The European Research Journal 2024;10(1):70-76 Original Article

DOI: https://doi.org/10.18621/eurj.1316381 *Radiology*

Effects of sarcopenia on in-hospital results and mid-term follow-up in patients with coronary artery disease and COVID-19

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ABSTRACT

Objectives: Sarcopenia is associated with atherosclerosis, vascular dysfunction, and poor in-hospital prognosis in the general COVID-19 population. Coronary artery disease (CAD) is also associated with poor prognosis in patients with COVID-19, however, the influencing factors in this association have not yet been fully documented. This study aimed to evaluate the effect of sarcopenia on both in-hospital acute-term and mid-term follow-up clinical results in patients with CAD and COVID-19.

Methods: The study population was selected from the general COVID-19 population. It consisted of 50 patients with CAD (group I) and 80 age- and gender-matched patients without CAD (group II). In-hospital acute term endpoints were determined as intensive care unit (ICU) admission, intubation, mortality, and its combination. Mid-term follow-up was also made for three-month. Sarcopenia was assessed by indexed skeletal muscle mass at T12 vertebrae level (T12-SMI) on initial chest computed tomography. Multivariable logistic regression analysis was used to detect independently related factors to endpoints.

Results: Group I had more severe COVID-19 disease and a higher rate of hospitalization, ICU admission, intubation as well as mortality compared to group II in acute-term. T12-SMI was lower and sarcopenia was more frequent in group I than in group II. During the three-month mid-term follow-up period, no additional adverse results occurred in both groups. In multivariate regression analysis; sarcopenia was independently related to in-hospital combined endpoint.

Conclusions: Sarcopenia is associated with in-hospital combined endpoint in patients with CAD during acute-term of COVID-19. However, it has no effect on three-month mid-term follow-up.

Keywords: COVID-19, coronary artery disease, sarcopenia

Coronavirus disease 2019 (COVID-19) caused by a new severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) has led to a worldwide pandemic in 2019 [1]. Unfortunately, it has caused millions of death. Its clinical course largely varies from patient to patient. Some patients can face life-threatening clinical disease that requires admission to the intensive care unit (ICU), intubation, and even death, while others may experience minimal symptoms or an asymptomatic situation. The presence

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How to cite this article: Erkan M, Zengin İ. Effects of sarcopenia on in-hospital results and mid-term follow-up in patients with coronary artery disease and COVID-19. Eur Res J. 2024;10(1): 70-76. doi: 10.18621/eurj.1316381

Received: June 18, 2023
Accepted: August 29, 2023
Published Online: September 13, 2023

of coronary artery disease (CAD) has been identified as one of the main determinants of poor prognosis in patients with COVID-19 [2-4]. However, the mechanism of this relationship has not been clearly understood yet.

Sarcopenia is a skeletal muscle disease that reflects the presence of low muscle quantity or quality, low muscle strength, and low physical performance [5]. Computed tomography (CT) is one of the most commonly used imaging methods to evaluate sarcopenia [6]. Currently, chest CT imaging is widely used as an initial evaluation tool in patients with COVID-19 that allows to assessment of sarcopenia by evaluating cross-sectional muscle areas at the level of T12 (thoracic 12) vertebrae. Clinically, it is associated with atherosclerosis and cardiovascular disease, lowered quality of life, increased hospitalization rate, and even death in the general population [7-13]. Recently, some studies evaluated the relationship between sarcopenia and in-hospital adverse clinical results in an unselected general population of COVID-19 have been published [14-16]. However, there is no data about the effect of sarcopenia on selected patient populations such as CAD.

Sarcopenia and CAD share some common pathophysiological mechanisms such as atherosclerosis, arterial stiffness, and vascular dysfunction. Therefore, sarcopenia may play a role in the development of prominent worse results in patients diagnosed with COVID-19 who have CAD. In addition, sarcopenia is a relatively chronic situation that may have a longer-term effect on the patients' results. Thus, in this study, we sought the effects of sarcopenia on both in-hospital acute term results and three-month mid-term follow-up in patients diagnosed with COVID-19 who have CAD that may suggest an etiopathological mechanism for poor prognosis.

METHODS

Patients Selection

The study population was prospectively selected among the patients diagnosed with COVID-19 by re-

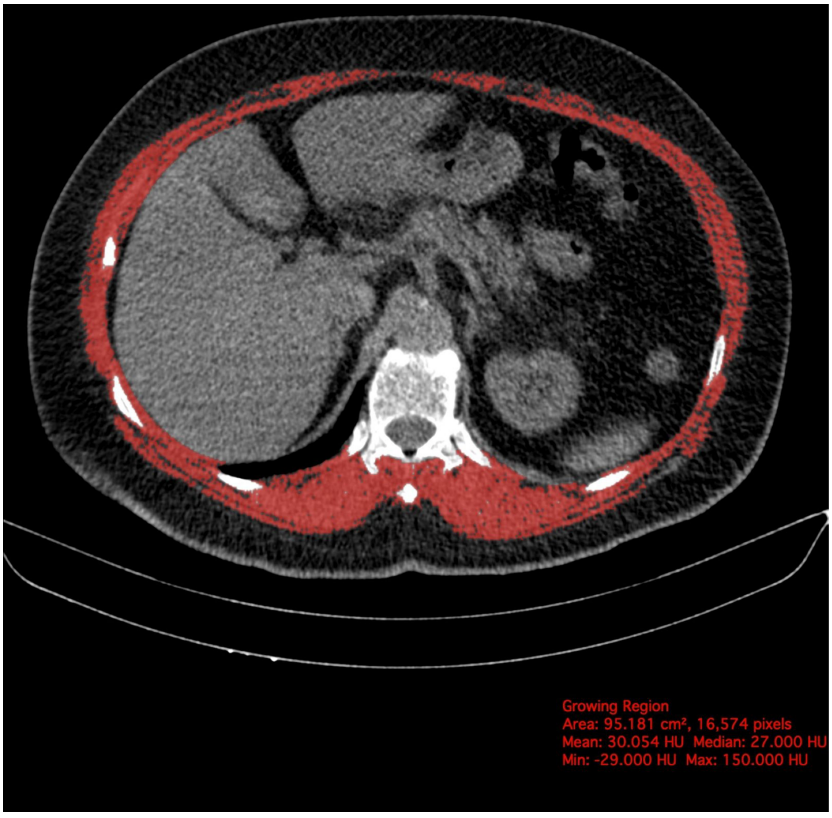

Fig. 1. T12-SMA measurement on chest CT image at the T12 vertebra level. Red zone indicates the cross-sectional skeletal muscle area identified using a threshold of -29 to +150 HU (T12-SMA: 95.18 cm² , T12-SMI: 34.99 cm²/m²).

verse transcription-polymerase chain reaction (RT-PCR) test. Group I consisted of 50 consecutive patients with CAD (previous coronary artery bypass graft operation, percutaneous coronary intervention, or known 50% stenosis of at least one epicardial coronary artery). Group II included 80 age- and gender-matched patients without CAD who served as a control subjects. Patients who underwent unenhanced chest CT examination during the initial clinical examination were included in the study but those with no or inadequate CT imaging were excluded from the study. In addition, patients who had heart failure (left ventricular ejection fraction <50%) and significant valvular heart disease, and the acute coronary syndrome were also excluded from the study. Hypertension (HT), diabetes mellitus (DM) and chronic obstructive pulmonary disease (COPD) were diagnosed by the presence of previous history and/or drug use. All laboratory values were obtained during the initial hospital presentation. The study was conducted by the guidelines in the Declaration of Helsinki. The Local Ethics Committee approved the study protocol. Written informed consent was obtained from all of the study participants.

Assessment and Definition of Sarcopenia

Sarcopenia was assessed by chest CT imaging obtained during the initial evaluation of patients with COVID-19. Chest CT images were acquired using a 64-slice multi-detector CT scanner (Somatom Sensation, Siemens, Germany). Initially, cross-sectional area (CSA, in cm^2) of all skeletal muscles at the level of the T12 (rectus abdominis, external and internal obliques, psoas, transverse abdominalis, rectus abdominalis, quadratus lumborum, and the erector spinae) were measured by using OsiriX Lite software (version 7.0.2, Pixmeo SARL, Bernex, Switzerland). The Hounsfield Units (HU) of -29 to 150 were used to isolate the skeletal muscle. Thus, the exact muscle area (T12-SMA, cm^2) was obtained based on HU, excluding vasculature and fat infiltration (Fig. 1). Then, CSA measurements were normalized to patient size by dividing CSA with height in square meters to provide the skeletal muscle index (T12-SMI; cm^2/m^2) [14, 15]. All T12-SMI values were divided into quartiles and stratified by gender. Finally, the patients in the first quartile of each gender that had the lowest SMI values were accepted as sarcopenia [14].

Disease Severity and End-Points

Patients were classified into four groups according to their clinical symptoms, signs, and chest imaging manifestations as being mild, moderate, severe, or critical COVID-19 cases [17]:

1. Mild cases: mild or minimal clinical symptoms, no sign of pneumonia on chest imaging
2. Moderate cases: fever and respiratory symptoms, pneumonia on chest imaging
3. Severe cases: severe respiratory distress and/or increased respiratory rate ≥30 breaths/min and/or decreased oxygen saturation (SpO_2) on room air with ≤93 % and/or arterial partial pressure of oxygen (PaO_2)/ fraction of inspired oxygen (FiO2)≦300 mmHg
4. Critical cases: respiratory failure requiring mechanical ventilation and/or septic shock and/or other organ failure requiring ICU admission.

In addition, the severity of COVID-19 disease was evaluated by chest CT severity score (CTSS). Involvement of each lung segment was assessed separately then a total score was computed by a predefined method [18]. According to this method, two lungs which were divided into 20 regions were evaluated for ground glass opacities. Each region was scored as 0 point for no parenchymal involvement, 1 point for ≤50% opacification and 2 point for >50% opacification. Finally, chest CT severity score was obtained by summing of points from each region.

In the study, there were two time-dependent end-points. First; short-term in-hospital adverse results included ICU admission, intubation, mortality, and their combined end-point. Second; thromboembolic event, hospitalization, and mortality at three-month mid-term follow-up.

Statistical Analysis

Categorical variables are expressed as numbers and percentages. The normal distribution of continuous variables was evaluated by using the Kolmogorov-Smirnov test and histogram. Then, continuous variables are expressed as mean±standard deviation for variables with normal distribution and as median (25^{th}-75^{th} quartiles) for variables without normal distribution. Continuous variables were analyzed by independent-sample t-test or Mann-Whitney U test according to normal distribution. Chi-square and Fisher's exact tests were used for categorical variables.

Table 1. The baseline demographic properties of study population

	Group I (n=50)	Group II (n=80)	P value
Age (years)	68 (60-76)	63 (58-70)	0.06
Gender (female), n (%)	30 (60)	49 (61.3)	0.89
Diabetes Mellitus, n (%)	25 (50)	29 (36.3)	0.12
Hypertension, n (%)	30 (60)	40 (50)	0.27
COPD, n (%)	5 (10)	6 (7.5)	0.78
T12-SMA (cm^2)	85.9±24.9	93.5±18.5	**0.03**
T12-SMI (cm^2/m^2)	30.9±7.3	34.3±5.5	**0.006**
Sarcopenia, n (%)	31 (62)	35 (43.8)	**0.04**

Data are shown as mean±standart deviation or median (25^{th}-75^{th} quartiles) or n (%). COPD=chronic obstructive pulmonary disease, T12-SMA=T12 skeletal muscle area, T12-SMI=T12 skeletal muscle index

Multivariable logistic regression analysis was used to detect independent variables of end-points. A *p* - value of less than 0.05 was considered statistically significant. All statistical analyses were carried out by the SPSS 21 statistical software (SPSS Inc., Chicago, Illinois, USA).

RESULTS

A total of 130 patients were included in the study (50 in group I and 80 in group II). The baseline demographic parameters of the study population were shown in Table 1. There were no differences between the two groups for HT, DM, and COPD. However, T12-SMA and T12-SMI were lower and the rate of sarcopenia was higher in group I than in group II (85.9±24.9 vs 93.5±18.5, P=0.03; 30.9±7.3 vs 34.3±5.5, P=0.006; 62% vs 43.8%, P=0.04, respectively). Laboratory parameters of the study population were given in Table 2. Group I had higher hs (high sensitivity) cardiac troponin I and lower blood oxygen saturation (SpO2) levels than group II.

In-hospital clinical course and end-point data were presented in Table 3. The rate of hospitalization, lung involvement, and in-hospital end-points (ICU admission, intubation, mortality, and combined end-point) were higher in group I than in group II. In addition, the patients in group I had more severe diseases compared to those in group II. During the three-month

Table 2. Laboratory values of study population

	Group 1 (n=50)	Group 2 (n=80)	P value
Creatinine (mg/dL)	0.91 (0.7-1.3)	0.9 (0.8-1.2)	0.78
hs cardiac troponin I (ng/mL)	16.1 (7.3-25.1)	8.7 (4.7-13.4)	**0.001**
SpO_2 (%)	92 (88-96)	95.5 (92.3-97)	**0.006**
CRP, (mg/L)	42.25 (12.3-112.5)	24.7 (10.6-58.7)	0.09
WBC (K/µL)	6.9 (4.9-8.9)	5.9 (4.6-7.9)	0.14
Ferritin (ng/mL)	153.95 (70-426.5)	198.5 (93-390.8)	0.95
D-dimer (µg/mL)	0.8 (0.28-1.7)	0.7 (0.4-1.1)	0.48

Data are shown as median (25^{th}-75^{th} quartiles). hs Troponin I=High sensitivity cardiac troponin I, SpO_2=Arterial blood partial oxygen pressure, CRP=C-reactive protein, WBC=White blood count

Table 3. In-hospital clinical course and end-points of study population

	Group I (n=50)	Group II (n=80)	P value
Hospitalization, n (%)	38 (76)	39 (48.8)	**0.002**
Lung involvement, n (%)			
No	3 (6)	16 (20)	**0.002**
Unilateral	3 (6)	4 (5)	
Bilateral	44 (88)	60 (75)	
Chest CT severity score	14 (7-23.3)	11.5 (2.3-19.8)	0.07
Disease severity, n (%)			
Mild	3 (6)	16 (20)	**0.03**
Moderate	20 (40)	38 (47.5)	
Severe	18 (36)	20 (25)	
Critical	9 (18)	6 (7.5)	
In-hospital end points, n (%)			
ICU admission	17 (34)	14 (17.5)	**0.03**
Intubation	14 (28)	10(12.5)	**0.03**
Mortality	14 (28)	8 (10)	**0.008**
Combined end-point	18 (36)	14 (17.5)	**0.02**

Data are shown as median (25^{th}-75^{th} quartiles) or n (%). CT=Computed tomography, ICU=Intensive care unit, Combined end point=Combination of in-hospital mortality, intubation and ICU admission

mid-term follow-up, there were no additional thromboembolic events, hospitalization, and mortality.

Only one multivariate regression model was created for the in-hospital combined end-point in the acute term because of the absence of additional adverse events during mid-term follow-up. The results of the univariate and multivariate analysis were shown in Table 4. In univariable analysis; C-reactive protein, white blood count, D-dimer, sarcopenia, and CTSS were associated with in-hospital combined end-point. But, in the multivariable model; sarcopenia (OR: 3.648, 95% CI: 1.081-12.03, P=0.037) and CTSS (OR: 1.121, 95% CI: 1.049-1.198, P=0.001) were independently associated with in-hospital combined end-point.

Table 4. The predictors of in-hospital combined end-point in the study population

	Univariable analysis				Multivariable analysis			
	OR	95% CI		P value	OR	95% CI		P value
		Upper	lower			Upper	lower	
CRP	1.016	0.008	1.023	**<0.001**	0.993	0.980	1.005	0.25
WBC	1.213	1.068	1.378	**0.003**	1.144	0.989	1.323	0.07
D-dimer	1.695	1.248	2.301	**0.001**	1.435	1.004	2.051	**0.05**
Sarcopenia	8.169	2.898	23.030	**<0.001**	3.648	1.081	12.307	**0.037**
CTSS	1.131	1.078	1.188	**<0.001**	1.121	1.049	1.198	**0.001**

CRP=C-reactive protein, WBC=white blood count, CTSS=Computed tomography severity score

DISCUSSION

In this study, we assessed the effect of sarcopenia on acute-term in-hospital results and three-month follow-up in a selected population of COVID-19. We found that the patients with CAD had a higher rate of sarcopenia, hospitalization, and more severe disease as well as more frequent in-hospital end-points compared to those without CAD. In addition, sarcopenia was independently associated with acute-term in-hospital combined end-point in this population. There were no additional events during the three-month mid-term follow-up that reflects it has no long-term effect in this population.

The COVID-19 pandemic has led to millions of cases and death around the world. The clinical picture during COVID-19 varies from asymptomatic situations to life-threatening clinical diseases such as respiratory collapse and thromboembolic events. Unfortunately, there is no effective and specific treatment for quickly controlling the disease. Therefore, predicting the patients at risk and detecting the factors associated with poor prognosis are critical to patient management. CAD has reported as an important contributing clinical situation to more severe disease and poor prognosis in COVID-19 [2-4]. However, the mechanism of this relationship and influential factors have not been clearly understood yet.

Sarcopenia has found in associated with increased morbidity and mortality in different populations during the last decade [7-13]. During the pandemic, its impact on outcomes for the general COVID-19 population has been evaluated in several recent studies [14-16]. Some of them have reported that sarcopenia is a contributing factor to poor prognosis in this population, while others have not found any relationship. In fact, sarcopenia and CAD share some common pathophysiological mechanisms such as atherosclerosis, arterial stiffness, and chronic inflammation. Therefore, we thought that sarcopenia may have a role in the development of poor results in patients with CAD who were diagnosed with COVID-19. Furthermore, sarcopenia may have a long-lasting effect on the results of patients with COVID-19 because it is a relatively chronic clinical entity. Therefore, in this study, we intended to evaluate the effect of sarcopenia on in-hospital acute-term and three-month mid-term follow-up results in this population. We found that sarcopenia is an independent predictor for in-hospital acute adverse outcomes, but it has no long-term effect in this population.

Vascular effects of sarcopenia can be proposed to explain this relationship. It is known that sarcopenia is associated with atherosclerosis and vascular dysfunction detected by several indicators such as arterial stiffness, carotid-intima media thickness, flow-mediated dilatation, endothelial progenitor cell counts [19, 20]. In this study, the group I had higher hs-cardiac troponin I compared to group II which reflects myocardial damage at in-hospital stage of COVID-19. We did not detect any additional adverse result during follow-up. Therefore, we thought that sarcopenia and its vascular effects are a predisposing factor for adverse results only active phase of COVID-19 disease characterized by a hyperinflammatory response. After an active inflammatory phase of COVID-19, chronic vascular effects of sarcopenia do not associate with poor results.

To our knowledge, this is the first study that evaluated the effect of sarcopenia on acute and mid-term results of patients with CAD and COVID-19. Our results have some clinical implications; first, the patients with sarcopenia in this population are at risk for poor prognosis in the acute term. Second, sarcopenia-related vasculopathy may be an etiopathological mechanism for this poor prognosis. Third, the presence of sarcopenia may be used as a criterion in the initial risk assessment of the patients with CAD during the acute term of COVID-19, but not follow-up.

Limitations

This study has some limitations. First, our study population was relatively small. Second, this was not a randomized study. However, it should be accepted that doing a randomized study has some ethical issues during the COVID-19 pandemic. Thus, we tried to eliminate this limitation using age- and gender-matching of groups. Third, we could not assess the vascular function of the study population by an objective method such as arterial stiffness. However, it was unlikely to be done in the pandemic setting, especially in intensive care patients who were intubated. Therefore, further studies are needed to investigate this issue.

CONCLUSION

Sarcopenia is independently associated with acute term in-hospital combined end-points including ICU admission, intubation, and mortality in patients with CAD and COVID-19. But, it does not affect results at a three-month mid-term follow-up.

Authors' Contribution

Study Conception: ME, İZ; Study Design: ME, İZ; Supervision: ME, İZ; Funding: ME, İZ; Materials: ME, İZ; Data Collection and/or Processing: ME, İZ; Statistical Analysis and/or Data Interpretation: ME, İZ; Literature Review: ME, İZ; Manuscript Preparation: ME, İZ and Critical Review: ME, İZ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

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