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Muscle density analysis in COVID-19

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Abstract

Aim: Coronavirus-2019 (COVID-19) was declared a pandemic by the World Health Organization, continues to spread globally, and patients may not exhibit specific musculoskeletal involvement symptoms.

Materials and Methods: Clinical data and images of 389 consecutive patients, who applied to the pandemic outpatient clinic with a COVID-19 pre-diagnosis with musculoskeletal complaints, and 203 consecutive control patients who underwent thoracic computed tomography (CT) for an unrelated reason and diagnosed as normal were included in the study. Bilateral sternocleidomastoid and trapezius muscle CT density and blood creatine kinase (CK) levels of all participants were obtained.

Results: In COVID-19 patients, a significant decrease in sternocleidomastoid muscle density was observed when compared to radiological grade; however, a significant increase in the density of the trapezius muscle was identified. In CK values, there was a significant increase in trapezius density.

Conclusion: Although the cause or effect was controversial, respiratory muscles were affected due to forced breathing and muscle damages were determined. This study demonstrated the need for multicenter studies with detailed neurological and electrophysiological tests and pathological correlations with an adequate number of patients.

Introduction

Coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus belonging to the Coronaviridae family, which was first detected in Wuhan, China at the end of 2019, was declared as an pandemic by the World Health Organization (WHO) and continues to spread globally [1-3]. While struggling with this pandemic all over the world, many new symptoms and transmission areas of the disease are discovered in human [2, 4]. Although common symptoms of COVID-19 are known as fever, cough and respiratory system involvement, central nervous system and sometimes peripheral nervous system involvement has also been reported [1, 2, 5-7]. Patients with musculoskeletal involvement may not show specific symptoms, and only 25% of symptomatic patients have symptoms such as myalgia and general muscle weakness that may delay diagnosis and hence treatment [5, 8-10]. In COVID-19 disease, there is a hyper-inflammatory condition caused by a reticular activating system (RAS) disorder, and this viral infection can induce it, causing severe muscle destruction [11, 12]. Although some data show that the severity of COVID-19 does not increase the occurrence of muscle pain, myalgia is an important predictor of disease severity in patients with abnormal radiological findings [13]. As is known, studies have shown that patients have high levels of blood creatine kinase (CK) accompanying myalgia [5].

Computed Tomography (CT), which can be used as a marker to evaluate muscle quality, is the gold standard for density assessment, shows the fat content of skeletal muscle and is the most used imaging method for this procedure [14-16].

Real-time reverse transcription polymerase chain reaction (rRT-PCR) test is positive in most of the patients who present to the pandemic outpatient clinic with muscle pain and the blood CK levels of these patients are also high [17].

In present study, it was aimed to measure of densities of the trapezius muscle, which that does not contribute to respiration, and the sternocleidomastoid muscle (SCM), which is the auxiliary respiratory muscle, in patients diagnosed with COVID-19. In addition, it was aimed to reveal the possible relationship between high blood CK levels, which is an indicator of muscle breakdown, muscle densities.

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Materials and Methods

The required permission from the Ministry of Health and the approval of the local Ethics Committee (Date: 04/12/2020, Number: 2020/16-17) was obtained for present study. The study was retrospective and there was no need for an informed consent form as there were no new or additional risks for the participants. However, the study was conducted according to the principles of the Declaration of Helsinki.

Study population and management

Diagnostic and demographic information, laboratory values and images of the patients were scanned retrospectively from the hospital information system (HIS). The clinical data and images of 500 consecutive patients who applied to the pandemic outpatient clinic with a pre-diagnosis of COVID-19 between March and September 2020 and who presented to the Physical Therapy and Rehabilitation outpatient clinic due to musculoskeletal complaints were examined. Patients with a past history of lung disease, heart disease, rheumatic disease, myositis, trauma, muscle disease, thyroid or parathyroid disease, malignancy or steroid use were excluded from the study. According to the Radiological Society of North America (RSNA) Expert Consensus Document on Reporting Chest CT Findings Related to COVID-19 criteria [18], 389 patients (183 female and 206 male) have positive findings on thoracic CT and undergoing COVID-19 treatment were selected for the study. In the same period, 203 patients (93 female and 110 male) who were evaluated as normal due to the absence of lung involvement in thoracic CT examination performed for another reason and who could not be diagnosed with COVID-19 and whose rRT-PCR test was negative were selected as controls.

COVID-19 patients were divided into three subgroups, atypical, indeterminate and typical, with CT findings according to the above-mentioned RSNA criteria. Atypical cases were excluded because of the very small number and the majority of those with negative rRT-PCR tests. Blood CK levels of all parcipitants were obtained at the time of first admission.

Image acquisition

All imaging procedures were performed with a multidetector sequential CT scanner (Ingenuity Elite, Philips Healthcare, Best, Netherlands). The CT protocol consisted of 120 kV-100 mA tube current, 2 mm slice thickness, and the patient in supine position and inspiration without using contrast media.

Image analysis

The analysis of the images was carried out using the DICOM viewer (FONET, v4.1, Ankara, TR) of the PACS system integrated into HIS. The densities of the right and left SCM and trapezius muscles of all participants were measured by an 8-year experienced radiologist (P.G.B.) on axial thoracic CT images, where they are best seen at the level of the thyroid gland. The muscle densities in the axial sections were evaluated as the average of three measurements taken in Hounsfield units (HU) using equal ROIs (Region of Interest) from each muscle (Figure 1).

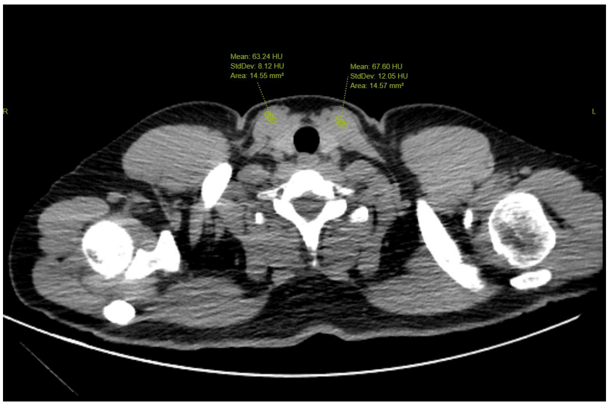

Figure 1. Measurements of SCM muscle (a) and trapezius muscle (b) densities are shown on axial Thorax CT images adjusted to the mediastinal window.

Table 1. Gender distributions of groups.

p=0.376*	Female	Male	Total
Control	93 (45.8%)	110 (54.2%)	203
Indeterminate	98 (50.5%)	96 (49.5%)	194
Typical	85 (43.6%)	110 (56.4%)	195
Total	276 (46.6%)	316 (53.4%)	592

*Chi-square test

Statistical analysis

All statistical analyzes were performed using SPSS version 25.0 (SPSS Inc, Chicago, IL). Data were expressed as mean ± standard deviation. Chi-square test was used for gender comparison between the two groups. Student t test and ANOVA test were used to compare groups according to Kolmogorov-Smirnov test results. Tukey HSD test was used for post hoc analysis. ROC curve analysis was performed for all parameters. Pearson correlation test was used for correlation between variables in study group. In addition, logistic regression analysis was performed for all parameters. $p < 0.05$ was considered significant.

Results

The gender distribution of all patients is shown in Table 1 and the age values of the groups are shown in Table 2. While there was no significant difference in gender ($p=0.376$) between the groups, there was an age difference ($p < 0.001$) (Figure 2a, and 2b).

Since there was no statistically significant difference between paired regions in cross-sectional views of neither the whole study group nor the subgroups ($p > 0.05$), the values of both sides were used together for evaluation. rRT-PCR test was positive in 266 (68.38%) of COVID-19 patients (65.46% in the indeterminate group and 71.28% in the typical group). When the groups were compared in terms of the density values of the SCM muscle, a significant decrease was found in the muscle density of the COVID-19 patient groups with the radiological degree. On the contrary, when the groups were compared in terms of the density values of the trapezius muscle, a significant increase

Table 2. Distribution of data on age, muscle density and blood creatine kinase levels by groups.

	Control (406)		COVID-19 (778)				p*
			Indeterminate (388)		Typical (390)		
	Mean	S.D.	Mean	S.D.	Mean	S.D.	
Age (years)	42.80	13.04	51.76	11.90	48.05	12.88	< 0.001
Sternocleidomastoid muscle density (HU)	72.54	13.34	67.75	13.89	59.17	12.10	< 0.001
Trapezius muscle density (HU)	16.69	4.08	50.80	13.85	52.69	12.85	< 0.001
Creatine kinase level (U/L)	60.58	30.31	170.57	511.05	283.04	887.13	< 0.001

S.D.: Standard Deviation, *ANOVA test

Table 3. Multiple comparisons between groups.

	Multiple Comparisons*		
	Control vs Indeterminate	Control vs Typical	Indeterminate vs Typical
Age	< 0.001	< 0.001	< 0.001
Sternocleidomastoid muscle density	< 0.001	< 0.001	< 0.001
Trapezius muscle density	< 0.001	< 0.001	0.047
Creatine kinase level	0.023	< 0.001	0.021

*p value, according to Tukey HSD test, vs: versus

Table 4. Correlations between variables.

*	Sternocleidomastoid muscle density		Trapezius muscle density		Creatine kinase level	
	r	p	r	p	r	p
Age	-0.192	< 0.001	0.127	< 0.001	0.126	< 0.001
Imaging classification for CT	-0.379	< 0.001	0.726	< 0.001	0.511	< 0.001
Sternocleidomastoid muscle density			-0.154	< 0.001	-0.164	< 0.001
Trapezius muscle density					0.426	< 0.001

*Pearson Correlations (2-tailed)

Table 5. The logistic regression table of investigated parameters.

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
							Lower	Upper
Age	0.057	0.020	7.714	1	0.005	1.058	1.017	1.101
Sternocleidomastoid muscle density	-0.075	0.021	12.673	1	0.000	0.927	0.890	0.967
Trapezius muscle density	0.352	0.034	105.068	1	0.000	1.422	1.330	1.521
Creatine kinase level	0.031	0.006	23.709	1	0.000	1.032	1.019	1.045

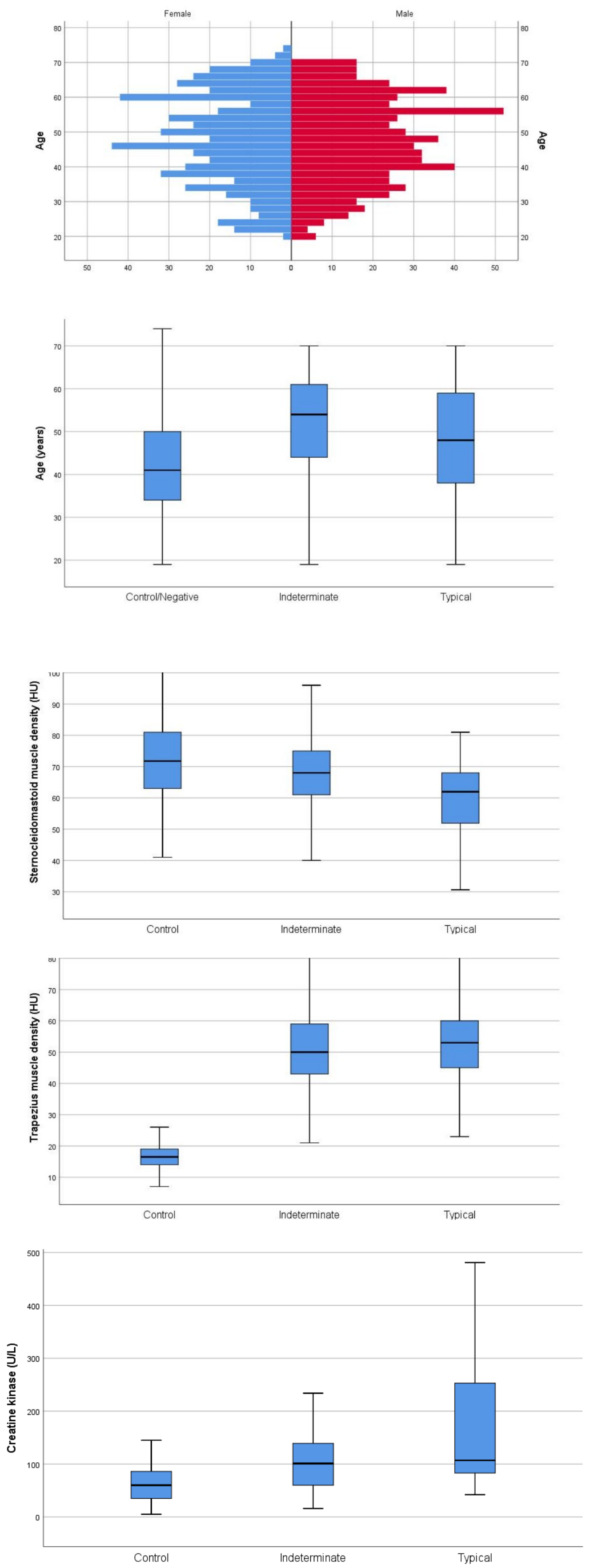

Figure 2. Distribution of age (a, and b), sternocleidomastoid muscle density (c), trapezius muscle density (d) and blood creatine kinase level (e) values of groups.

was found in the muscle density of the COVID-19 patient group. In addition, when the groups were compared in terms of CK values, a significant increase was found in the values of the COVID-19 patient group, such as the trapezius density. These findings above are explained and shown in Tables 2 and 3, and in Figure 2.

As shown in Table 4, a weak and negative correlation was found between SCM muscle densities and blood CK values. In contrast, there was a low and positive correlation between trapezius muscle densities and blood CK values. In addition, a weak and negative correlation was observed between trapezius muscle densities and SCM muscle densities. Whereas there was a weak and negative correlation between age and SCM muscle densities, there was a weak and positive correlation between age and trapezius muscle densities, and a weak and positive correlation between age and blood CK values. Also, whereas there was a low and negative correlation between CT classification degree and SCM muscle densities, there was a strong and positive correlation between CT classification degree and trapezius muscle densities, and a middle and positive correlation between CT classification degree and blood CK values.

A logistic regression was performed to ascertain the effects of age, SCM muscle density, trapezius muscle density and blood CK on the likelihood that participants have COVID-19. The logistic regression model was statistically significant, $\chi 2(4) = 129.05$, $p < 0.001$. The model explained 95.6% (Nagelkerke R2) of the variance in COVID-19 and correctly classified 99.1% of cases. Increasing age, trapezius muscle density and blood CK were associated with an increased likelihood of exhibiting COVID-19, but increasing SCM muscle density was associated with a reduction in the likelihood of exhibiting COVID-19 (Table 5).

Discussion

A pandemic disease called 'coronavirus disease 2019' (COVID-19), a novel coronavirus (SARS-CoV-2) infection, is on the rise worldwide since the WHO Emergency Committee declared a global health emergency on January 30, 2020 [1, 12, 19-21].

Although the diagnosis is based on rRT-PCR positivity for the presence of coronavirus, due to the high contagiousness and easy spread of the virus, fast and accurate diagnostic methods are needed to diagnose, isolate and treat patients, as soon as possible to reduce the risk of mortality and public transmission. While rRT-PCR results usually require 5 to 6 hours, CT examination has become prominent because of its much faster results. In addition, it remains unclear whether rRT-PCR is the gold standard and whether false positive and false negative results are common [18, 22].

Recent studies have reported the proportion of positive rRT-PCR tests taken from throat swab samples as 30-60%. Moreover, the sensitivity and specificity of the rRT-PCR assay varied greatly and lacked consistency because false-negative rates ranged from 2% to 29% (71-98% sensitivity) as seen in a systematic review [13, 23]. In studies where rRT-PCR test results of the patients were taken as reference, the sensitivity, specificity and accuracy of Thorax CT in demonstrating COVID-19 infection was found to be approximately 95-97% [22, 24-27].

As in recent studies, only 68.38% of patients diagnosed with COVID-19 had rRT-PCR positivity in present study, and thoracic CT scans of the patients were interpreted in terms of COVID-19 involvement according to the RSNA consensus criteria described above [18, 24-26].

Expression of angiotensin converting enzyme 2 (ACE2) has been identified in many tissues and organs, such as the nervous system and skeletal muscles. SARS-CoV-2 spreads through the bloodstream and endothelium and can cause infection in all tissues expressing ACE2, including the heart, brain, and musculoskeletal system. The virus can bind to ACE2 and affect cells such as muscle tissue cells alone or in combination with proinflammatory cytokines [28-30].

The clinical features and severity of COVID-19 disease vary greatly from asymptomatic to fatal. The most common symptoms are fever, cough, and fatigue, and a high prevalence of myalgia (63%) has been reported in patients. Additionally, as several studies have reported, 26% of severe patients have muscle pain, and 22% of these initially have myalgia symptoms [4, 6, 12].

The main complaints of COVID-19 patients who applied to the local hospital in the study area were weakness, fatigue, back pain and cough, and myalgia was 55% compatible with the literature.

The main respiratory muscles are the chest and abdominal muscles, and during inspiration the diaphragm, scalene, SCM, parasternal and intercostal muscles are activated [31, 32].

As patients diagnosed with COVID-19 have difficulty breathing and respiratory distress, the auxiliary respiratory muscles (SCM and scalene) are also activated [5, 15]. Imaging techniques such as CT, a method often used to evaluate skeletal muscle, have the potential to examine the contribution of respiratory muscles to lung function, while providing effective information about the integrity and structure of the airways and lung parenchyma [8, 9, 31].

Recent studies have shown that oxidative stress is one of the mechanisms involved in muscle dysfunction, and interestingly, myoglobin concentration and oxidative aerobic enzyme activity are reduced in muscles, lipofuscin accumulates in muscle fibers, and muscle dysfunction may be associated with respiratory distress [8, 33, 34].

Respiratory muscle fibers can change their properties to adapt to new requirements that may arise from respiratory diseases or functional physiological conditions. In muscle, there is a negative correlation between fat and muscle fiber amount, with a decrease in muscle fibers the amount of fat increases. The muscle density value (Hounsfield Units (HU)) in non-contrast CT reflects to some extent the muscle fat content and is also an indirect measure of the density of the contractile material, the number of muscle fibers, and the cross-sectional area, hence function and strength. Factors such as the amount of protein in the muscle, changes in perfusion status and extracellular water content can also affect the change in muscle density. A decrease in muscle density points to serious doubt regarding the existence of the above mostly adverse changes [15, 16, 32, 35, 36].

Although its levels are increased in many other diseases, blood CK level increase is an important indicator of neuromuscular diseases. Studies show that damage to muscle fibers increases CK values in the blood and the presence of increased CK levels associated with myalgia as an indicator of muscle involvement. In studies conducted on patients hospitalized due to COVID-19, it was found that approximately 10% of patients had CK values ($>$ 200 U/L) above normal values ($<$ 200 U/L), and patients who died had approximately 100 points higher values than survivors [5, 6, 12, 36, 37].

In present study, it was found that in contrast to significant increases in blood CK levels and trapezius muscle density, SCM muscle densities were significantly lower in patients with pulmonary involvement and respiratory distress, inversely proportional to the severity of the CT grade described above.

The decrease in SCM muscle CT density of COVID-19 patients can be explained by the fact that oxidative stress, which was mentioned in previous studies, causes muscle fiber damage and lipid accumulation with degenerative changes in the muscles. Accordingly, it was concluded that the increase in blood CK levels was a result of muscle fiber damage. A study in COVID-19 patients evaluating the relationship between muscle density and CK levels, which is considered to be an indicator of muscle involvement severity, could not be compared because it was not found in the literature.

In contrast to the reduction in the SCM muscle, the increased density of the trapezius muscle was thought to be secondary to immobility in patients who were bedridden during illness. While the SCM muscle is affected by the inflammatory process due to the increased workload, the trapezius muscle is atrophically weakened and concentrated secondary to immobility. These results can be explained by the presence of edema rather than fatty degeneration of the muscles.

Conclusion

In COVID-19 patients, the significantly higher blood creatine kinase levels detected and the significantly lower CT intensity values detected in the sternocleidomastoid muscle suggest that the compulsive breathing-associated respiratory muscles are affected and muscle damage has occurred, although the cause or effect is controversial.

Since the loss of muscle strength and physical performance that develops during the course of the COVID-19 disease will affect the treatment process and the quality of life of the patients, care should be taken in case of low muscle CT densities and high blood CK levels.

This present study demonstrates the need for large multicenter studies with detailed neurological and electrophysiological tests and pathological correlations in a sufficient number of patients with different distributions.

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Author contributions included conception and study design (PGB), data collection or acquisition (PGB and NPT), statistical analysis (MB), interpretation of results (MB and PGB), drafting the manuscript work or revising

it critically for important intellectual content (MB) and approval of final version to be published and agreement to be accountable for the integrity and accuracy of all aspects of the work (MB, PGB and NPT).

Limitations

The limitations of the study include the unicentricity, the number of patients with insufficient and asymmetrical distribution, the lack of detailed neurological and electrophysiological tests (such as electroneuromyography and somatosensory evoked potentials) due to the epidemic, and the lack of pathological correlation.

Ethical approval

Ethical approval for this study was received by the non-interventional research ethics committee of Fırat University.(2020/16-17)

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