the incidence of sarcopenia in critically ill patients is low. Sheean et al, found the incidence of sarcopenia as 62% in patients who were admitted to ICU due to respiratory failure and followed up in mechanical ventilator.[20] Joyce et al, reported the incidence of sarcopenia in their patients hospitalized in their ICU as 68%.[17] Baggerman et al, were reported that the prevalence of sarcopenia is approximately 30-70 % in ICUs.[21] In the present study, we found the incidence of sarcopenia in general ICU as 59%, similar to literature.

Malnutrition is closely related to sarcopenia in aged persons and plays an important role in the development of sarcopenia. Mundi et al, showed that 50% of the critically ill patients were malnourished, which is the reason for impaired immune function, long-term ventilator dependence, increased infectious complications, and increased morbidity and mortality.[22] It is important to evaluate the nutritional status of first admission in patients admitted to ICU, but it is difficult to assess the history of acute weight loss. Protein deficiency disrupts the immune system by increasing metabolic stress.[23] Baumgartner et al, found an association between albumin levels and sarcopenia.[24] Kim et al, reported that higher albumin levels were associated with a protective effect against declines in SMI.[25] Although there was no difference in albumin levels in our patients, we found prealbumin levels lower in patients with sarcopenia. Prealbumin is a protein produced by the liver. Serum prealbumin had historically been used as a biomarker of malnutrition and as an important indicator of overall nutrition status among aged adults not suffering from acute illness. Chen et al, reported that

lower prealbumin levels were associated with higher sarcopenia prevelance.[26] Therefore higher BMI and prealbumin levels may be protective factors against sarcopenia development among aged adults. We consider that muscle mass or strength might decline due to degradation of protein associated with low prealbumin, which may lead to an increased risk of sarcopenia in critical illness.

BMI is a parameter used in the evaluation of nutrition, based on height and weight. But body weight includes both fat and muscle mass. Therefore, it prevents us from making the accurate assessment for sarcopenia. Weijs et al, reported that the measurement of muscle mass was a more important indicator than BMI.[27] In some studies, acute sarcopenia due to muscle destruction and decreased protein synthesis has been shown in critically ill patients. Muscle volume decrement was shown as 17-30% in the first 10 days of the ICU.[28] The use of BMI may also cause inaccurate results in the presence of diffuse edema, especially in obese patients. Albumin or other serum proteins are affected by the acute phase response and changes in the intravascular volume so prevent the use of as a marker for the assessment of nutritional status in the critical patient.[23] In CT imaging, body compartments can be better distinguished, and abdominal fat tissue, visceral adipose tissue, intramuscular, and subcutaneous adipose tissue can be identified more accurately. Therefore, abdominal CT is defined as standard method for evaluating total body and skeletal muscle.[2,3] Sheetz et al, valuated SMI in abdominal CT preoperatively and reported sarcopenia.[29] Martin et al, reported that SMI was closely related to mortality and associated with poor prognosis, especially in the aged patients. In the present study, abdominal CT was used for SMI evaluation.[28] Patients were divided into two groups for SMI values based on Prado's threshold values.[18] SMI was found to be lower in patients over the age of 70 compared to those older than 40. The general ICU population is very heterogeneous. The mortality of critically ill patients is still one of the most important issues, especially for the elderly patients with comorbidities. Most patients have sepsis, and suffering from chronic comorbidities such as cardiovascular failure, trauma, malnutrition or cancer. These comorbidities are associated with a decline of skeletal muscle mass, potentially leading to sarcopenia. Various scoring systems are used to predict mortality in ICU. We used APACHE II and SOFA scores in ICU and there was no difference between the two groups.

In several studies, it has been stated that low levels of vitamin D cause a decrease in muscle tension. Vitamin D deficiency should be treated to maintain vitamin D levels of 40 ng/mL and above.[30] Any relationship between serum vitamin D levels and muscle mass was not found in the present study.

Kou et al, reported that sarcopenia may impair the function of respiratory muscles, which potentially leads to poor weaning outcomes.[31] So, in the presence of sarcopenia; length of mechanical ventilation, length of stay in ICU and hospital are longer and consequently an cost increases. Moisey et al, found the number of days on ventilator and the number of days of intensive care to be higher.[9] Hospital stay was longer and mortality was higher in the sarcopenic patients. Weijs et al reported that low muscle mass evaluated with CT was related to increased duration of mechanical ventilation and increased duration of hospitalization and mortality.[27] Kirk et al, reported that the presence of preoperative sarcopenia increases the incidence of admission to the intensive care unit and prolongs the duration of discharge.[23] The patients were admitted to ICU with a severe critical disease accompanied by comorbidities, protein catabolism, muscle atrophy and weakness. Sarcopenia caused an increase in mortality, a prolongation in the lenght of hospitalization and ICU stay. In the present study, although there are similar groups (Vitamin D, albumin, urea, creatinine, nutrition status and mechanical ventilation time, APACHE II and SOFA scores), we believe that prolonged mechanical ventilation, intensive care unit and hospital stay, and increased mortality are associated with sarcopenia.

There are some limitations of the study. It was a retrospective and single centered study. That is why the number of patients may relatively be low. The patients who performed abdominal computed tomography scan for any reason and any time during the treatment in the ICU were included in the study. So, primary or secondary sarcopenia could not be differentiated. Thirdly, there were considerable number of cases that could not be evaluated because of missing data. Lastly, response to treatment could not be evaluated (adequate nutrition, specifically protein and micronutrients such as Vit D), but this issue was out of the scope this study.

So, we demonstrated that sarcopenia is highly prevalent in the aged population in ICU. Traditonal measures of nutritional assessment such as BMI and measuring prealbumin levels is important but not always meaningful. The presence of sarcopenia in critically aged patients is important because it is associated with increased 30-day mortality, prolonged ICU and hospital stay.

ETHICS APPROVAL

The study was approved by the ethics committee of Health Sciences University Ankara Numune Training and Research Hospital (approval number is E. Kurul-E-18-1928).

CONFLICTS OF INTEREST

The authors affirm that there is no conflict of interest.

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