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Sarcopenia and Its Prognostic Role on Hospitalization and In-Hospital Mortality in Coronavirus Disease 2019 Patients with At Least One Cardiovascular Risk Factor

Kardiyovasküler En Az Bir Risk Faktörü Olan COVID-19 Hastalarında Sarkopeninin Hastaneye Yatış ve Hastane İçi Mortalite Üzerindeki Prognostik Rolü

ABSTRACT

Background: The coronavirus disease 2019 infection is a global pandemic that has affected the whole world population. We aimed to evaluate the prognostic role of cross-sectional area, muscle index, and muscle attenuation values in computed tomography-based skeletal groups [erector spinae muscle, pectoralis muscle, and total skeletal muscle] of patients hospitalized for coronavirus disease 2019 and with at least 1 cardiovascular risk factor.

Methods: A total of 232 patients with coronavirus disease 2019 and at least 1 cardiovascular risk factor were enrolled in the study, retrospectively. The cross-sectional area, muscle index, and attenuation of erector spine muscle, pectoralis muscle, and total skeletal muscle were automatically measured on computed tomography images. The study population was assigned into tertiles on the basis of the total SM_{csa} index. The relationship between the values obtained and the length of hospital stay, admission to intensive care unit, the need for invasive mechanical ventilation, and mortality was investigated.

Results: Admission to intensive care unit, need for invasive mechanical ventilation, and mortality were higher at tertile 3 groups than in the other groups (all *P* values <.001). Statistically, all muscle measurements were significantly lower in tertile 3 (*P* <.001). Diabetes mellitus, hypertension, and total SM_{csa} index were predictors of in-hospital mortality in patients with coronavirus disease 2019 on the basis of Cox regression analysis. In the Kaplan–Meier analysis for the proportion of survivors relative to the total SM_{csa} index, tertile 3 had the highest mortality (survival rates 57%, *P* < .001).

Conclusions: Sarcopenia and attendant cardiovascular comorbidities can effectively assess disease severity and predict outcome in patients with coronavirus disease 2019.

Keywords: COVID-19, cardiovascular disease, sarcopenia, mortality, prognosis

ÖZET

Amaç: Koronavirüs hastalığı 2019 (COVID-19) enfeksiyonu, tüm dünyada etkili olan küresel bir salgındır. COVID-19 nedeniyle hastaneye yatırılan ve en az bir kardiyovasküler risk faktörü olan hastaların bilgisayarlı tomografi (BT) ile iskelet kas gruplarında [erektör spina (ESK), pektoral (PK) ve toplam iskelet kasında (Toplam İK)] kesitsel alanı (kda), kas indeksi ve kas atenüasyonunun (ka) prognostik rolünü değerlendirmeyi amaçladık.

Yöntemler: Çalışmaya COVID-19 ve en az bir kardiyovasküler risk faktörü olan 232 hasta geriye dönük olarak dahil edildi. ESK, PK ve Total İK'nin kda, kas indeksi ve atenüasyonu BT görüntülerinde otomatik olarak ölçüldü. Çalışma popülasyonu, Toplam $İK_{kda}$ indeksine göre tertillere bölündü. Elde edilen değerler ile hastanede kalış süresi, yoğun bakım ünitesine (YBÜ) yatış, invaziv mekanik ventilasyon (IMV) ihtiyacı ve mortalite arasındaki ilişki araştırıldı.

Bulgular: YBÜ'ye başvuru, IMV ihtiyacı ve mortalite tertil 3'de diğer gruplara göre daha yüksekti (tüm *P* değerleri <,001). Tüm kas ölçümleri, tertil 3'te istatistiksel olarak anlamlı derecede düşüktü (*P* <,001). Diabetes mellitus, hipertansiyon ve Toplam $İK_{kda}$ indeksi çok değişkenli Cox regresyon analizine göre COVID-19 hastalarında hastane içi mortalitenin öngördürücülerindendir. Hayatta kalanların oranı için Kaplan–Meier eğrileri, tertil 3'teki Toplam $İK_{kda}$ indeksi en yüksek mortaliteye sahipti (hayatta kalma oranları %57, *P* <,001).

Sonuçlar: Sarkopeni ve eşlik eden kardiyovasküler komorbiditeler, COVID-19 hastalarında hastalık şiddetini etkili bir şekilde değerlendirebilir ve sonucu tahmin edebilir.

Anahtar Kelimeler: COVID-19, kalp-damar hastalığı, sarkopeni, ölüm, prognoz

ORIGINAL ARTICLE
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In Wuhan, Hubei province, China, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first identified in December 2019, after which the virus was defined coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO).[1] In Turkey, from January 3, 2020, to June 28, 2021, there were 5 449 464 confirmed COVID-19 cases and 49 959 patients died.[2] While real-time reverse transcription polymerase chain reaction (RT-PCR) is the important test for diagnosis, chest computed tomography (CT) is a cornerstone in the evaluation of patients diagnosed and treatment management.[3]

Sarcopenia is a generalized, progressive disease with a decrease in muscle quality and quantity.[4] Comorbidities such as coronary artery disease (CAD), diabetes mellitus (DM), and chronic obstructive pulmonary disease (COPD) are common with sarcopenia, and mortality is higher in these patients.[5-7] Many studies have shown that relationship between mortality and erector spinae muscle (ESM), pectoralis muscle (PM), and total skeletal muscle (total SM) cross-sectional area and index (divided by height squared) obtained from thorax CT.[8-11] The relationship of PM, ESM, and total SM_{csa}, muscle index, and muscle attenuation with prognosis and especially mortality in patients hospitalized for COVID-19 with at least 1 cardiovascular risk factor is unknown. We aimed to evaluate the relationship between CT-based skeletal measurements of COVID-19 patients with at least 1 cardiovascular risk factor and duration of hospitalization, admission to intensive care unit (ICU), the need for invasive mechanical ventilation (IMV), and mortality.

Methods

Study Design, Definitions, and Follow-Up

In this single-center study, a total of 232 consecutive patients with proven SARS-COV-2 by RT-PCR and with at least 1 cardiovascular risk factor were analyzed in a retrospective manner. Our hospital is a designated, large-volume hospital capable of receiving severe COVID-19 patients. According to the report of the diagnosis and treatment protocol for novel coronavirus pneumonia (Trial Version 7), patients with COVID-19 were divided into mild (laboratory confirmed, without pneumonia), moderate (laboratory confirmed and with pneumonia), severe (dyspnea, blood oxygen saturation ≤ 93%, respiratory frequency ≥30/min, PaO_2/FiO_2 ratio < 300, and/or lung infiltrates > 50% of the lung field within 24-48 hours), and critical (respiratory failure requiring mechanical ventilation, shock, or other organ failure that requires intensive care). Severe and critical patients were admitted to ICU whereas patients within mild to moderate group were admitted to the infectious disease service. The study was approved by the Ankara City Hospital Ethics Commission No. 1, and the requirement for written informed consent was waived by the Ethics Commission (No: E1-20-505 Date: May 21, 2020).

The median follow-up duration of the participants was 11 (8-15) days. Minimum and maximum follow-up durations were 1 and 48 months, respectively. The primary end-point of the study was in-hospital all-cause mortality.

Data Collection and Analysis

Information on demographic characteristics (gender and age), presence of COPD, hypertension (HTN), DM, CAD, cerebrovascular disease, peripheral vascular disease, dyslipidemia, renal and liver failure, smoking, clinical manifestations, laboratory findings, treatment and outcomes (duration of hospitalization/ICU/IMV/discharge/death) were extracted from electronic medical records using a standardized data collection form. Coronary artery disease was defined as a history of myocardial infarction or primary percutaneous intervention or a stenosis of more than 50% in any coronary vessel. Hypertension was defined as receiving antihypertensive treatment and/or arterial blood pressure > 140/90 in more than 1 measurement. Diabetes mellitus diagnosis, history of DM and/or antidiabetic therapy, or postprandial blood glucose level > 200 mg/dL were accepted as DM. Total cholesterol >200 mg/dL, low-density lipoprotein > 130 mg/dL, history of dyslipidemia, and/or being under antilipidemic treatment were accepted as hyperlipidemia. Data on medical treatments of the patients (renin-angiotensin-aldosterone system (RAAS) blockers, beta blockers, diuretics, calcium channel blockers, statins, antiplatelets, anticoagulations, and oral antidiabetics) were noted.

Routine blood examinations were complete blood count (CBC), coagulation profile, serum biochemical tests (including renal and liver function, creatine kinase, lactate dehydrogenase, and electrolytes), myocardial enzymes, C-reactive protein (CRP), procalcitonin (PCT), serum ferritin, interleukin-6 (IL-6), D-dimer, and arterial blood gases (lactate and PaO_2/FiO_2 ratio) were collected at admission. Peripheral venous blood samples were obtained from a large antecubital vein at admission. Total CBC test (Sysmex K-1000, Kobe, Japan) and blood chemistry parameters (Roche Diagnostic Modular Systems, Tokyo, Japan) were carried out at the biochemistry laboratory of our hospital. Blood samples were taken in standardized EDTA-containing tubes for total CBC test, and measurements were performed immediately after the blood sampling. Serum CRP levels were measured by immune nephelometric method (NFL BN-II; Dade Behring, Siemens). PCT was determined by bioMérieux MINI VIDAS automatic fluorescence immunoanalyzer. Serum ferritin levels were detected by electrochemiluminescence method (Cobas E601, Roche). Interleukin-6 was measured by Roche Cobas

ABBREVIATIONS

CAD	Coronary artery disease
CBC	Complete blood count
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
CT	Computed tomography
DM	Diabetes mellitus
ESM	Erector spinae muscle
HR	Hazard ratio
HTN	Hypertension
ICU	Intensive care unit
IL-6	Interleukin-6
IMV	Invasive mechanical ventilation
MDCT	Multidetector CT
PCT	Procalcitonin
PM	Pectoralis muscle
RAAS	Renin-angiotensin-aldosterone system
ROC	Receiver operating characteristic
RT-PCR	Real-time reverse transcription polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SM	Skeletal muscle
WHO	World Health Organization

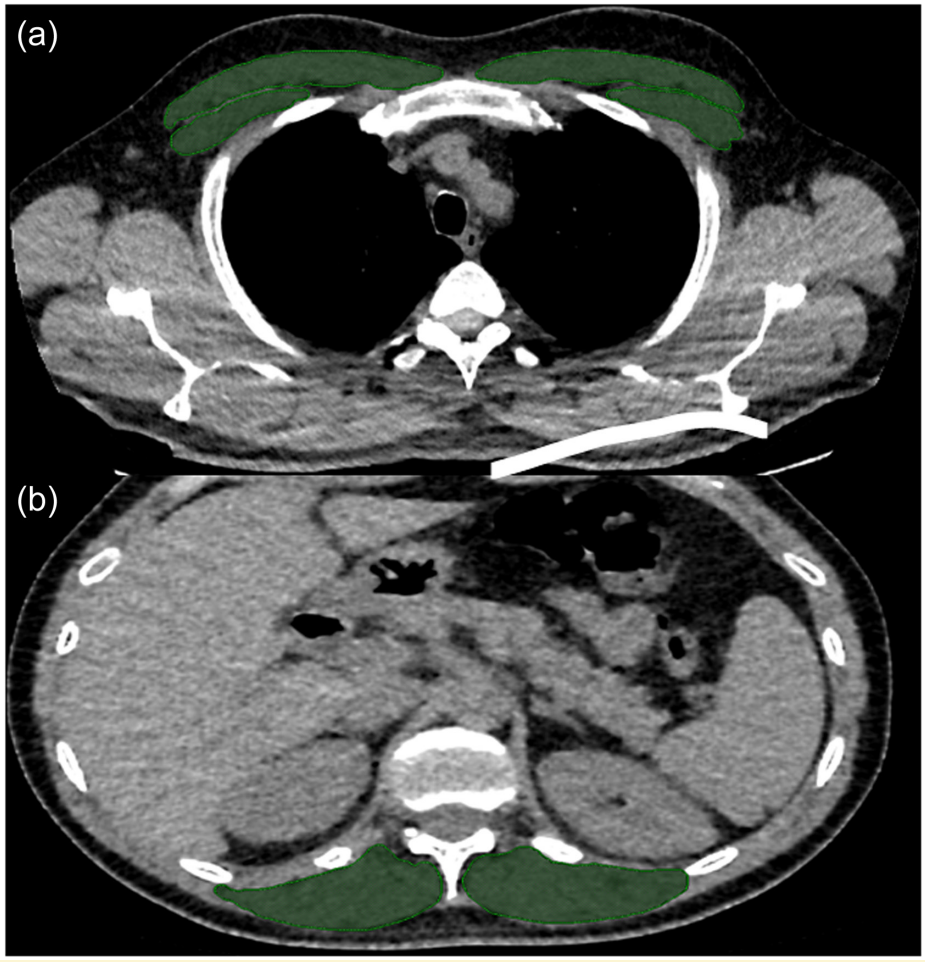

Figure 1. (A) Single-slice axial computed tomography (CT) images taken at the lower margin of the 12th thoracic vertebra to measure cross-sectional area and muscle attenuation of erector spinae muscle (ESM). (B) The quantitative analysis of the pectoralis muscle (PM) (pectoralis major and minor muscles) was applied on an axial slice just above the aortic arch. Bilateral muscles are colored green (ESM and PM).

E601 electrochemical luminescence immune detector, using the corresponding reagent. D-dimer was quantitatively determined using Sysmex CS-5100 hemagglutinin analyzer. Chest radiographs and CT scan were also performed for all inpatients.

Throat swab samples were obtained from all suspected patients, and laboratory validation of COVID-19 was performed using RT-PCR in accordance with the manufacturers' protocol (Dade Behring, Siemens, Deerfield, Illinois, USA; Beijing Genomics Institute, Beijing, China; Shanghai Geneodx Biotechnology Co. Ltd, Shangai, China). Repeated testing for COVID-19 was performed on confirmed patients to verify viral clearance before hospital discharge.

Computed Tomographic Image Analysis and Acquisition

For patients who applied to the hospital with suspicion of COVID-19, multidetector CT (MDCT) examination was performed at the time of admission. All imaging was performed using a 128-slice (Revolution EVO, General Electric (GE) Boston, Massachusetts, USA) MDCT scanner. The CT images were reconstructed using the mediastinal setting for quantitative analysis (Advantage Workstation 4.7 (Revolution, GE Healthcare, USA). We analyzed single-slice axial CT images taken at the lower margin of the 12th thoracic vertebra to measure the cross-sectional area and muscle attenuation of ESM. The quantitative analysis of the PM (pectoralis major and minor muscles) was applied on an axial slice just above the aortic arch. The borders of the dual ESMs and PMs were determined manually using a predefined range of –29 to 150 Hounsfield units. The cross-sectional area and muscle attenuation were calculated. The cross-sectional areas of ESM and PM were acquired by summing bilateral muscle areas. The muscle attenuations of ESM and PM were defined as the mean of the average CT attenuation of the bilateral muscles (Figure 1).[12] The sum of PM and ESM provided total SM.[13] Muscle index was measured with the specified formula: csa/patient's square height (m^2). All measurements were performed by a trained radiologist who was blinded to the data of the patients.

Statistical Analysis

Statistical analyses were carried out using IBM Statistical Package for the Social Sciences Statistics for Macintosh, Version 24.0 (IBM Corp., Armonk, NY, USA). One-sample Kolmogorov–Smirnov test was used to evaluate the distribution of numerical variables. One-way analysis of variance test was applied to the numerical data which conform to the normal distribution, and

the results were entered as mean and standard deviation. On the other hand, Kruskal–Wallis test which is one of the non-parametric tests was used for the non-normal distribution variables. Considering the results of this test, the median and interquartile range values were used. Chi-square test was used for categorical variables. Fisher's exact test was applied in cases where chi-square test could not be applied. For correlation analyses regarding CT-based skeletal measurements (PM_{csa} index, PM_{ma}, ESM_{csa} index, ESM_{ma}, and total SM_{csa} index), Pearson's correlation analysis was preferred for data with normal distribution, and Spearman's correlation analysis was preferred for data with non-normal distribution. The study population was assigned into tertiles on the basis of total SM_{csa} index.

Cumulative survival rates were calculated by the Kaplan–Meier method and compared between the 2 groups using the log-rank test. Cox proportional hazard regression analysis was performed through enter method to identify predictors for in-hospital mortality. Total SM_{csa} index was investigated in multivariate models. The models were adjusted for clinical and laboratory features (age, gender, DM, HTN, CAD, and high-sensitive troponin I (hs-TnI) levels). The multicollinearity assessment was checked with correlation coefficient (r) value. Independent variables with correlation coefficient (r) above 0.7 were considered to have multicollinearity and were not included in the same multivariate model. The results of Cox regression analysis were reported with hazard ratio (HR) and 95% CI. Receiver operating characteristic (ROC) curve analyses were used to determine the cut-off values for the sensitivity and specificity of CT-based SM measurements for predicting survival. The area under the ROC curve (AUC) was reported with 95% CI in addition to sensitivity and specificity. A two-tailed test was used and P values lower than .05 were considered to be statistically significant.

Results

The demographic, clinical, and in-hospital status of the study subjects are shown in Table 1. The median age of tertiles 1, 2, and 3 was 43 (34-55), 51 (36-63), and 73 (47-80) years, respectively ($P < .001$). Male gender was the highest in tertile 1 group than in the other groups ($P < .001$). Diabetes mellitus, HTN, COPD, CAD, and dyslipidemia were the highest in tertile 3 group (all P values < .05). The usage of RAAS blockers, beta blockers, statins, oral antidiabetics, antiplatelet, and anticoagulant agents

Table 1. Patient Characteristics and Comparisons Between the Groups with the Tertiles (T1, T2, and T3) of Total Skeletal Muscle Cross-Sectional Area Index

Variables	All (n=232)	Tertile 1 (highest) (n=78)	Tertile 2 (middle) (n=77)	Tertile 3 (lowest) (n=77)	*P*
Age (years)	51 (37-71)	43 (34-55)	51 (36-63)	73 (47-80)	<.001
Sex (male)	117 (50%)	57 (73%)	28 (36%)	32 (42%)	<.001
Diabetes mellitus	84 (36%)	21 (27%)	28 (37%)	35 (46%)	.021
Hypertension	101 (43%)	21 (27%)	28 (36%)	52 (67%)	<.001
Dyslipidemia	47 (20%)	11 (14%)	10 (21%)	26 (33%)	.001
Coronary artery disease	42 (18%)	6 (8%)	13 (12%)	23 (30%)	<.001
COPD	20 (9%)	2 (3%)	3 (4%)	15 (20%)	<.001
Medication					
RAAS blockers	67 (29%)	10 (13%)	17 (22%)	40 (52%)	<.001
Beta blockers	34 (15%)	4 (5%)	8 (10%)	22 (29%)	<.001
Diuretics	48 (21%)	9 (11%)	11 (23%)	28 (36%)	<.001
Calcium channel blockers	31 (13%)	9 (11%)	8 (10%)	14 (18%)	.308
Statins	28 (12%)	2 (3%)	7 (9%)	19 (25%)	<.001
Antiplatelets	33 (14%)	4 (5%)	9 (12%)	20 (26%)	.001
Anticoagulations	8 (3%)	0 (0%)	2 (3%)	6 (8%)	<.001
Oral antidiabetics	68 (30%)	15 (19%)	25 (33%)	28 (36%)	.016
Outcomes					
ICU	73 (31%)	11 (14%)	16 (21%)	46 (60%)	<.001
Stays in ICU, days	10 (4.5-18.5)	6 (3-11)	12 (8-20.5)	10.5 (5-20)	.185
Duration of hospitalization, days	11 (8-15)	10 (7-13)	11 (8-15)	12 (8-19)	.183
IMV	46 (20%)	4 (5%)	9 (12%)	33 (43%)	<.001
In-hospital mortality	44 (19%)	3 (4%)	8 (10%)	33 (43%)	<.001

COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IMV, invasive mechanical ventilation; RAAS blockers, renin-angiotensin-aldosterone system.
Parameters are mean ± standard deviation or median (interquartile range), n (%). P value less than .05 was considered significant for statistical analyses.

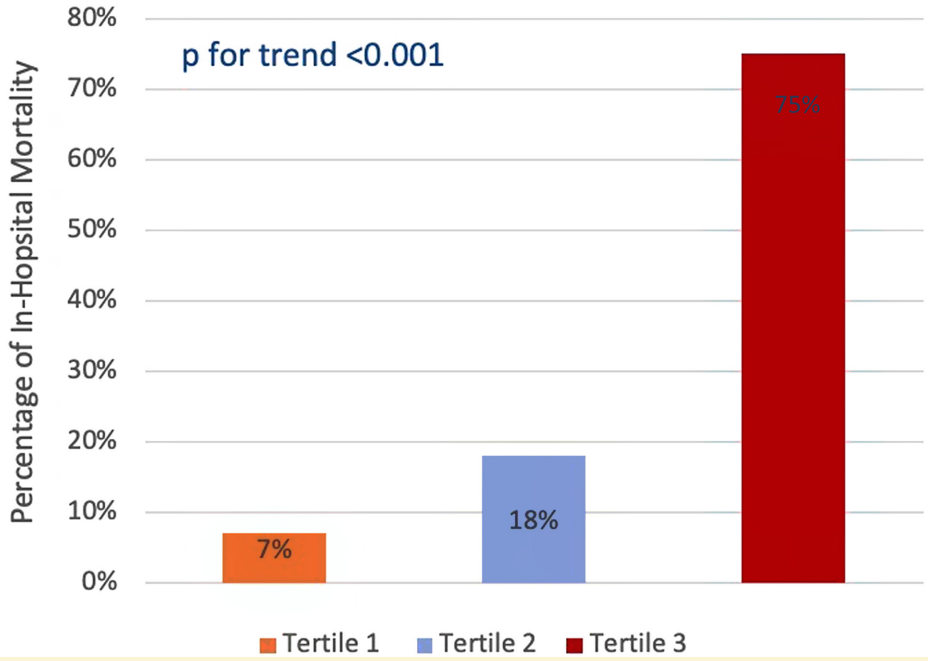

Figure 2. Percentage of patients developing in-hospital mortality stratified by tertile of total skeletal muscle cross-sectional area index.

were the highest in tertile 3 group than the other groups (all *P* values < .05).

Admission to ICU, need of IMV, and in-hospital mortality were common in tertile 3 group than the other groups (all *P* values < .001) (Figure 2). There were no differences between the 3 groups in terms of stays in ICU and duration of hospitalization (*P* = .185 and *P* = .183, respectively).

As shown in Table 2, there were no significant differences in terms of glucose, serum creatinine, and platelet counts between 3 groups on the admission (all *P* values > .05). The levels of D-dimer, ferritin, CRP, PCT, neutrophil counts, lymphocyte counts, and hemoglobin were the highest in tertile 3 group (all *P* values < .05). In CT-based SM measurements in Table 2, all muscle measurements (PM_{csa}, PM_{csa} index, PM_{ma}, EScsa, ES_{csa} index, and ES_{ma}) were statistically significantly lower in tertile 3 (*P* < .001).

As shown in Table 3, there were significant correlations between total SM_{csa} index and multiple variables (in terms of age, albumin, D-dimer, PTC, CRP, hs-TnI, neutrophil count, and lymphocyte count; all *P* values < .05).

Univariate and multivariate Cox proportion regression analyses revealed that (Table 4) DM, HTN, and total SM_{csa} index were shown to be associated with predicted in-hospital mortality in patients with COVID-19 on the basis of multivariable Cox regression analysis (HR 2.63, 95% CI 1.35-5.11, *P* .005; HR 2.98, 95% CI 1.20-7.37, *P* .018; HR 0.90, 95% CI 0.85-0.95, *P* < .001, respectively). The total SM_{csa} index cut-off value at admission for predicting in-hospital mortality in the entire study population based on ROC analysis was determined as <21.7 cm^2, with a sensitivity of 75% and a specificity of 80% (AUC 0.85, 95% CI: 0.78-0.91, *P* < .001) (Table 5) (Figure 3).

Figure 4 represents the Kaplan–Meier curves for the rate of survivals according to total SM_{csa} index, PM_{csa} index cut-off level of 10.3 cm^2/m^2, and ESM_{csa} index cut-off level of 11.4 cm^2/m^2. For total SM_{csa} index group, tertile 3 group had higher mortality rate than tertile 2 and 1 groups (survival rates 57%, 89%, and 96%, respectively, *P* < .001), for PM_{csa} index <10.3 cm^2/m^2 group, survival rate was lower than PM_{csa} index ≥10.3 cm^2/m^2 (survival rates 59% and 92%, respectively, *P* < .001), for ESM_{csa} index <11.4 cm^2/m^2 group, survival rate was lower than ESM_{csa} index ≥11.4 cm^2/m^2 (survival rates 62% and 93%, respectively, *P* < .001).

Discussion

In our study, we found that age, DM, HTN, and total SM_{csa} index in patients with COVID-19 is the independent predictor of the mortality. Sarcopenia is a progressive SM disease related with an increased likelihood of worse outcomes, including falls, fractures, physical disability, morbidity, and mortality. Sarcopenia is defined with 3 criteria: (1) low muscle strength, (2) low muscle quantity or quality, and (3) low physical performance.[14] Several studies have observed that the region of the psoas, PM, and paravertebral muscles is related with lean muscle mass, handgrip strength, health, and sarcopenia on CT scans.[9,14,15] There are many advantages of measuring SM to detect sarcopenia. First, the measurement is easy and reliable to perform using open source software (3D Slicer). Previous researches have shown that the slice used to make the measurement is easily identified in CT scans.[10,16]

Progressive reduction in muscle mass and accompanying decrease in muscle strength are related with pathologies including cardiovascular disease, type 2 DM, disability and frailty, increased risk of falls and fractures, decreased physical independence, cognitive

Table 2. Biochemical and Radiological Parameters of Patients with Total Skeletal Muscle Cross-Sectional Area Index Tertile Comparison

Variables	All (n=232)	Tertile 1 (Highest) (n=78)	Tertile 2 (Middle) (n=77)	Tertile 3 (Lowest) (n=77)	*P*
Glucose (mg/dL)	102 (91-126)	102 (91-116)	97 (91-122)	107 (89-155)	.405
BUN (mg/dL)	31 (24-41)	29 (24-36)	30 (23-39)	38 (24-54)	.001
Creatinine (mg/dL)	0.84 (0.67-1.04)	0.86 (0.70-1.05)	0.78 (0.65-0.96)	0.84 (0.64-1.11)	.090
Sodium (mEq/L)	139 (136-141)	139 (138-141)	139 (137-141)	138 (134-141)	.136
Potassium (mEq/L)	4.1 (3.9-4.4)	4.0 (3.8-4.3)	4.1 (3.9-4.4)	4.1 (3.9-4.5)	.325
AST (U/L)	26 (18-42)	27 (19-39)	22 (16-32)	31 (18-57)	.003
Albumin (g/dL)	4.4 (3.9-4.7)	4.5 (4.3-4.7)	4.5 (4.1-4.7)	3.8 (3.4-4.5)	<.001
Total protein (g/dL)	6.9 (6.3-7.2)	7.0 (6.7-7.3)	7.0 (6.4-7.2)	6.5 (6.0-7.0)	<.001
D-Dimer (μg/mL)	0.5 (0.3-1.1)	0.4 (0.3-0.7)	0.5 (0.3-0.8)	1.1 (0.4-2.5)	<.001
Ferritin (μg/L)	172 (54-410)	207 (83-339)	88 (31-326)	230 (58-555)	.012
Procalcitonin (μg/L)	0.05 (0.03-0.12)	0.05 (0.03-0.10)	0.04 (0.03-0.08)	0.10 (0.03-0.47)	.003
C-reactive protein (mg/L)	12.4 (3.1-73.9)	9.1 (3.0-35.3)	6.9 (1.8-24.4)	40.6 (6.8-144)	<.001
hs-TnI (ng/L)	4.0 (1.9-11.0)	3.0 (1.8-5.0)	3.0 (1.8-8.0)	9.0 (2.1-66)	<.001
Leucocytes ($\times10^9$/L)	5.65 (4.56-7.59)	5.32 (4.53-6.36)	5.51 (4.53-6.70)	6.63 (4.66-8.97)	.017
Neutrophils ($\times10^9$/L)	3.59 (2.77-5.36)	3.22 (2.76-4.61)	3.50 (2.64-4.72)	4.76 (3.16-7.66)	.001
Lymphocytes ($\times10^9$/L)	1.17 (0.78-1.63)	1.30 (0.96-1.69)	1.18 (0.74-1.74)	0.99 (0.55-1.43)	.001
Platelets ($\times10^9$/L)	231 ± 85	230 ± 79	224 ± 67	239 ± 105	.536
Monocytes ($\times10^9$/L)	0.34 (0.25-0.47)	0.36 (0.26-0.48)	0.33 (0.23-0.45)	0.32 (0.26-0.50)	.347
Hemoglobin (g/L)	13.8 (12.4-14.7)	14.6 (13.7-15.5)	13.6 (12.5-14.6)	12.8 (11.7-13.8)	<.001
CT-based skeletal muscle measurements					
PM_{csa} (cm^2)	32.6 ± 10.2	42.8 ± 7.7	31.3 ± 5.3	23.6 ± 6.4	<.001
PM_{csa} index (cm^2/m^2)	11.9 ± 3.7	15.6 ± 2.6	11.8 ± 1.6	8.4 ± 2.2	<.001
PM_{ma}	33.9 (25.3-39.3)	38.4 (33.1-42.2)	35.1 (28.0-39.2)	28.0 (20.3-33.8)	<.001
ES_{csa} (cm^2)	32.9 ± 9.8	42.7 ± 7.1	32.1 ± 4.6	23.7 ± 6.1	<.001
ES_{csa} index (cm^2/m^2)	12.1 ± 3.5	15.5 ± 2.2	12.1 ± 1.5	8.5 ± 2.3	<.001
ES_{ma}	41.9 (30.6-47.7)	45.9 (40.4-49.7)	42.5 (33.5-47.8)	31.7 (19.1-42.9)	<.001

AST, aspartate amino transaminase; BUN, blood urea nitrogen; CT, computed tomography; ESM_{csa}, cross-sectional area of the erector spinae muscles; ESM_{ma}, muscle attenuation of the erector spinae muscles; hs-TnI, high-sensitive Troponin I, PM_{ma}, muscle attenuation of the pectoralis muscles; PM_{csa}, cross-sectional area of the pectoralis muscles; total SM_{csa}, cross-sectional area of the total skeletal muscle.
Parameters are mean ± standard deviation or median (interquartile range), n (%). *P* value less than .05 was considered significant for statistical analyses.

decline and depression, poor quality of life, and all-cause morbidity and mortality.[17]

A new type of coronavirus (SARS-CoV-2) was detected, and the WHO named the infection of SARS-CoV-2 as "coronavirus disease 2019 (COVID-19)" in December 2019.[17] The COVID-19 pandemic is an extraordinary global emergency with over 183.9 million confirmed cases and more than 3 800 000 deaths as of July 06, 2021.[2]

Hospitalization due to COVID-19 can lead to prolonged bed rest. The more severe presentation of COVID-19 infection may result in the need for ICU or IMV. Such long periods of bed rest and hospitalization as a result of COVID-19 isolation/quarantine or hospitalization pose a greater risk of muscle loss, especially for older individuals.[18]

Du et al[19] reported that advanced age and concomitant cerebrovascular or cardiovascular diseases were robust and independent predictors of mortality in patients with COVID-19.[19] In addition, Petrilli et al[20] reported that advanced age (>75 years of age), male gender, malignancy, and heart failure were independent factors of the mortality in 5279 COVID-19 patients. Zhou et al[21] found that older age is the independent factor for poor prognosis in patients with COVID-19. Kumar et al[22] found that DM is an independent predictor of the mortality in patients with 16 003 COVID-19 patients. Also, Ufuk et al showed similar results. They found that the presence of DM in COVID-19 patients is a significant and powerful risk factor for mortality.[17] In our study, we found similar results to the literature. Hypertension is commonly accompanied by many comorbidities that are major determinant factors for the severity of COVID-19. However,

Table 3. CT-Based Skeletal Muscle Measurements and Their Correlation with Other Clinical and Laboratory Variables

	PM_{csa} index		PM_{ma}		ESM_{csa} index		ESM_{ma}		Total SM_{csa} index	
Variables	***r***	***P***	***r***	***P***	***r***	***P***	***r***	***P***	***r***	***P***
Age	−0.44	<.001	−0.50	<.001	-0.39	<.001	−0.70	<.001	−0.46	<.001
Duration of hospitalization	−0.06	.334	−0.14	.028	−0.08	.240	−0.17	.010	−0.09	.188
Creatinine	0.04	.492	−0.07	.321	0.05	.417	−0.14	.031	0.06	.378
AST	−0.04	.513	−0.25	<.001	−0.08	.191	−0.35	<.001	−0.06	.338
Albumin	0.41	<.001	0.42	<.001	0.36	<.001	0.56	<.001	0.41	<.001
D-dimer	−0.34	<.001	−0.33	<.001	−0.32	<.001	−0.42	<.001	−0.36	<.001
Ferritin	−0.02	.720	−0.08	.228	−0.05	.473	−0.23	<.001	−0.02	.739
Procalcitonin	−0.21	.001	−0.26	<.001	−0.12	.069	−0.33	<.001	−0.16	.012
C-reactive protein	−0.27	<.001	−0.31	<.001	−0.24	<.001	−0.44	<.001	−0.26	<.001
hs-Troponin I	−0.29	<.001	−0.36	<.001	−0.24	<.001	−0.45	<.001	−0.28	<.001
Neutrophil count	−0.20	.002	−0.08	.226	−0.26	<.001	−0.21	.001	−0.24	<.001
Lymphocyte count	0.28	<.001	0.24	<.001	0.23	<.001	.024	<.001	0.27	<.001

AST, aspartate amino transaminase; CT, computed tomography; ESM_{csa}, cross-sectional area of the erector spinae muscles; ESM_{ma}, muscle attenuation of the erector spinae muscles; hs-TnI, high-sensitive troponin I; PM_{ma}, muscle attenuation of the pectoralis muscles; PM_{csa}, cross-sectional area of the pectoralis muscles; total SM_{csa}, cross-sectional area of the total skeletal muscle.

Table 4. Prediction of In-Hospital Mortality in Patients with COVID-19 by Univariate and Multivariate Cox Proportion Regression Analyses

	Univariate Analysis		Multivariate Analysis	
Variables	**Unadjusted HR (95% CI)**	***P***	**Adjusted HR (95% CI)**	***P***
Total SM_{csa} index				
Age	1.06 (1.03-1.08)	<.001	1.01 (0.98-1.04)	.427
Gender	1.34 (0.73-2.44)	.339	..	..
Diabetes mellitus	3.62 (1.91-6.83)	<.001	2.63 (1.35-5.11)	.005
Hypertension	4.68 (2.21-9.94)	<.001	2.98 (1.20-7.37)	.018
hs-Troponin I	1.00 (1.00-1.01)	.001	1.00 (1.00-1.00)	.151
Coronary artery disease	3.28 (1.74-6.17)	<.001	1.36 (0.68-2.72)	.381
Total SM_{csa} index	0.90 (0.86-0.95)	<.001	0.90 (0.85-0.95)	<.001

CT, computed tomography; HR, hazard ratio; hs-TnI, high-sensitive troponin I; total SM_{csa}, cross-sectional area of the total skeletal muscle.

Table 5. Optimal Cut-Off Value of Each Computed Tomography-Derived Skeletal Muscle Mass Measurements Predicting for In-Hospital Mortality

	Sensitivity (%)	Specificity (%)	AUC (95% CI)	*P*
PM_{csa} index <10.3 cm^2/m^2	74	76	0.81 (0.74-0.88)	<.001
PM_{ma} < 33.15	60	75	0.74 (0.67-0.82)	<.001
ESM_{csa} index < 11.4 cm^2/m^2	68	80	0.83 (0.76-0.90)	<.001
ESM_{ma} < 37.1	73	77	0.81 (0.74-0.88)	<.001
Total $skeletal\ muscle_{csa}$ index < 21.7 cm^2	75	80	0.85 (0.78-0.91)	<.001

AUC, area under the curve; CT, computed tomography; ESM_{csa}, cross-sectional area of the erector spinae muscles; ESM_{ma}, muscle attenuation of the erector spinae muscles, PM_{ma}, muscle attenuation of the pectoralis muscles, PM_{csa}, cross-sectional area of the pectoralis muscles.

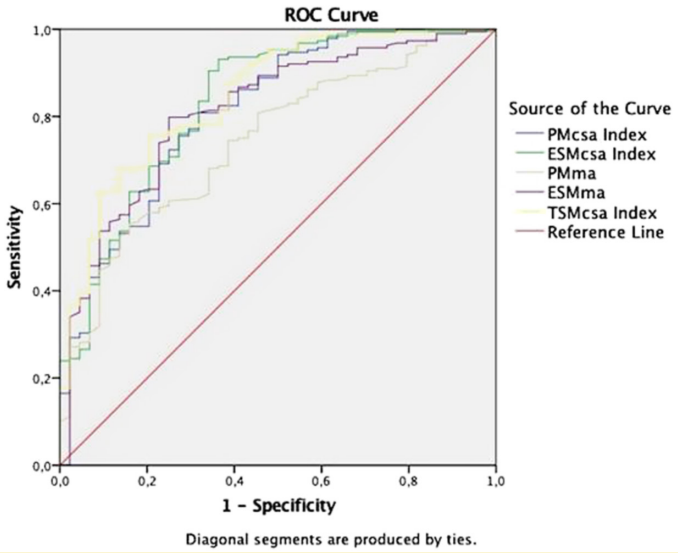

Figure 3. Receiver operating characteristic curve analysis of computed tomography-derived skeletal muscle mass measurements predicting for survival. PM_{csa}, cross-sectional area of the pectoralis muscles; ESM_{csa}, cross-sectional area of the erector spinae muscles; PM_{ma}, muscle attenuation of the pectoralis muscles; ESM_{ma}, muscle attenuation of the erector spinae muscles; TSM_{csa},cross-sectional area of the total skeletal muscles.

there are conflicting results about the HTN and the severity of COVID-19.[23] Hypertension was not found as an independent factor for COVID-19 severity based on multivariable-adjusted analysis, despite being identified as a risk factor by univariate analysis.[21,24] Otherwise, several studies showed that HTN may be an independent risk factor for severe COVID-19.[25] In our study, we found an independent relationship between HTN and mortality of COVID-19.

Short periods of reduced activity have been found to result in rapid loss of muscle mass and physical function, even in younger adults.[26] Due to the COVID-19 measures, the sudden decrease in activities and the increase in sedentarism may closely reflect the "catabolic crisis" model of sarcopenia, according to the study conducted by English and Paddon-Jones.[27]

Inflammation has been shown to increase catabolic pathways and inhibit anabolic pathways, thus reducing net muscle protein synthesis.[28] Tumor necrosis factor (TNF)-α, the key transcription factor in SM atrophy, downregulates the myogenesis and upregulates nuclear factor-kappa beta.[29] In some patients with cytokine storm observed during the current COVID-19 outbreak, it becomes more pronounced with increased levels of pro-inflammatory cytokines such as interferon, IL-6, IL-12. Also, increment of TNF-α, CRP, and MCP1 has been observed in severe COVID-19 patients. These cytokines not only directly contribute to tissue damage but can also contribute to sarcopenia by blunting muscle protein synthesis (MPS) during and after immobilization.[18,29]

Ufuk et al[17] found a significant association of pneumonia severity, PM_{csa} index, and PM_{csa} with length of stay, IMV, and mortality among COVID-19 patients who underwent CT at admission.[17] In light of this information, we found DM, HTN, and total SM_{csa} index on chest CT in patients with COVID-19 are the independent predictors of the mortality.

In our study, the relationship between skeletal groups [ESM, PM, and total SM] and mortality in this patient group was assessed. Therefore, unlike similar studies, not a single muscle group but 3 different muscle groups were evaluated. Moreover, in our study, muscle attenuation was assessed in addition to other studies, and it was shown to be a predictor of in-hospital mortality. The patient population was larger than similar studies. Due to the high number of patients, the mortality data of our study were more powerful. In addition to cardiovascular risk factors, cardiac drug groups and percentages of use were shown. It was shown that cardiovascular risk factors and cardiac medical treatment intensity are high in the sarcopenic group.

Limitations

This study had some limitations. Primarily, the study has been retrospectively conducted in a single tertiary hospital, and the sample size was not large enough. As a result, PM_{csa} index, ESM_{csa} index, and total SM_{csa} index are significantly associated with mortality in COVID-19 patients. These parameters can be easily evaluated in chest CT images of COVID-19 patients, and we propose that these parameters might be beneficial in routine clinical practice because these parameters with prognostic value are obtained without additional examination.

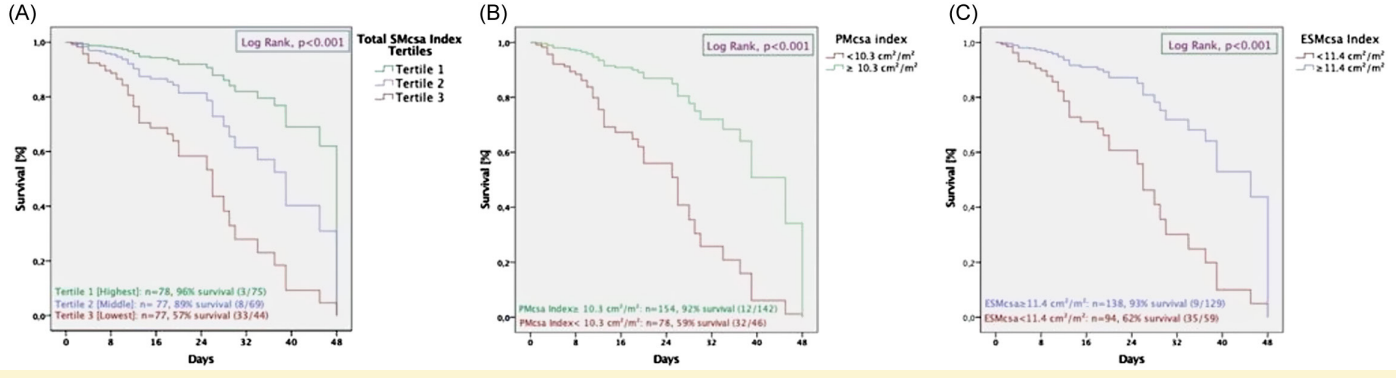

Figure 4. Kaplan–Meier curves of patients according to total SM_{csa} index (A), PM_{csa} index (B), and ESM_{csa} index (C). Total SM_{csa}, cross-sectional area of the total skeletal muscles; PM_{csa}, cross-sectional area of the pectoralis muscles; ESM_{csa}, cross-sectional area of the erector spinae muscles.

Conclusion

This study has shown that sarcopenia is a predictor of survival in COVID-19 patients with cardiovascular risk factors.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Committee Approval: Ethics committee approval was received from the Ankara City Hospital Ethics Commission No. 1 (Approval Date: May 21, 2020; Approval Number: E1-20-505).

Informed Consent: Written informed consent was waived by the Ethics Commission.

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