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Muscle ultrasonographic changes in critically ill COVID-19 patients

Cambios ultrasonográficos musculares en pacientes críticamente enfermos con COVID-19.

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Abstract

Background: Patients with severe forms of COVID-19 (coronavirus disease 2019) present a systemic inflammatory response and hypermetabolism. The objective of this study was to identify the change in muscle mass of the rectus femoris and vastus internal in patients with severe COVID-19 who required invasive mechanical ventilation and to establish the correlation between the change in muscle size and the amount of calories and proteins administered.

Materials & Methods: This prospective observational longitudinal study was conducted in the adult intensive care unit in a tertiary care clinic. Muscle mass was measured with ultrasound from admission, with intervals of seven days, until discharge from the unit. Anthropometric and biochemical data and the amount of calories and proteins administered were taken into account.

Results: A total of 39 patients were included (59.6 ± 11.3 years; 79.5% men) with a median BMI of 27.7 kg/m2 (IQR 24.2–29.7). The size of the rectus femoris and vastus internal had diminished significantly at seven days of hospitalization: right middle third 0.38 cm (IQR 0.16-0.47), left middle third 0. 29 cm (IQR 0.08-0.54) and right middle third 0.37 cm (IQR 0.11-0.71) left middle third 0.25 cm (IQR 0.09-0.52), respectively. The changes in both muscles were directly correlated with caloric and protein intake during nutritional support.

Conclusions: It is observed that critically ill patients with COVID-19 progressively lost muscle mass by receiving less coverage of caloric and protein requirements.

Keywords: SARS-CoV-2, malnutrition, ultrasonography, critical care

Resumen

Introducción: Los pacientes con formas graves de COVID-19 (enfermedad por coronavirus 2019) presentan una respuesta inflamatoria sistémica e hipermetabolismo. El objetivo de este estudio fue identificar el cambio en la masa muscular del recto femoral y vasto interno en pacientes con COVID-19 grave que requirieron ventilación mecánica invasiva y establecer la correlación entre el cambio en el tamaño muscular y la cantidad de calorías y proteínas administradas.

Materiales y métodos: Este estudio longitudinal observacional prospectivo, se realizó en la unidad de cuidados intensivos para adultos en una clínica de atención terciaria. La masa muscular se midió con ecografía desde el ingreso, con intervalos de siete días, hasta el alta de la unidad. Se

tuvieron en cuenta los datos antropométricos y bioquímicos y la cantidad de calorías y proteínas administradas.
Resultados: Se incluyeron un total de 39 pacientes (59,6 ± 11,3 años; 79,5% hombres) con una mediana de IMC de 27,7 kg/m2 (IQR 24,2-29,7). El tamaño del recto femoral y del vasto interno había disminuido significativamente a los siete días de hospitalización: tercio medio derecho 0,38 cm (IQR 0,16-0,47), tercio medio izquierdo 0. 29 cm (IQR 0.08-0.54) y tercio medio derecho 0.37 cm (IQR 0.11-0.71) tercio medio izquierdo 0.25 cm (IQR 0.09-0.52), respectivamente. Los cambios en ambos músculos se correlacionaron directamente con la ingesta calórica y proteica durante el apoyo nutricional.
Conclusiones: Se observa que los pacientes críticos con COVID-19 perdieron progresivamente masa muscular al recibir una menor cobertura de requerimientos calóricos y proteicos.

Palabras clave: SARS-CoV-2, desnutrición, ecografía, cuidados intensivos

INTRODUCTION

The new strain of coronavirus called SARS-CoV-2 (severe acute respiratory syndrome coronavirus type 2) is the causative agent of coronavirus disease 2019 (COVID-19), which was described in China in late 2019 and was declared a pandemic in March 2020. It has been found that 10% of infected people have severe symptoms, and 5% progress to a critical state, requiring hospitalization and/or a stay in the intensive care units (ICUs) for additional supply of oxygen, noninvasive, or invasive mechanical ventilation [1]. Patients admitted to the ICU lose weight, particularly muscle mass, due to bedrest, reduced nutritional intake, and inflammation associated with critical illness [2-4]. Consequently, loss of muscle mass can lead to a prolonged hospital stay, failed extubation, increased care costs, and heightened morbimortality. Likewise, the long-term forecast for patients who survive intensive care is affected by the deterioration of physical, mental, and cognitive functions, known as debility acquired in the ICU [5]. In addition, it is estimated that 20% of patients admitted to the ICU already present a loss of muscle mass to varying degrees. Not only in size but also in functionality, this is due to a combination of critical illness myopathy and polyneuropathy [4].

Similarly, it has been described that a loss of 1% of the size of the rectus femoris during the first week of critical illness is associated with an increase of 5% in the possibility to pass away in 60 days [5]. Hence, it is important to monitor the volume and quality of muscle mass in ICU patients. As a result, bedside ultrasound has become valuable tool to observing changes in the size and quality of muscle mass, given that it is a low-cost technique, and the equipment allows easy transportation [6-8]. The process is non-invasive and is conducted through the measurement of muscle volume in the quadriceps and the rectus femoris. It is important to consider that most of the accurate muscle mass measurement methods and techniques (i.e., bioimpedance analysis, DEXA, and computed tomography scan) are not routinely feasible in clinical ICU practice [4]. Therefore, in recent years, the use of ultrasound in assessing muscle mass in critically ill patients has gained much attention. The objective of this study was to 1) identify the evolution of the muscle mass of the rectus femoris and vast interior in patients with severe COVID-19 who required invasive mechanical ventilation, 2) analyze the correlation between the change in muscle size and the number of calories and proteins provision.

MATERIALS AND METHODS

This was a prospective observational longitudinal study of a diagnostic intervention carried out at the Santa María del Lago Children's Clinic in Bogotá from June 1 to August 30, 2020. Patients who met the following inclusion criteria were recruited: 1) age ≥18 years and 2) admitted to the ICU for confirmed illness associated with COVID-19 with a requirement for invasive ventilatory support. The exclusion criteria were a stay of less than 24 hours in the ICU and a high risk of short-term mortality or imminent death.

Patients who met the inclusion criteria underwent quadriceps muscle layer thickness measurement (QMLT) through the rectus femoris and vastus internal, serially every week (Days 7, 14, and 21) until discharge from the ICU. In addition, clinical data were collected, such as sedation requirement, vasopressor support, neuromuscular relaxation, route of nutritional support, grams per kg of prescribed protein, calories per kg prescribed, percentage of caloric and protein coverage, and state at discharge from the ICU.

To quantify the caloric and protein intake, the data from the ICU nursing records of the volume of nutrition supplied were selected, then the caloric and protein intake of the day was calculated according to the volume of the product supplied to the patient. This record was made daily until the day the patient stopped receiving nutrition. It should be noted that the calories provided by propofol and hemodialysis were not counted.

The weight of the patients is obtained from the ICU nursing record, which was obtained by means of a scale before invasive ventilation, and the patients who entered the unit ventilated, the information was reported by relatives.

To establish the nutritional diagnosis of malnutrition, the GLIM criteria were taken into account [9]. To determine the excess weight, the BMI classification given by the World Organization was used (BMI= weight in kg/m2 of 25–29.9 Overweight, 30–34.9 kg/m^2 Obesity type 1, 35-35.9 kg/m^2 obesity type 2, and >40 kg/m^2 obesity type 3) [10]. The nutritional requirements calculation in terms of calories and proteins was in accordance with ESPEN expert statements and practical guidance for nutritional management of individuals with SARS-CoV-2 infection [11].

Description of the quadriceps muscle layer thickness measurement technique by ultrasonography

The quadriceps muscle layer thickness (QMLT) was measured by ultrasonography with the Mindray DC-70 X-Insight equipment with a linear transducer with the technique validated in critical patients and described in the study of Gruther and collaborators with a coefficient of variation of 1.3%. This measurement includes the vastus internal and rectus femoris, referred to as QMLT. The patient is placed in a supine position with the legs relaxed and in extension. With the transducer at 90° of the thighs and in maximum compression, two measurements are made at different thigh heights in both legs, and then the average of the four measurements was calculated. The first reading was made at the midpoint of a drawn line of the anterior superior iliac spine (ASIS) at the upper edge of the patella. The second reading was at the level of the junction of the middle third with the lower third of a line drawn from the ASIS to the upper edge of the kneecap [12].

Before the measurement, staff training was carried out for two weeks with a radiology specialist to perform the identification of the rectus femoris muscle and vast internal means. The measurement was carried out in the period of June-August 2020, with weekly follow-up until discharge from the intensive care unit.

The present study was approved by the Research Ethics Committee of the University Institution Unisanitas - CEIFUS 1787-20.

Statistical analysis

Categorical variables by absolute and relative frequencies and quantitative variables by measures of central tendency and dispersion are presented. Descriptive results are presented as mean ± standard deviation or median with interquartile range. The Shapiro-Wilk test was used to assess normality. The prevalence of a lack of physical conditioning was calculated by subgroups of sex, age, ventilation strategy, and nutritional diagnosis at admission. For subgroup analysis, absolute and relative frequencies were also calculated. The Wilcoxon range statistic was performed to measure the statistical significance between the first and second ultrasound observations for the eight measurements (7-day difference in measurement). Finally, the relationship between the loss of muscle mass to the second measurement concerning caloric and protein coverage was graphed using a scatter plot for the eight observations. All analyses were run on Stata version 15 statistical software licensed for Unisanitas.

RESULTS

The study included a total of 39 patients, with an average age of 59.6 years (±11.3), 79.5% male, with a median ICU stay of 13 days (IQR 8-23), and a mortality of 33% (Table 1).

Muscle mass through ultrasound measurement

All patients were measured at least on Day 1 and Day 7. The maximum follow-up number corresponded to 4 ultrasound measurements. The initial measurement was made between the first 24 and 48 hours of orotracheal intubation, and then the follow-up measurements were made at 7 (± 0.5), 14 (± 0.5), and 21 (± 1) days. Table 2 shows the variation in muscle mass per week of the patients included, and comparing measurements on Day 1 with Day 7 showed significant differences. Figures 1 and 2 show the percentages of reduction of muscle mass in the rectus femoris and vast interior through the days in the ICU and the serial measurements performed.

Muscle mass and administration of protein-caloric nutritional requirements

Scatter plots were made to establish the correlation between the coverage of caloric requirements, proteins, and loss of muscle mass. We observed a trend between a better caloric and protein administration, and less muscle loss at the level of the rectus femoris and vast internal means (Figures 3 and 4).

DISCUSSION

The main objective of the present work was to evaluate the percentage loss of muscle mass of the rectus femoris and vast internal means and to compare it with the intake of caloric and protein requirements in patients diagnosed with COVID-19 who required invasive mechanical ventilation between June and August 2020. The results obtained provide evidence that people diagnosed with COVID-19 have a loss of muscle mass during their stay in the ICU and when the coverage of calorie and protein requirements is lower.

Several authors agree that the loss of muscle mass in ICU patients with invasive mechanical ventilation can be affected by factors such as immobilization during sedation, the use of neuro relaxants, corticosteroids, sepsis, hyperglycemia, and the use of insulin [13-15]. In the present study, an important prevalence of these factors was observed, where 69% of the patient's required sedation, 41% required neuromuscular relaxation, 63% initiated vasopressor support, and in some cases required insulin infusion for better metabolic control as therapeutic management.

Parry et al. [6] in 2015 reported that the decrease in the rectus femoris and the vast interior during the first 10 days produced a loss of its mass close to 30% concerning its initial mass of stay in the ICU. These results are similar to those found in our study, with a loss in the first 14 days of 37% in the right middle third and 30.4% in the left middle third in the rectus femoris.

Similarly, Puthucheary et al. [16] measured the muscle volume of the rectus femoris and vast interior using ultrasound and histopathological analysis on the first, seventh, and tenth days of their ICU stay in patients on mechanical ventilation. On Day 7, there was a loss of 12% of muscle mass, and three days later, it increased to 17% [16]. Lee et al. [8] performed ultrasound measurements of patients with mechanical ventilation in the ICU in the first seven days and showed a decrease between 8 and 19% of the muscle mass of the rectus femoris and at Day 14 a loss between 15 and 25% of muscle mass. In the present study, the decrease in muscle mass of the rectus femoris was greater in the first week than in the two studies previously described.

Three different authors reported a decrease of 1 to 3% per day in muscle mass in ventilated patients with different pathologies [8,15,16]. Bury et al. [17] showed a decrease in quadriceps muscle mass of 2% per day in patients with major abdominal surgery. Our study reports that muscle loss from ventilated patients with COVID-19 is double that reported in the literature in mechanically ventilated patients with different comorbidities.

As for possible relevant factors in the loss of muscle mass in the ICU, the study by Puthucheary et al. [16] reported a greater loss of muscle mass in patients who were ventilated for respiratory disease, followed by patients with abdominal surgeries. Additionally, other factors increase this loss of muscle mass, such as the involvement of two organs or more during the stay in the ICU [18]. We observed in the study that the patients not only had respiratory failure but that 61.3% simultaneously presented hemodynamic instability and 41% required the use of neurorelaxation to favor the coupling to the ventilator and comply with the supine-pronation cycles.

Weijs et al. [19], in a prospective study, showed that when both protein and energy targets were achieved in mechanically ventilated ICU patients, there was a 50% reduction in mortality at 28 days, while if only energy targets were achieved, it was not associated with a reduction in mortality. Considering the recommendations of ESPEN for the management of patients with

COVID-19, which suggest a caloric intake between 25 and 30 kcal/kg/day and a protein intake of 1.3 and 1.5 g/kg/day [11]; it is observed that in our study, the calorie prescription was 23 kcal/kg and 1.26 g/kg of protein, with a requirement coverage of 81,9% and 80,4%, respectively, with a mortality of 33% of patients.

LIMITATIONS

The main limitation of the study was the number of patients included (n = 39), and the loss to follow-up was given by mortality 33% (n = 13), and the median stay in the ICU was 13 days (IQR 8-32), on the other hand, the nutritional contribution did not include the calories of dextrose or propofol. Therefore, a cohort with a greater number of patients is needed, which mitigates these limitations due to the lethality of the disease, promoting multicenter studies. On the other hand, the ultrasound measurement is observer-dependent, and the present study did not present a consistency analysis through the kappa coefficient, given the exposure time required for the measurement in patients with COVID-19.

CONCLUSION

The present study shows that the loss of muscle mass is progressive in critically ill patients with COVID and is probably proportional to the coverage of caloric and protein requirements. Therefore, it becomes relevant to carry out objective monitoring of muscle mass in critical patients, nutritional objectives, and therapeutic objectives with an interdisciplinary approach to mitigate the weakness acquired in the ICU of patients suffering from COVID-19.

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AUTHOR CONTRIBUTIONS

Torres J: Writing - Original Draft, Writing – Review and Editing, Visualization. Merchan-Chaverra R: Data Collection, Writing - Original Draft, Writing - Review and Editing, visualization, Project administration, Funding acquisition. Cuellar- Fernández Y: Writing - Original Draft, Writing – Review and Editing, Visualization. Medina-Parra J: Methodology, Software, Formal analysis, Data Curation. Cárdenas D: Review and Editing, Visualization. All authors have reviewed the manuscript, agree to be fully responsible for ensuring the completeness and accuracy of the paper, and have read and approved the final manuscript.

CONFLICT OF INTEREST

The authors Torres J and Medina-Parra J, declare they don’t have conflict of interest in this work. The author Merchan-Chaverra R, have been a speaker for Boydorr nutrition, Abbott nutrition, Baxter, Fresenius Kabi, Medtrition, B-braun, Amarey nova medical.

The author Cuellar -Fernández Y, have been a speaker for Boydorr nutrition, Alpina, Abbott nutrition.

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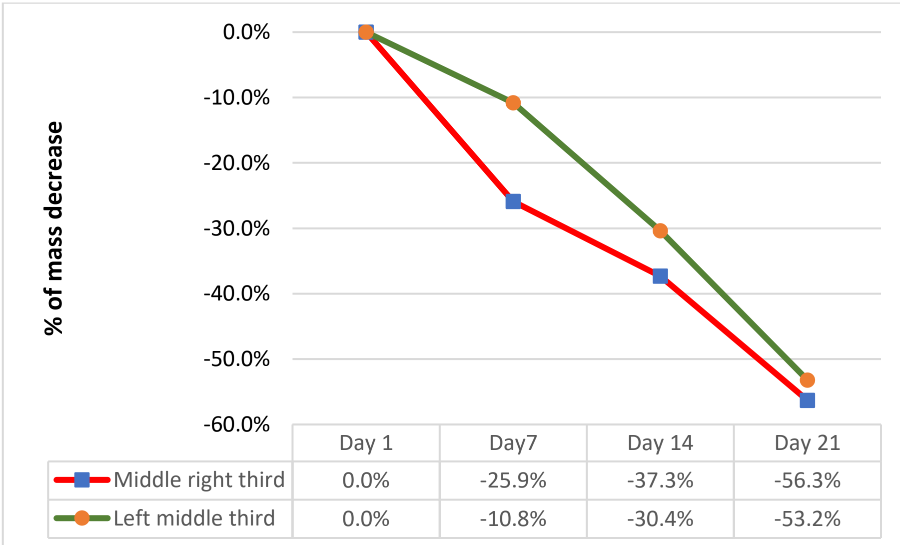
FIGURE AND TABLE

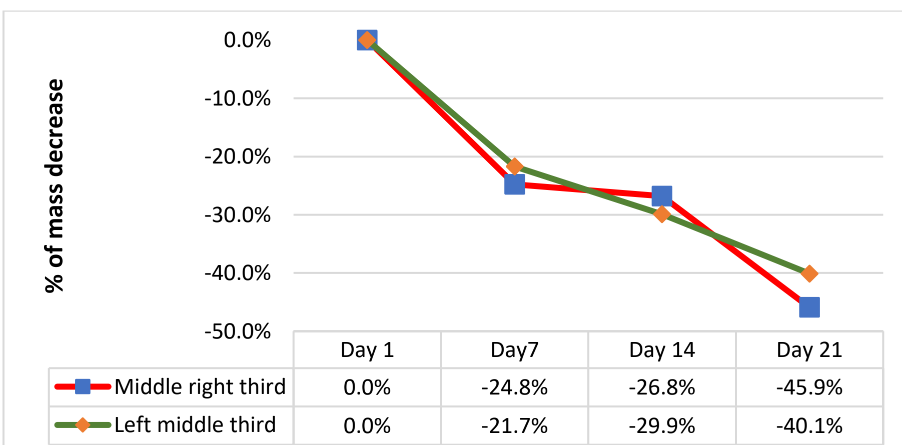
Figure 1. Percentage of mass decrease in the rectus femoris of ICU patients with COVID-19.



	Day 1	Day7	Day 14	Day 21
Middle right third	0.0%	-25.9%	-37.3%	-56.3%
Left middle third	0.0%	-10.8%	-30.4%	-53.2%

The decrease in muscle mass of the right and left rectus femoris in the first week is approximately 25% and 10%, respectively, in the second week of 37% in the right and 30% in the left, and the third week a decrease of 50% in relation to the initial measure.

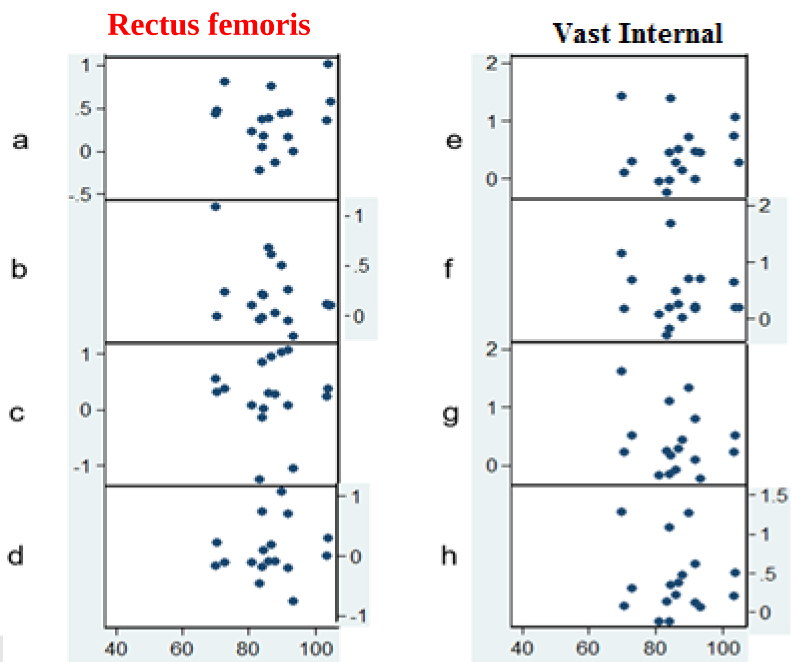
Figure 2. Percentage decrease in the mass of the vast internal of patients in the ICU with COVID-19. -



	Day 1	Day7	Day 14	Day 21
Middle right third	0.0%	-24.8%	-26.8%	-45.9%
Left middle third	0.0%	-21.7%	-29.9%	-40.1%

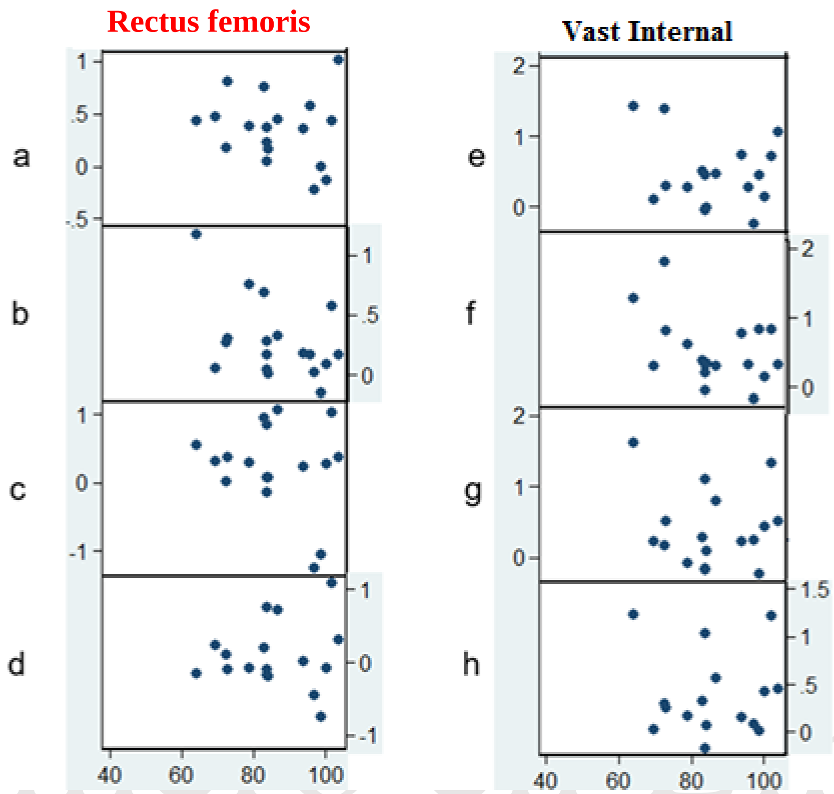
The decrease in muscle mass of the right and left vastus internal in the first week is approximately 24% and 21%, respectively, in the second week of 26% in the right and 29% in the left, and the third week a decrease of 40% in relation to the initial measure.

Figure 3. Correlation between the loss of muscle mass and coverage of caloric intake during nutritional support.



(a) Distal middle third. (b) Distal middle third contracted. (c) Middle internal third. (d) Internal middle third contracted. (e) Distal middle third. (f) Distal middle third contracted. (g) Internal middle third. (h) Contracted middle third.

Figure 4. Correlation between the loss of muscle mass and protein intake coverage during nutritional support.



(a) Distal middle third. (b) Distal middle third contracted. (c) Middle internal third. (d) Internal middle third contracted. (e) Distal middle third. (f) Distal middle third contracted. (g) Internal middle third. (h) Internal middle third contracted.

Table 1. Clinical and nutritional characteristics of patients admitted to the ICU with a diagnosis of SARS/VOC 2 and COVID-19 infection.

	Frequency n= 39
Age (Mean/SD)	59,6 (11,3)
Gender (Male) n (%)	31(79,5)

With nutritional support n (%)	37 (94,9)
Weight kg (Mean/SD)	76,1(11,7)
Height cm (Mean /SD)	166,2 (8,1)
ICU days (Median/IQR)	13 (8-23)
Sedation (%)	27 (69,2)
Hemodynamic support	
Vasopressor (%)	23 (59)
Vasopressor and inotropic (%)	1 (2,6)
Neuromuscular relaxation (%)	16 (41)
Hospital discharge	
Alive (%)	26 (66,7)
Dead (%)	13 (33,3)
Nutritional diagnosis	
Moderate malnutrition (%)	1 (2,6)
Eutrophic (%)	13 (34,2)

Overweight (%)	14 (36,8)
Obesity Grade I (%)	7 (18,4)
Obesity Grade II (%)	2 (5,3)
Obesity Grade III (%)	1 (2,6)
Type of nutrition support	
Enteral nutrition (%)	36 (97,3)
Mixed nutrition (%)	1 (2,7)
Nutritional support days (Median/IQR)	9 (6-15)
Prescribed protein: g/kg/day (Mean/SD)	1,26 (0,16)
Average protein covering % (Mean/SD)	81,9 (14,8)
Prescribed kilocalorie: Kcal/kg/day (Medium/DS)	23,1 (4,3)
Average caloric covering: % (Medium/SD)	80,4 (15,8)

SD: Standard deviation; IQR: Interquartile range

Table 2. Evolution of muscle mass per week of ICU patients diagnosed with SARS/COV 2 infection, COVID-19.

	Day 1	**Day 7**	**Day 14**	**Day 21**	**Change Day 1 to 7**	**1 to 7 days (p-value)**
Internal Femoral Rectum (Median cm/IQR)						
Right middle third	1,58 (1,21-1.83)	1,13 (0,97-1,37)	0,99 (0,76-1,23)	0,69 (0.29,1.1)	0,38 (0,16-0,47)	<0.001

Right middle third contracted	1,12 (0,83-1,40)	0,77 (0,59-0,91)	0,74 (0,52-0,85)	0,57 (0.26,0.89)	0,17 (0,05-0,32)	0,002
Left middle third	1,50 (1,14-2,0)	1,23 (1,06-1,69)	1,22 (0,76-1,29)	0,74 (0.29,1.2)	0,29 (0,08-0,54)	0,149
Left middle third contracted	1,03 (0,87-1,42)	0,94 (0,72-1,34)	0,85 (0,57-1,00)	0,49 (0.2,0.78)	0,03 (-0,06-0,34)	0,119
Vast Internal (Median cm/IQR)						
Right middle third	1,54 (1,24-1,92)	1,22 (0,94-1,28)	1,27 (0,75-1,42)	0,85 (0,36-1,34)	0,37 (0,11-0,71)	0,001
Right middle third contracted	1,08 (0,94-1,45)	0,85 (0,58-0,98)	0,82 (0,63-0,95)	0,53 (0,26-0,81)	0,215 (0,18-0,69)	0,002
Left middle third	1,44 (1,21-1,81)	1,18 (1,06-1,44)	1,12 (0,80-1,36)	0,94 (0,36-1,53)	0,25 (0,09-0,52)	0,006
Left middle third contracted	1,10 (0,93-1,48)	0,9 (0,78-1,00)	0,89 (0,66-1,05)	0,63 (0,29-0,97)	0,26 (0,08-0,46)	0,004

Median cm/IQR, *IQR: Interquartile Range*