Original Investigation

# Prognostic Role of the Pectoralis Musculature in Patients with COVID-19. A Multicenter Study

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**Rationale and Objectives:** To evaluate the impact of low skeletal muscle mass in patients with COVID-19 on relevant outcomes like 30-day mortality, need for intubation and need for intensive care unit admission.

**Materials and Methods:** For this study, data from six centers were acquired. The acquired sample comprises 1138 patients. There were 547 women (48.1%) and 591 men (51.9%) with a mean age of $54.5 \pm 18.8$ years; median age, 55 years; range, $18-84$ years). In every case, thoracic CT without intravenous application of contrast medium was performed. The following parameters of the pectoralis muscles were estimated: muscle area as a sum of the bilateral areas of the pectoralis major and minor muscles, muscle density, muscle index (PMI) (pectoralis muscle area divided by the patient's body height square) as a ratio pectoralis major and minor muscles divided by the patient's body height$^2$, and muscle gauge as PMI x muscle density.

**Results:** Overall, 220 patients (19.33%) were admitted to the intensive care unit. In 171 patients (15.03%), mechanical lung ventilation was performed. Finally, 154 patients (13.53%) died within the observation time of 30-day. All investigated parameters of pectoralis muscle were lower in the patients with unfavorable courses of Covid-19. All pectoralis muscle parameters were associated with 30-day mortality in multivariate analyses adjusted for age and sex: pectoralis muscle area, HR = 0.93 CI 95% $(0.91-0.95)$ $p < 0.001$; pectoralis muscle density, HR = 0.94 CI 95% $(0.93-0.96)$ $p < 0.001$; pectoralis muscle index, HR = 0.79 CI 95% $(0.75-0.85)$ $p < 0.001$, pectoralis muscle gauge, HR = 0.995 CI 95% $(0.99-0.996)$ $p < 0.001$.

**Conclusion:** in COVID-19, survivors have larger areas and higher index, gauge and density of the pectoralis muscles in comparison to nonsurvivors. However, the analyzed muscle parameters cannot be used for prediction of disease courses.

**Key Words:** COVID-19; sarcopenia; survival.

## INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic represents a great problem for the global health. The clinical course of COVID-19 is very variable. In fact, although it has been identified that most patients had a relatively mild course, some patients still had a rapid progression with fatal outcome [1,2]. However, some patients had a rapid progression of disease with fatal outcome [1,2].

Therefore, prediction of unfavorable outcomes of COVID-19 is essential. Already established prognostic factors are age and sex [3,4]. Comorbidities, such as dementia, heart failure and peripheral vascular diseases are also predictors of an unfavorable course of the disease [3,4].

Computed tomography (CT) is the imaging modality of choice in COVID-19, especially for detection of pulmonary consolidations [5–7]. Typical imaging findings in COVID-19 are bilateral, peripheral dominant ground-glass opacities with lower lobe and posterior predilection [5–7].

Also, extrapulmonary findings play an important role in COVID-19 (8). It has been shown that pleural effusion, pericardial effusion and mediastinal lymphadenopathy can be used as predictors of severe course of COVID-19 (6,8). In fact, pleural effusion and coronary calcifications are strong predictors of mortality in COVID-19, odds ratio (OR) = 4.6 (95% CI 2.97−7.12), $p < 0.00001$, and OR = 2.68 (95% CI 1.78−4.04), $p < 0.00001$, respectively (8).

Similarly, low skeletal muscle mass (LSMM) measured on CT can also predict unfavourable courses of COVID-19 (9).

The purpose of the present multi-center study was to evaluate the impact of LSMM in COVID-19 patients on relevant outcomes like 30-day mortality, need for intubation and need for intensive care.

## METHODS

### Data Acquisition and Patients

This retrospective study was approved by our institutional review board (Medical Faculty, Otto-von-Guericke-University Magdeburg, number 145–21).

This study comprises data from six centers:

- Radiology Unit, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy;
- Department of Radiology, University of Hacettepe School of Medicine, Ankara, Turkey;
- Department of Radiology and Nuclear Medicine, Otto-von-Guericke University Magdeburg;
- Department of Radiology, University of Health Sciences, Bakirkoy Dr. Sadi Konuk Research and Training Hospital, Radiology;
- Department of Radiology, Mustafa-Kemal-University, Antakya, Turkey;
- Department of Radiology, Istanbul University, Istanbul, Turkey.
- In the centers, the data were acquired retrospectively. Inclusion criteria were as follows:
- diagnosis of COVID-19 confirmed by PCR;
- available thoracic CT images without intravenous administration of contrast medium;
- available data regarding the following clinical outcomes: 30-day mortality, need for mechanical ventilation, and admission on an intensive care unit.
- Exclusion criteria were as follows:
  - cases with missing data regarding the previously-mentioned outcomes;
  - CT images after intravenous application of contrast medium;
  - missing confirmation of COVID-19 infection by PCR.

The acquired sample comprises 1138 patients. There were 547 women (48.1%) and 591 men (51.9%) with a mean age of 54.5 ± 18.8 years; median age, 55 years; range, 18−84 years). In every case, thoracic CT without intravenous
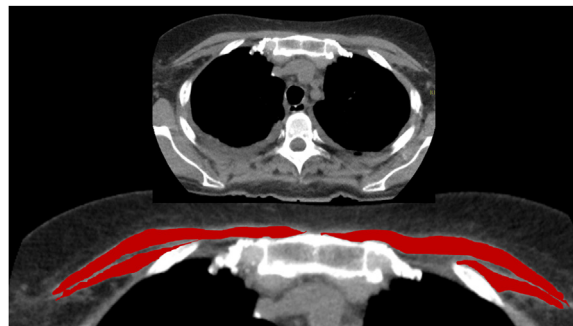


**Figure 1.** Imaging findings in a 55- year-old woman with COVID-19. Pectoralis muscle area = 14,48 cm$^2$, pectoralis muscle density = 28 HU, pectoralis muscle index = 5.19, pectoralis muscle gauge = 145.3. The patient died on the day 19 after admission. (Color version of figure is available online.)

application of contrast medium was performed on different clinical CT scanners or on each center's CT units.

### Measure of the Pectoralis Musculature on CT

In every case, the first CT scan of patients after hospital admission was used. In all six centers, measurements were performed by experienced radiologists blinded to the clinical course of patients. The measurements were performed on axial images at the T4 level in the soft tissue window on dedicated workstations. A polygonal region of interest (ROI) was drawn along the contours of the pectoralis major and minor muscles on both sides (Figs 1 and 2). Pectoralis muscle area (PMA) was defined as a sum of the bilateral areas of the pectoralis major and minor muscles. Furthermore, pectoralis muscle density was measured within the ROIs. Pectoralis muscle index (PMI) was calculated as a ratio PMA divided by the patient's body height square. Additionally, skeletal muscle gauge (SMG) was calculated by multiplying PMI with mean muscle density as reported previously (10).
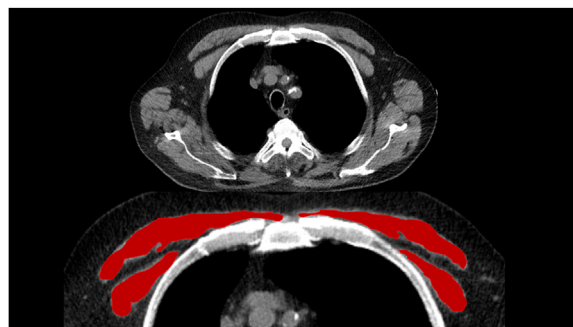


**Figure 2.** Imaging findings in a 61- year-old old man with COVID-19. Pectoralis muscle area = 28.17 cm$^2$, pectoralis muscle density = 30 HU, pectoralis muscle index = 8.69, pectoralis muscle gauge = 260.7. The patient was discharged in good health. (Color version of figure is available online.)

## Statistical Analysis

Statistical analysis was performed using the SPSS package (IBM SPSS Statistics for Windows, version 225.0, Armonk, NY: IBM corporation). Continuous variables were described by mean value, median and standard deviation. Categorical variables were given as relative frequencies. The comparison of pectoralis muscle parameters was performed by Mann-Whitney-U tests and the $p$-values were adjusted for multiple testing (Bonferroni correction). To assess the impact of the pectoralis musculature on clinical outcomes, uni- and multivariable logistic regression models were used to assess the impact of pectoralis muscle on clinical outcomes. Odds ratios are presented together with 95 % confidence intervals (95 % CI). In all instances, $p$values $< 0.05$ were taken to indicate statistical significance.

## RESULTS

The estimated values (Mean $\pm$ SD) of the pectoralis muscles were as follows: pectoralis muscle area, $28.91 \pm 13.60$ cm$^2$; skeletal muscle index, $10.85 \pm 4.47$ cm$^2$/m$^2$; pectoralis muscle density, $35.50 \pm 13.77$ HU; pectoralis muscle gauge, $401.30 \pm 251.87$.

Overall, 220 patients (19.33%) were admitted to intensive care unit. Furthermore, in 171 patients (15.03%), mechanical lung ventilation was performed. Finally, 154 patients (13.53%) died within the observation time of 30-day. All investigated muscle values or parameters of pectoralis muscles were lower in the patients with unfavorable courses of COVID-19 (Table 1).

Regression analysis identified that all pectoralis muscle parameters were associated with unfavorable courses (Table 2). Also, all pectoralis muscle parameters were associated with unfavorable courses after adjusting for age and sex (Table 3).

## DISCUSSION

The present study showed at the first time the prognostic role of the pectoralis musculature in COVID-19 based on a large sample in a multicenter setting.

According to the literature, parameters of body composition measured on cross sectional imaging techniques like CT play an important clinical role and are strong predictors for several relevant outcomes in different disorders (11−15). Importantly, muscle measurement is a by-product of cross-sectional imaging and does not need additional investigations. So far, in patients with abdominal trauma, low skeletal muscle mass on CT is significantly associated with longer hospitalization, longer intensive care length of stay, higher cost, higher frequency of mechanical ventilation, longer duration of vasopressor use, and higher incidence of massive transfusion and transfusion-related complications (11). Furthermore, in trauma patients, LSMM increases risk of 30-day mortality, RR = 1.60 CI 95% (1.21−2.13) and risk of 1-year mortality, RR = 3.11 CI 95% (1.94−4.96) (12).

There are numerous large meta-analyses suggesting that LSMM is an essential biomarker in oncology. In short, in lung cancer, LSMM is associated with a shorter overall survival HR = 2.23 CI 95% (1.68−2.94) (13). In head and neck cancer, LSMM is associated with occurrence of severe postoperative complications, OR = 4.79, CI 95% (2.52−9.11), and predicts disease free survival HR = 1.64, CI 95% (1.33−2.03), as well as overall survival, HR = 1.87, CI 95% (1.53−2.29) (14). Finally, LSMM predicts worse overall survival in gastric cancer, HR = 2.12, CI 95% (1.89−2.38) (15). Similar findings are known for pancreatic cancer, colorectal cancer, esophageal cancer, prostatic cancer, and malignant hematological diseases (16−20). In intensive care units, LSMM predicts short-term mortality, HR = 2.78 CI 95% (2.05−3.75) (21).

**TABLE 1. Comparison of the Pectoralis Muscle Parameters in Patients With COVID-19**

**a. Pectoralis Muscle Values and Need for ICU Admission**

| Muscle Parameters | No ICU Admission | ICU Admission | $p$ Values |
|---|---|---|---|
| Pectoralis muscle area, cm$^2$ | $29.80 \pm 14.17$ | $25.20 \pm 10.09$ | $<0.001$ |
| Pectoralis muscle density, HU | $37.29 \pm 12.98$ | $28.03 \pm 14.56$ | $<0.001$ |
| Pectoralis muscle index, cm$^2$/m$^2$ | $11.03 \pm 4.60$ | $9.23 \pm 3.54$ | $<0.001$ |
| Pectoralis muscle gauge | $436.77 \pm 252.03$ | $274.55 \pm 206.89$ | $<0.001$ |

**b. Pectoralis Muscle Values and Need for Mechanical Ventilation**

| Muscle Parameters | No Mechanical Ventilation | Mechanical Ventilation | $p$ Values |
|---|---|---|---|
| Pectoralis muscle area, cm$^2$ | $29.754 \pm 13.95$ | $24.156 \pm 10.16$ | $<0.001$ |
| Pectoralis muscle density, HU | $36.916 \pm 13.06$ | $27.484 \pm 15.06$ | $<0.001$ |
| Pectoralis muscle index, cm$^2$/m$^2$ | $11.242 \pm 4.53$ | $8.866 \pm 3.57$ | $<0.001$ |
| Pectoralis muscle gauge | $429.678 \pm 250.47$ | $257.508 \pm 206.24$ | $<0.001$ |

**c. Pectoralis Muscle Values and 30-day Mortality**

| Muscle Parameters | Survivors | Nonsurvivors | $p$ Values |
|---|---|---|---|
| Pectoralis muscle area, cm$^2$ | $30.189 \pm 13.74$ | $20.757 \pm 9.13$ | $<0.001$ |
| Pectoralis muscle density, HU | $36.841 \pm 13.15$ | $26.929 \pm 14.71$ | $<0.001$ |
| Pectoralis muscle index, cm$^2$/m$^2$ | $11.277 \pm 4.49$ | $8.0365 \pm 3.15$ | $<0.001$ |
| Pectoralis muscle gauge | $428.305 \pm 250.02$ | $223.505 \pm 182.80$ | $<0.001$ |

**TABLE 2.** Associations Between Pectoralis Muscle Values and Unfavorable Outcomes in COVID-19 (Univariate Analysis)

**a. Associations Between Pectoralis Muscle Values and Need for Intensive Care Admission**

| Muscle Parameters | OR | CI95% | p Values |
|---|---|---|---|
| Pectoralis muscle area, $cm^2$ | 0.97 | (0.96, 0.98) | <0.001 |
| Pectoralis muscle density, HU | 0.95 | (0.93, 0.96) | <0.001 |
| Pectoralis muscle index, $cm^2/m^2$ | 0.88 | (0.85, 0.92) | <0.001 |
| Pectoralis muscle gauge | 0.996 | (0.996, 0.997) | <0.001 |
| **b. Associations Between Pectoralis Muscle Values and Need for Mechanical Ventilation** | | | |
| Pectoralis muscle area, $cm^2$ | 0.97 | (0.95, 0.98) | <0.001 |
| Pectoralis muscle density, HU | 0.95 | (0.93, 0.96) | <0.001 |
| Pectoralis muscle index, $cm^2/m^2$ | 0.86 | (0.82, 0.90) | <0.001 |
| Pectoralis muscle gauge | 0.996 | (0.995, 0.997) | <0.001 |
| **c. Associations Between Pectoralis Muscle Values and 30-day Mortality** | | | |
| Pectoralis muscle area, $cm^2$ | 0.93 | (0.91, 0.95) | <0.001 |
| Pectoralis muscle density, HU | 0.94 | (0.93, 0.96) | <0.001 |
| Pectoralis muscle index, $cm^2/m^2$ | 0.79 | (0.75, 0.85) | <0.001 |
| Pectoralis muscle gauge | 0.995 | (0.993, 0.996) | <0.001 |

In COVID-19, data concerning the role of LSMM are mixed (9,22−25). So far, Schiaffino et al. indicates that LSMM is strongly associated with either ICU admission, OR = 4.8, CI 95% (2.7−8.5), $p < 0.001$ and mortality, OR = 2.3, CI 95% (1.0−2.9), $p < 0.027$ (9). Kim et al. reports that LSMM is associated with prolonged hospital stay in patients with COVID-19 but not with mortality (22). However, other authors do not report significant relationships between LSMM and relevant outcomes in patients with COVID-19 (24,25). For example, according to Moctezuma-Velázquez et al., skeletal muscle index is not associated with negative outcomes, such as in-hospital mortality, need of invasive mechanical ventilation, and intensive care unit admission, in hospitalized patients with COVID-19 (24).

Our results based on the largest cohort to date show that all pectoralis muscle values including muscle area, index, density and gauge are statistically significant higher in survivors vs nonsurvivors. It indicates that patients with more metabolic reserve and predominance of anabolic processes may have a better prognosis. However, according to the regression analysis, the investigated pectoralis muscle parameters cannot discriminate patients with favorable vs unfavorable disease courses. This finding suggests that the status of the pectoralis musculature cannot be used for patients stratifying in COVID-19.

Associations between LSMM and unfavorable courses of COVID-19 are multifactorial. The presence of LSMM may reflect a state of malnutrition and/or catabolism. It is also known that anemia and hypoalbuminemia are associated with low muscle density (26). Furthermore, there are significant interactions between the skeletal musculature and immune system. So far, skeletal muscles release numerous myokines with autocrine, paracrine, and immune effects (27). For instance, interleukin (IL)-15 is a myokine that stimulates proliferation and activation of natural killer cells and CD8+

**TABLE 3.** Associations Between Pectoralis Muscle Values and Unfavorable Outcomes in COVID-19 (Multivariate Analysis)

**a. Associations Between Pectoralis Muscle Values and Need for Intensive Care Admission**

| Muscle Parameters | OR | CI95% | p Values |
|---|---|---|---|
| Pectoralis muscle area, $cm^2$ | 0.99 | (0.98, 1.007) | 0.391 |
| Pectoralis muscle density, HU | 0.96 | (0.95, 0.97) | <0.001 |
| Pectoralis muscle index, $cm^2/m^2$ | 0.94 | (0.90, 0.99) | <0.001 |
| Pectoralis muscle gauge | 0.998 | (0.997, 0.999) | <0.001 |
| **b. Associations Between Pectoralis Muscle Values and Need for Mechanical Ventilation** | | | |
| Pectoralis muscle area, $cm^2$ | 0.98 | (0.97, 0.99) | 0.033 |
| Pectoralis muscle density, HU | 0.96 | (0.94, 0.97) | <0.001 |
| Pectoralis muscle index, $cm^2/m^2$ | 0.87 | (0.87, 0.96) | <0.001 |
| Pectoralis muscle gauge | 0.997 | (0.996, 0.999) | <0.001 |
| **c. Associations Between Pectoralis Muscle Values and 30-day Mortality** | | | |
| Pectoralis muscle area, $cm^2$ | 0.96 | (0.94, 0.98) | <0.001 |
| Pectoralis muscle density, HU | 0.96 | (0.95, 0.98) | <0.001 |
| Pectoralis muscle index, $cm^2/m^2$ | 0.86 | (0.80, 0.91) | <0.001 |
| Pectoralis muscle gauge | 0.996 | (0.995, 0.998) | <0.001 |

T lymphocytes (28). These cells play an essential role in anti-viral immune defense (28). Furthermore, IL 15 induces activation and phagocytosis of neutrophils (29). IL 15 also delays human neutrophil apoptosis (30). Presumably, in patients with reduced muscle quantity and/or quality a smaller number of myokines is produced.

Notably, different measurements and values for estimation of LSMM in patients with COVID-19 are used. According to the literature, SMI estimation on CT at the level of the third lumbar vertebra (L3) represents a standardized method to quantify the skeletal musculature (31). In patients with COVID-19, often only thoracic CT investigations for the analysis of pulmonary damage are performed. Therefore, the estimation of the standardized SMI values at the L3 level is impossible. Hence, in the previous studies, other vertebral levels for the quantification of the skeletal musculature are proposed, such as thoracic vertebra 5 (32), thoracic vertebra 12 (22,24,33), or lumbar vertebra 1 (34).The pectoralis muscles as surrogate marker is also used (35,36).

The present study has several limitations. Firstly, it is based on retrospective cohorts. Secondly, only patients, who underwent CT investigations without intravenous administration of contrast medium, were included. Thirdly, we did not analyze virus subtypes in our patients. It is well known that several viruses provoke different disease severity. However, to date, it is the largest multicenter cohort and our results represent evidence based data regarding associations between skeletal musculature and clinical outcomes in COVID-19.

In conclusion, in COVID-19, survivors have larger areas and higher index, gauge and density of the pectoralis muscles in comparison to nonsurvivors. However, the analyzed muscle parameters cannot be used for prediction of disease courses.

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