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RESEARCH ARTICLE

The Impact of Sarcopenia on Post-COVID Pulmonary Sequelae

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Abstract

Introductıon: Following COVID-19 pneumonia, some patients experience symptoms such as weakness, fatigue, dyspnea, exertional dyspnea, and a persistent cough. This condition is defined as post-COVID-19 syndrome. Residual chest CT findings can be detected in some of these patients. Sarcopenia, a concept reflecting skeletal muscle mass loss, is a condition that occurs during the development of many diseases. This study aims to investigate the impact of sarcopenia on pulmonary sequelae following COVID-19 infection.

Methods: A total of 142 patients were included in our study. Among them, 73 patients had post-COVID sequelae on CT scans and served as the patient group, while 69 patients had no sequelae on CT scans and formed the control group. Muscle measurements derived from thoracic CT scans were manually obtained using PACS software. The areas and densities of the total pectoral muscles at the upper half level of the T4 vertebra and the paraspinal muscles at the lower half level of the T12 vertebra were recorded.

Results: There were no statistically significant differences in the mean values of T4 vertebra total pectoral muscle area, T12 vertebra paraspinal muscle area, T4 vertebra pectoral muscle density and T12 vertebra paraspinal muscle density between the groups. However, both the patient and control groups were sarcopenic according to reference values

Conclusion: In our study, we could not find an association between lung CT findings, respiratory symptoms of the patients, and sarcopenia, which was the main focus. We attributed this to the separate mechanisms and pathophysiological processes of sarcopenia and pulmonary sequelae.

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Introduction

Since its emergence in Wuhan, China, in December 2019, the virus known as SARS-CoV-2 has spread worldwide, leading to the deaths of more than 60 million people and infecting millions more as of 2023.[1] It is well known that the disease can manifest with either asymptomatic or mild symptoms, while approximately 20% of cases exhibit severe symptoms requiring hospitalization. The morbidity and mortality of COVID-19 are predominantly associated with acute viral pneumonia and subsequent acute respiratory distress syndrome (ARDS).[2] Some patients who have recovered from COVID-19 may experience symptoms such as prolonged weakness, fatigue, dyspnea, exertional dyspnea, and persistent cough weeks after the initial infection, leading them to seek care at post-COVID follow-up clinics. This condition is defined as long COVID if the infection persists for more than 4 weeks, and as post-COVID syndrome if it persists for more than 12 weeks, according to the guidance from The British Medical Journal.[3] Several studies have indicated that there is a high incidence of post-infectious complications, particularly pulmonary fibrosis, following severe COVID-19 infection. Acute COVID-19 infection can result in long-term sequelae such as organizing pneumonia.[4] In some studies, histological patterns such as usual interstitial pneumonia, desquamative interstitial pneumonia, and acute organizing pneumonia have been identified in patient groups with residual findings after COVID-19 pneumonia.[5]

Sarcopenia, a concept that reflects the loss of skeletal muscle mass, is a physiological change that occurs during the development of many diseases. Since the European Working Group on Sarcopenia in Older People proposed diagnostic criteria for sarcopenia based on muscle mass, muscle strength, and physical performance in 2010, it has been recognized as an important factor for not only the elderly but also many other diseases.[6] Therefore, the presence of sarcopenia is associated with poor prognosis for many medical conditions. Measurement of the cross-sectional skeletal muscle area (SMA) at the L3 vertebral level using computed tomography (CT) and the calculation of the SMA index (SMI) by dividing it by the square of the height play a significant role in the evaluation of sarcopenia.[7] Another important concept closely related to sarcopenia is muscle quality, which refers to microscopic and macroscopic changes in muscle structure and composition. Fat infiltration in skeletal muscles, also known as myosteatosis, is one of the commonly used indicators for assessing muscle quality.[8] Measurement of muscle density in Hounsfield Units (HU) using CT provides information about muscle quality.

The aim of our study is to investigate whether there is a difference in terms of sarcopenia between patients who still have symptoms and residual lung changes on CT after recovering from COVID-19, and patients whose lung findings completely resolved on follow-up CT after COVID-19. In this study, we examined the impact of sarcopenia on pulmonary sequelae following COVID-19 infection.

Material and Methods

Ethics approval and consent to participate

This study was conducted at Ankara City Hospital as an observational and retrospective. Permissions were obtained from the hospital ethics committee (file number: E2-23-3716) and the Ministry of Health of the Republic of Turkey. All procedures were in accordance with the Declaration of Helsinki. Written informed consent was not required, and verbal information and consent were sufficient.

Thoracic CT Imaging Technique

The imaging technique used for all patients was standard, and non-contrast-enhanced thoracic CT scans (GE Healthcare, Chicago, Illinois, USA). The scans were obtained in the supine position during inspiration. The imaging parameters were set as follows: tube voltage of 100 kV, tube current ranging from 50 to 399 mAs, and a slice thickness of 1.3 mm.

Evaluation of Thoracic CT

The evaluation of lung parenchyma on thoracic CT scans was performed separately by two radiologists with more than 5 years of experience in thoracic CT interpretation. The patients were classified into two groups based on the presence or absence of abnormal CT findings. In cases where there was a disagreement in the findings, a consensus was reached by consulting a third radiologist experienced in thoracic radiology. We assessed lung parenchymal findings for fibrosis/possible fibrosis. We looked for the following changes: ground-glass opacities (GGO), consolidation, subpleural irregular reticulation (SIR), traction bronchiectasis (TB), honeycombing, parenchymal bands, subpleural lines, and subsegment atelectasis. In the control group, none of these paren-

chymal findings were present. The measurements of muscle parameters were performed by two different radiologists at different times. Muscle measurements derived from thoracic CT scans were manually obtained using PACS software (GE Healthcare, Chicago, Illinois, USA) (Figure 1). The areas and densities of the total pectoralis muscles at the upper half level of the T4 vertebra and the paraspinal muscles at the lower half level of the T12 vertebra were recorded. Both pectoralis minor and pectoralis major muscles were included in the measurements of the pectoralis muscles area. The areas of muscle structures were recorded in cm^2 and their densities were recorded in HU, after using standard density threshold between -29 to +150 HU for excluding non-muscle structures.

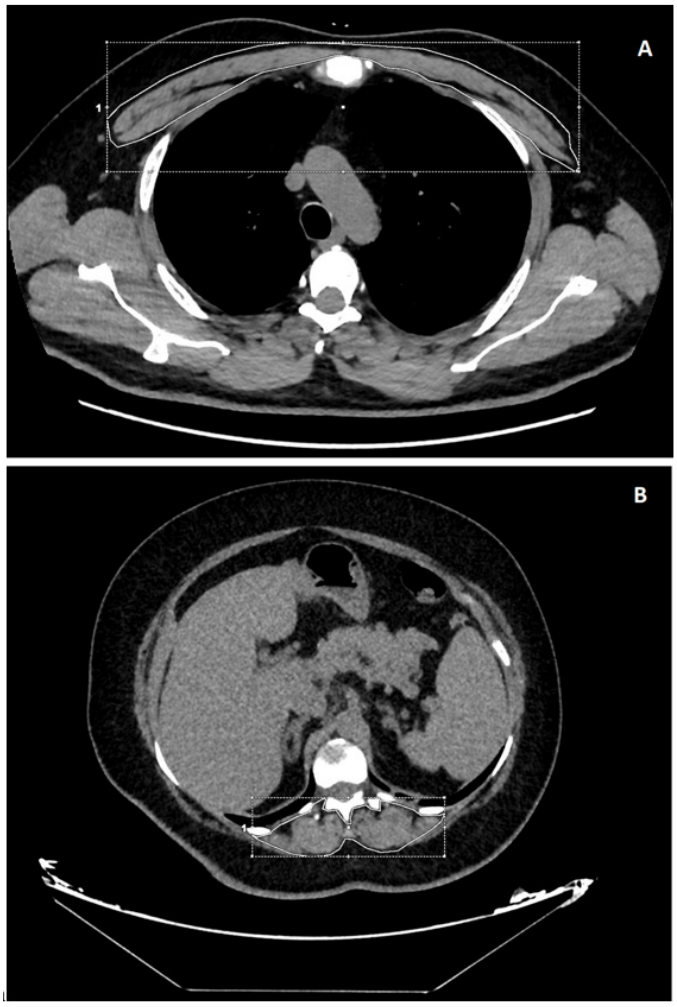

Figure 1 A: Region of interest (ROI) was circumscribed manually by two different radiologists for obtain PMA and PMD at the upper half level of T4 vertebra. B: PSMA and PSMD at the lower half level of T12 vertebra.

Case Selection, Demographic, and Clinical Data

Our study included adult patients (aged 18 years and older) who previously had COVID-19 infection and were being followed up at COVID-19 outpatient clinics. Many patients had ongoing complaints such as chest pain, shortness of breath, fatigue, and persistent cough. Most patients had undergone multiple thoracic CT scans after a negative PCR test for COVID-19. In our study, we considered the most recent CT scan performed after a minimum of 4 months following the negative test result. We included 150 patients in the study. Firstly, we divided them into two groups: those with abnormal lung CT findings (73 patients) and those with normal lung CT findings (69 patients) in the control group. Eight patients were excluded from the study due to positioning errors and artifacts that hindered proper measurements. Along with the demographic data of the patients, we evaluated comorbid conditions such as smoking history, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, and heart disease, as well as hospitalization, intensive care unit admission, mechanical ventilation, and the use of steroid and antiviral treatments.

Statistical Analysis

The data were analyzed using IBM SPSS Statistics Standard Concurrent User V26 (IBM Corp., Armonk, New York, USA) statistical software package. Descriptive statistics were presented as the number of units (n), percentage (%), mean (M), standard deviation (SD), median (Mdn), minimum (min), and maximum (max) values. The normal distribution of numerical variables was evaluated using the Shapiro-Wilk normality test. Differences between two dependent measurements were evaluated using the dependent samples t-test. Intra-class correlation coefficient (ICC) was examined to assess the agreement between evaluators. A correlation coefficient of 70% or higher is considered sufficient for reliability. The Cronbach's alpha and ICC coefficients were found to be above 0.70 for all items and total score, indicating sufficient reliability. Independent samples t-test was used to examine differences in numerical variables between study groups, and chi-square tests (Pearson chi-square/Fisher's exact test) were used to evaluate the relationships between categorical variables and groups. One-sample t-test was used to determine the differences between means and population means. A p-value of less than 0.05 was considered statistically significant.

Results

Clinical and Demographic Data of the Cases

A total of 142 patients were included in our study. Among them, 73 patients had post-COVID sequelae on CT scans and constituted the patient group, while 69 patients had no sequelae on CT scans and formed the control group. The mean age of the patient group was 64, and the mean age of the control group was 60. In the patient group, the CT scans were evaluated on average 6.5 months after the resolution of the disease, while in the control group, the CT scans were performed 6 months later. The patient and control groups were predominantly male, accounting for 74% and 58%, respectively. Females comprised 26% of the patient group and 42% of the control group. Additionally, we evaluated the patient and control groups based on their smoking history, hypertension (HT), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), heart disease, as well as hospitalization, requirement for mechanical ventilation, and treatment methods (Table 1). The mean age of the patient group was statistically higher than that of the control group. Other characteristics were similar between the groups.

Table 1: Clinical and demographic data

Characteristics	Patient Group n=73	Control Group n=69	p-value
Age	64.84±8.98	59.99±9.13	**0.004**
Gender (male)	54 (%74)	40 (%58)	0.066
CT Scan after negative PCR (month)	6.59±3.13	6.14±2.07	0.977
Smoking	34 (%46.6)	32 (%46.4)	0.981
Hypertension	34 (%46.6)	23 (%33.3)	0.108
Diabetes Mellitus	13 (%17.8)	13 (%18.8)	0.874
Chronic obstructive pulmonary disease (COPD)	8 (%11)	2 (%2.9)	0.061
Heart Disease	16 (%21.9)	11 (%15.9)	0.364
Hospital History	67 (%91.8)	57 (%82.6)	0.101
Mechanical Ventilation	6 (%8.2)	1 (%1.4)	0.063
Antiviral Treatment	72 (%98.6)	69 (%100)	0.329
Steroid Treatment	63 (%86.3)	56 (%81.2)	0.406

Summary statistics presented as mean ± standard deviation (SD) and frequency (n) with percentage (%).

Evaluation of Lung Parenchymal Findings with CT

In our patient group, BCO was present in 66 patients (89.2%), subpleural reticulation was present in 64 patients (86.5%), traction bronchiectasis was detected in 44 patients, and consolidation was observed in 4 patients (5.4%) (59.5%) (Figure 2 and 3). Additionally, 7 patients (9.5%) exhibited honeycombing, 2 patients (2.7%) showed volume loss, 14 patients (18.9%) had parenchymal bands, 28 patients (37.8%) displayed subpleural lines, and 15 patients (20.3%) presented subsegment atelectasis (Table 2). None of these lung parenchyma findings were observed in our control group.

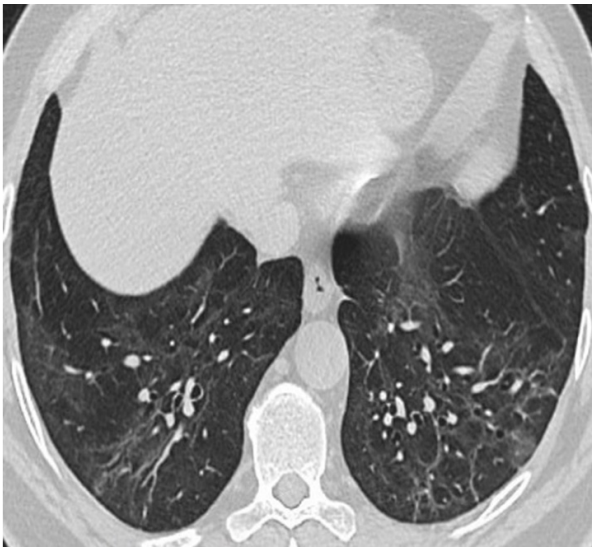

Figure 2: Post-COVID 9th month CT scan ground-glass opacities (GGO), subpleural irregular reticulation at bilateral lower lobes

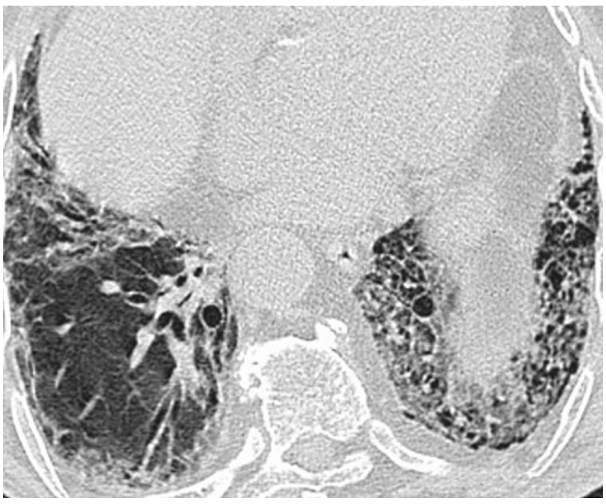

Figure 3: Post-COVID 14th month CT scan honeycombing and traction bronchiectasis at bilateral lower lobes

Table 2: Evaluation of Post-COVID Sequelae Changes by CT Scan

	n	%
Ground Glass Opacities (GGO)	66	89.2
Consolidation	4	5.4
Subpleural Reticular Pattern	64	86.5
Traction Bronchiectasis	44	59.5
Honeycomb	7	9.5
Parenchymal Bands	14	18.9
Subpleural Lines	28	37.8
Subsegmental Atelectasis	15	20.3

Evaluation of Thoracic Muscles with CT

In our study, the mean T4 vertebra pectoral muscle area (T4 PMA) was measured as 32.46 cm² and the T4 vertebra pectoral muscle density (T4 PMD) was 30.49 HU in the patient group. The mean T12 vertebra paraspinal muscle area (T12 PSMA) was determined as 40.91 cm², and T12 vertebra paraspinal muscle density (T12 PSMD) was 35.07 HU. In the control group, the mean T4 PMA was 31.66 cm², the T4 PMD was 31.42 HU, the mean T12 PSMA was 42.45 cm² and the T12 PSMD was 37.25 HU (Table3). There were no statistically significant differences between the groups in terms of T4 PMA, T12 PSMA, T4 PMD and T12 PSMD averages. When the agreement among the evaluators was examined, statistically significant excellent-level correlations were found (ICC-95% Confidence Interval).

Table 3: Muscle Analysis Results

		Patient Group (n=73)	Control Group (n=69)	Test Value	p
Evaluator 1	T4 PMA (cm²)	32.46±10.28	31.66±10.51	-0.909 *	0.363
	T4 PMD (HU)	30.49±10.35	31.42±10.91	-0.458 *	0.647
	T12 PSMA (cm²)	40.91±10.66	42.45±10.52	-0.821 *	0.412
	T12 PSMD (HU)	35.07±9.73	37.57±10.71	-1.753 *	0.080
Evaluator 2	T4 PMA (cm²)	32.2±9.95	31.72±10.52	0.704 *	0.481
	T4 PMD (HU)	30.4±10.2	31.28±10.77	-0.408 *	0.683
	T12 PSMA (cm²)	40.76±10.75	42.36±10.61	-0.967 *	0.333
	T12 PSMD (HU)	34.88±9.78	34.88±9.78	-1.743 *	0.081

*: Independent Samples t-Test (t); Summary statistics presented as mean ± standard deviation.
T4 PMA: T4 vertebra pectoral muscle area, T4 PMD: T4 vertebra pectoral muscle density, T12 PSMA: T12 vertebra paraspinal muscle area, T12 PSMD: T12 vertebra paraspinal muscle density, HU: Hounsfield Unit

In previous studies, the T4 PMA was reported as 41.6 cm² for males and 27.1 cm² for females,[9] while the T12 PSMA was stated as 56.0 cm² for males and 36.5 cm² for females.[10] Based on these values, we compared the measurements of our patient group. According to Table 4, both the first and second evaluators had similar average T12 paraspinal muscle measurements in females, but for other measurements, the study average was statistically lower than the population average.

Table 4: Comparison of muscle area measurements in the patient group compared to the previous average

		Gender	Mean±SD	Mean Value	Test Value	p
Evaluator 1	T4 PMA (cm²)	Male	36.77±7.66	41.6	-4.583	<0.001
		Female	20.43±6.31	27.1	-4.614	<0.001
	T12 PSMA (cm²)	Male	43.4±10.64	56.0	-8.615	<0.001
		Female	33.97±7.21	36.5	-0.984	0.383
Evaluator 2	T4 PMA (cm²)	Male	36.45±7.29	41.6	-5.091	<0.001
		Female	20.58±6.28	27.1	-4.529	<0.001
	T12 PSMA (cm²)	Male	43.21±10.82	56.0	-8.608	<0.001
		female	33.92±7.15	36.5	-1.023	0.320

One Sample t-test was used. SD: Standard deviation, T4 PMA: T4 vertebra pectoral muscle area, T4 PMD: T4 vertebra pectoral muscle density, T12 PSMA: T12 vertebra paraspinal muscle area, T12 PSMD: T12 vertebra paraspinal muscle density.

According to Table 5, the T12 muscle measurement taken from females in the study by the first evaluator was similar to the population average, but for other measurements, the study average was statistically lower than the population average. The same situation was applicable for the second evaluator as well.

Table 5: Comparison of muscle area measurements in the control group compared to the previous average

		Gender	Mean±SD	Mean Value	Test Value	p
Evaluator 1	T4 PMA (cm²)	Male	37.09±9.37	41.6	-3.048	0.004
		Female	22.69±6.79	27.1	-4.505	<0.001
	T12 PSMA (cm²)	Male	45.74±9.45	56.0	-6.866	<0.001
		Female	36.36±9.37	36.5	-0.105	0.917
Evaluator 2	T4 PMA (cm²)	Male	36.92±9.54	41.6	-3.107	0.004
		Female	22.98±7.00	27.1	-4.079	<0.001
	T12 PSMA (cm²)	Male	45.73±9.35	56.0	-6.866	<0.001
		female	36.21±9.51	36.5	-0.213	0.833

One Sample t-test was used. SD: Standard deviation, T4 PMA: T4 vertebra pectoral muscle area, T4 PMD: T4 vertebra pectoral muscle density, T12 PSMA: T12 vertebra paraspinal muscle area, T12 PSMD: T12 vertebra paraspinal muscle density.

Discussion

Sarcopenia is characterized by the progressive loss of skeletal muscle mass and quality associated with aging.[11] It is considered an independent negative prognostic factor in various diseases, including major surgeries, oncological, and cardiovascular diseases.[12-13] Sarcopenia can also affect respiratory muscles. As a result, it can impair the production of sufficient respiratory volume and the performance of high-force expiratory maneuvers.[14] One of the most current methods for evaluating sarcopenia is CT. It offers several advantages, such as providing detailed anatomical information, distinguishing between muscle, fat, and surrounding tissues, and easily calculating parameters such as muscle area and density. Some studies have shown that pectoral muscle analysis and segmentation derived from thoracic CT sections are associated with sarcopenia.[15]

Although the COVID-19 storm has ended, a process called post-COVID syndrome has emerged, particularly in patients who experienced severe pneumonia, lasting for weeks and manifesting with symptoms such as weakness, fatigue, myalgia, dyspnea or exertional dyspnea, and persistent cough.[16] In one-year follow-ups, it has been found that lung CT findings in these patients largely improve, but in some cases, residual lung changes such as ground-glass opacities, irregular reticulations, fibroatelectatic bands, air trapping areas, and even honeycombing persist.[17] .[16]These residual anomalies may be associated with respiratory complaints in patients following COVID-19 infection.

In our study, we included 142 patients with post-COVID symptoms. By examining their chest CT scans taken approximately 6 months after COVID-19 infection, we divided them into two groups. The first group consisted of patients with residual changes after COVID-19 infection in their chest CT scans, while the second group served as the control group, consisting of patients whose lung findings almost completely resolved on chest CT scans. We compared the muscle areas and muscle densities at the T4 and T12 levels between the two groups to assess sarcopenia. In our study, no significant differences were found in muscle areas and muscle densities at both the T4 and T12 levels. This indicates that there is no direct relationship between residual lung changes and sarcopenia. These results suggest that findings such as ground-glass opacities, irregular reticulation, and traction bronchiectasis, which can be detected even months after the disease on lung CT scans, may occur independently of sarcopenia, affecting respiratory muscles through different pathophysiological processes. This study may be the first to examine the relationship between post-COVID lung changes and sarcopenia, as we did not find a substantial amount of literature on this topic. Most studies focused on the impact of sarcopenia on the course of COVID-19 infection and its emergence in the post-COVID period. In conclusion, we can say that we did not find much information in the literature that would support or criticize our findings.

However, when comparing the measurements of muscle areas at T4 and T12 in both the patient group and the control group with the normal values gathered from previous studies, they were found to be significantly lower. This indicates that post-COVID syndrome may be associated with sarcopenia. In other words, although sarcopenia may not be directly related to residual lung anomalies in the pulmonary parenchyma, it may be associated with post-COVID syndrome.

In suspected sarcopenia cases, MRI and CT scans are recommended for measuring muscle quality and quantity, with CT scans at the L3 level being particularly useful for assessing body composition, though there is limited research on thoracic CT body composition in COVID-19 patients, who typically receive chest X-rays or thoracic CT scans. Molwitz et al. finds that fat and muscle measurements at T12 and L3 levels on CT scans are closely correlated. In COVID-19 patients who only have thoracic CT scans, T12 data can predict L3 values, which are commonly used for assessing sarcopenia and obesity. [18]

Antonarelli et al. conducted a study to investigate the prognostic effect of sarcopenia on patients infected with COVID-19, measuring the pectoral muscle area and density at the T4 level. The results showed no statistically significant differences in pectoral muscle area and density in relation to the severity and mortality of pneumonia assessed by the CT pneumonia severity score. However, the researchers found an association between sarcopenia and prolonged intensive care unit (ICU) stay and failed extubation.[12] In patients with low pneumonia severity score (less than 7), the pectoral muscle area was measured as 40.4±9.8 cm2 and muscle density as 29.2±5.9 HU, while in patients with high pneumonia severity score, the pectoral muscle area was measured as 38.9±7.8 cm2 and muscle density as 27.8±5.2 HU. The pecto-

ral muscle area measurements in both our patient and control groups were lower than these values (patient group: 32.2±9.95 cm2, control group: 31.72±10.52 cm2). The muscle density values of our patients were approximately similar. This suggests a potential association between COVID-19 infection and sarcopenia.

However, some researchers have argued that sarcopenia grading based on muscle analysis derived from CT can correlate with certain clinical outcomes related to COVID-19 infection. Of course, this aspect was not covered in our study, which focused on post-COVID pulmonary findings. Kim et al. concluded in their study that there might be a relationship between sarcopenia and death associated with COVID-19 infection.[19] Schiaffino et al. believe that sarcopenia is associated with longer ICU stays and mortality.[20] The same researchers measured the muscle area at the T12 level and found an average of 31 cm2 and muscle density of 37 HU. In our study, the T12 muscle area measurement was slightly higher (patient group: 40.76±10.75 cm2, control group: 42.36±10.61 cm2). The T12 muscle density was approximately similar (patient group: 34.88±9.78 HU, control group: 34.88±9.78 HU). Several studies have demonstrated the potential association of various clinical conditions with sarcopenia and COVID-19 infection.

In studies focusing on sarcopenia in lung diseases other than COVID-19, low muscle mass has been found to be associated with poor prognosis. For example, Kinsey et al. emphasized the association between low pectoral muscle mass and decreased overall survival in small cell lung cancer.[21] Moon et al. concluded that a decrease in thoracic muscle mass correlates with mortality in idiopathic pulmonary fibrosis.[22]

A study examining the frequency of sarcopenia and its relationship with clinical course in the post-COVID period found sarcopenia in 41% of the total 92 patients. However, the same study stated that there was no relationship between clinical course, disease severity, and sarcopenia.[23]

Muscle weakness and exercise intolerance are prominent symptoms in patients with post-acute sequelae of Covid-19, potentially resulting from muscle atrophy, reduced neural activation, and disruptions in metabolic function and blood flow. These symptoms are influenced by various factors like systemic inflammation, viral infection, inactivity, and comorbid conditions, with some patients reporting persistent symptoms for up to a year after infection. [24]

Research on COVID-19 infection and sarcopenia has indicated that musculoskeletal system involvement may occur during COVID-19 infection, as a result of medications used in infection treatment, or as part of post-COVID syndrome.[25-26] In our study, both the patient group and the control group had measurements indicating low muscle mass. This could be due to the factors mentioned above, or simply a natural process of aging. Our data on this matter is limited, and we believe that more detailed clinical research is needed.

There were several limitations to our study. First, it was a retrospective study conducted at a single center with a relatively small number of patients. Additionally, we were unable to calculate the Skeletal Muscle Index (SMI), by normalizing muscle mass to the square of the patient's height (cm^2/m^2) for many patients, because we did not have access to their height information.

According to Table 5, the T12 muscle measurement taken from females in the study by the first evaluator was similar to the population average, but for other measurements, the study average was statistically lower than the population average. The same situation was applicable for the second evaluator as well.

Conclusion

Numerous studies have been conducted on the relationship between sarcopenia and COVID-19 infection and its clinical course, which has been a popular research topic in recent years. While some studies have found no correlation with disease severity and progression, others have highlighted correlations in various aspects such as prolonged ICU stay, ease of extubation, and even mortality. However, one fact stands out in all studies, which is the association between COVID-19 infection and sarcopenia, particularly in elderly patients, regardless of whether it correlates with clinical course and conditions. More research and knowledge accumulation are needed in this regard. In our study, which primarily focused on lung CT findings and their association with the patient's respiratory symptoms, we did not identify a relationship with sarcopenia. We attributed this to the possibility of separate mechanisms and pathophysiological processes for sarcopenia and sequelae in the lungs.

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