



Muscle ultrasonographic changes in critically ill COVID-19 patients

Cambios ultrasonográficos musculares en pacientes críticamente enfermos con COVID-19

Alterações musculares ultrassonográficas em pacientes críticos com COVID-19

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Summary

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 rectus femoris and vastus medialis muscle mass 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, at seven-day intervals, until discharge from the unit. Anthropometric and biochemical data as well as 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/m^2 (IQR 24.2–29.7). The size of the rectus femoris and vastus medialis muscles 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

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 el 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 (UCI) para adultos en una clínica de atención terciaria. La masa muscular se midió al ingreso con ecografía, 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 ($59,6 \pm 11,3$ años; 79,5 % hombres) con una mediana de índice de masa corporal (IMC) de $27,7 \text{ kg/m}^2$ (rango intercuartílico [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-

Resumo

Introdução: Pacientes com formas graves de COVID-19 (doença por coronavírus 2019) apresentam resposta inflamatória sistêmica e hipermetabolismo. O objetivo deste estudo foi identificar a alteração na massa muscular do reto femoral e vasto medial em pacientes com COVID-19 grave que necessitaram de ventilação mecânica invasiva e estabelecer a correlação entre a alteração no tamanho do músculo e a quantidade de calorías e proteínas administradas.

Materiais e métodos: Este estudo prospectivo observacional longitudinal foi realizado na unidade de terapia intensiva de adultos de um hospital de atenção terciária. A massa muscular foi medida com ultrassonografia desde a admissão, em intervalos de 7 dias, até a alta da unidade. Foram levados em consideração os dados antropométricos e bioquímicos e a quantidade de calorías e proteínas administradas.

Resultados: Foram incluídos 39 pacientes ($59,6 \pm 11,3$ anos; 79,5% homens) com mediana de IMC de $27,7 \text{ kg/m}^2$ (IQR 24,2-29,7). O tamanho do reto femoral e do vasto medial tinha diminuído significativamente aos sete dias de hospitalização: terço médio direito 0,38 cm (IQR 0,16-0,47), terço médio esquerdo 0,29 cm (IQR 0,08-0,54) e terço médio direito 0,37 cm (IQR 0,11-0,71) e terço médio esquerdo 0,25 cm (IQR 0,09-0,52), respectivamente. As alterações em ambos os músculos foram diretamente correlacionadas com



with caloric and protein intake during nutritional support.

Conclusions: Critically ill patients with COVID-19 were found to lose muscle mass progressively as a result of lower coverage of caloric and protein requirements.

Keywords: SARS-CoV-2; Malnutrition; Ultrasonography; Critical care.

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 la masa muscular al recibir una menor cobertura de requerimientos calóricos y proteicos.

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

a ingestão calórica e protéica durante o suporte nutricional.

Conclusões: Observa-se que pacientes críticos com COVID-19 perderam massa muscular progressivamente ao receber menor cobertura das necessidades calóricas e proteicas.

Palavras-chave: SARS-CoV-2, desnutrição, ultrassonografia, cuidados intensivos.

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INTRODUCTION

SARS-CoV-2 (severe acute respiratory syndrome coronavirus type 2), the new coronavirus strain, is the causal agent of coronavirus disease 2019 (COVID-19) described in China in late 2019 and 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 admission to the intensive care unit (ICU) for additional supply of oxygen and non-invasive 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 morbidity and mortality. Likewise, the long-term prognosis for patients who survive intensive care is affected by the deterioration of physical, mental, and cognitive functions, known as ICU-acquired weakness⁽⁵⁾. In addition, it is estimated that 20% of patients admitted to the ICU already present varying degrees of loss of muscle mass loss, not only in terms of size but also of 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 a 5% increase in the possibility

of dying within the next 60 days⁽⁵⁾. Consequently, it is important to monitor the volume and quality of muscle mass in ICU patients. As a result, bedside ultrasound has become a valuable tool to observe changes in muscle mass size and quality, because of its low cost and portability⁽⁶⁻⁸⁾. The process is non-invasive and is based on quadriceps and rectus femoris muscle volume measurements. 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 muscle mass evolution in the rectus femoris and vastus medialis of patients with severe COVID-19 who required invasive mechanical ventilation, and 2) analyze the correlation between the change in muscle size and the number of calories and proteins provided.

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) ICU admission due to confirmed COVID-19-

associated illness requiring 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 serial quadriceps muscle layer thickness measurement (QMLT) through the rectus femoris and vastus medialis every week (Days 7, 14, and 21) until discharge from the ICU. In addition, clinical data were collected, including 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 patient status on discharge from the ICU.

To quantify caloric and protein intake, data from the ICU nursing records regarding the volume of nutrition supplied were selected for estimating daily energy and protein intake based on 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 was obtained from the ICU nursing record. This measurement was done using a scale before initiation of invasive ventilation. In patients who arrive at the unit already on ventilation, the information was provided by the relatives.

GLIM criteria were taken into account to establish the nutritional diagnosis of malnutrition⁽⁹⁾. The World Health Organization classification of BMI was used to determine excess weight (BMI= weight in kg/m² of 25–29.9 overweight; 30–34.9 kg/m² obesity type 1; 35–39.9 kg/m², obesity type 2; and >40 kg/m² obesity type 3)⁽¹⁰⁾. Nutritional requirements in terms of calories and proteins were calculated 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 using a linear transducer and the technique validated in critical patients and described in the study by Gruther and collaborators with a coefficient of variation of 1.3%. This measurement includes the vastus medialis 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 were 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 line drawn from the anterior superior iliac spine (ASIS) to the upper edge of the patella. The second reading was at the level of the junction between the middle third and the lower third of a line drawn from the ASIS to the upper edge of the patella⁽¹²⁾.

Before the measurement, staff were trained by a radiology specialist to ensure proper identification of the rectus femoris muscle and the vastus medialis. Measurements were carried out in the period of June-August 2020, with weekly follow-up until discharge from the intensive care unit.

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

STATISTICAL ANALYSIS

Categorical variables by absolute and relative frequencies and quantitative variables by measures of central trend and scatter are presented. Descriptive results are presented as mean \pm 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 a mean age of 59.6 years (\pm 11.3), 79.5% male, with a median ICU stay of 13 days (IQR 8-23), and mortality of 33% (Table 1).

Table 1. Clinical and nutritional characteristics of patients admitted to the ICU with a diagnosis of SARS-CoV-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 kilocalories: Kcal/kg/day (Mean/SD)	23.1 (4.3)
Average caloric covering: % (Mean/SD)	80.4 (15.8)

IQR: Interquartile range; SD: Standard deviation.

Muscle mass through ultrasound measurement

All patients were measured at least on Day 1 and Day 7. The maximum follow-up ultrasound measurement was 4. The initial measurement was made within the first 24-48 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 weekly muscle mass variation for the patients included, with measurements between Day 1 and Day 7 showing significant differences. Figures 1 and 2 show rectus femoris and vastus medialis muscle mass reduction percentages during the days in the ICU, and the serial measurements performed.

Muscle mass and administration of protein-calorie nutritional requirements

Scatter plots were made to establish the correlation between the coverage of calorie and protein requirements and loss of muscle mass. A trend was observed between better calorie and protein administration, and less rectus femoris and vastus medialis muscle loss (Figures 3 and 4).

DISCUSSION

The main objective of this work was to evaluate the percentage of rectus femoris and vastus medialis muscle loss and to compare it with calorie and protein intake 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 lose muscle mass during their stay in the ICU and also 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 neuromuscular relaxants, corticosteroids, sepsis, hyperglycemia, and the use of insulin⁽¹³⁻¹⁵⁾. In this study, an important prevalence of these factors was observed, with 69% of the patients requiring sedation, 41% neuromuscular relaxation, 63% vasopressor support and, in some cases, insulin infusion for better metabolic control as therapeutic management.

Parry et al.⁽⁶⁾ in 2015 reported a loss of rectus femoris and vastus medialis mass of nearly 30% compared with the initial mass upon admission to the ICU. These

Table 2. Evolution of muscle mass per week in 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 rectus femoris (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
Vastus medialis (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.

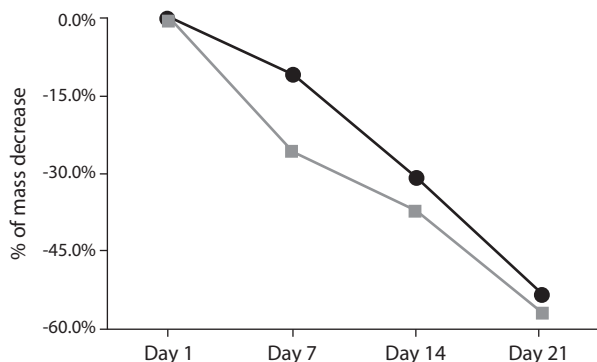


Figure 1. Percentage of mass decrease in the rectus femoris of ICU patients with COVID-19. The decrease in muscle mass of the right and left rectus femoris in the first week is approximately 25% and 10%, respectively, with a decrease of 37% in the right and 30% in the left in the second week, and of 50% in the third week, as compared to the initial measurement.

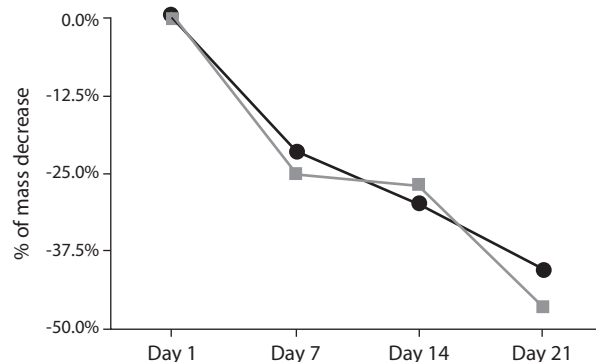


Figure 2. Percentage decrease in vastus medialis muscle mass of patients in the ICU with COVID-19. The decrease in muscle mass of the right and left vastus medialis in the first week is approximately 24% and 21%, respectively, 26% in the right and 29% in the left in the second week of, and 40% in the third week, as compared to the initial measurement.

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 of the rectus femoris.

Similarly, Puthuchery et al.⁽¹⁶⁾ measured the muscle volume of the rectus femoris and the vastus medialis using ultrasound and histopathological analysis on days 1, 7 and 10 of ICU stay in patients on mechanical ventilation. On Day 7, there was a loss of 12% of muscle

mass, which increased to 17% three days later⁽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 rectus femoris muscle mass, with a loss ranging between 15 and 25% by Day 14. In this study, the decrease in rectus femoris muscle mass was greater in the first week than in the two studies previously described.

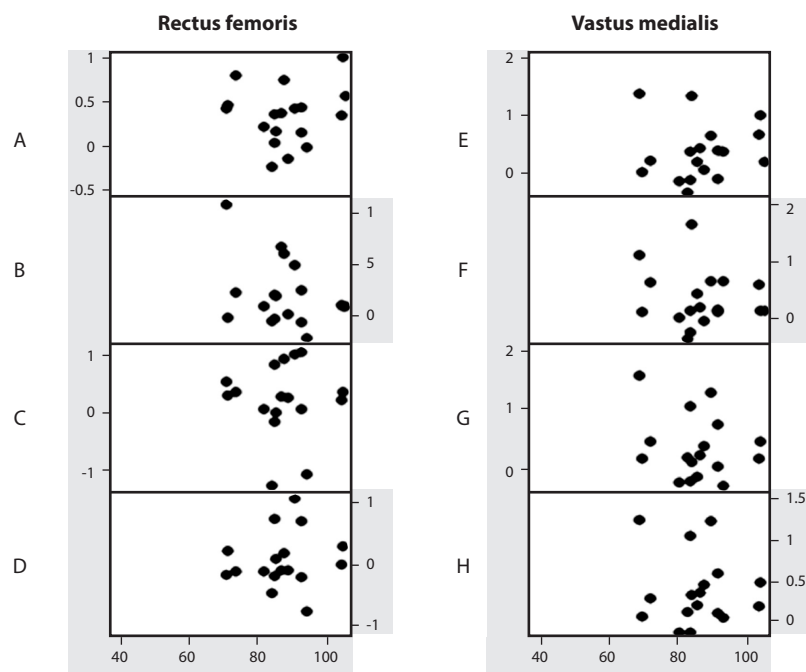


Figure 3. Correlation between the loss of muscle mass and coverage of caloric intake during nutritional support. **A.** Distal middle third. **B.** Distal middle third contracted. **C.** Middle internal third. **D.** Internal middle third contracted. **E.** Distal middle third. **F.** Distal middle third contracted. **G.** Internal middle third. **H.** Contracted middle third.

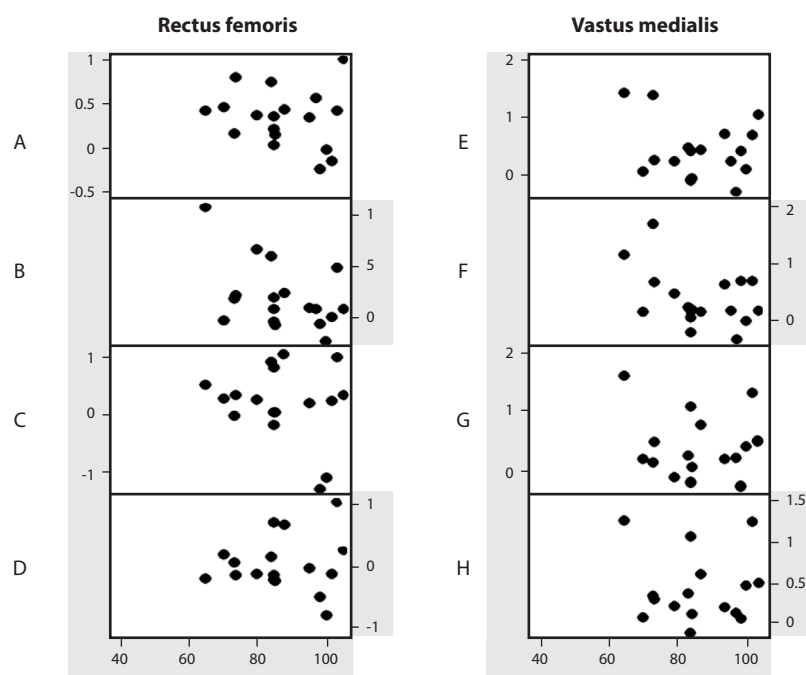


Figure 4. Correlation between the loss of muscle mass and protein intake coverage during nutritional support. **A.** Distal middle third. **B.** Distal middle third contracted. **C.** Middle internal third. **D.** Internal middle third contracted. **E.** Distal middle third. **F.** Distal middle third contracted. **G.** Internal middle third. **H.** Contracted middle third.

Three different authors reported a decrease in muscle mass of 1 to 3% per day 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 shows that muscle loss in ventilated patients with COVID-19 is

twice as high as 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 Puthuchery 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 contribute to increased muscle mass loss, including the involvement of two or more organs during ICU stay⁽¹⁸⁾. We observed in the study that patients not only had respiratory failure but 61.3% also had hemodynamic instability and 41% required the use of neurorelaxation to favor coupling to the ventilator and compliance with supination-pronation cycles.

Weijts 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 compliance with energy targets only was not associated with a reduction in mortality. Considering the ESPEN recommendations 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⁾, in our study, calorie and protein prescription was 23 kcal/kg and 1.26 g/kg, respectively, resulting in requirement coverage of 81.9% and 80.4%, with a mortality of 33% of patients.

LIMITATIONS

The main limitation of the study was the number of patients included ($n = 39$); loss to follow-up was determined by mortality 33% ($n = 13$); and the median stay in the ICU was 13 days (IQR 8-32). Moreover, calories from dextrose or propofol were not included in the nutritional contribution. Therefore, cohorts with a greater number of patients in multi-center studies are needed in order to mitigate these limitations, given the lethality of the disease. On the other hand, ultrasound measurements are observer-dependent, and no consistency analysis using the kappa coefficient was performed as part of the study, given the exposure time required for this measurement in patients with COVID-19.

CONCLUSION

This study shows that muscle mass loss is progressive in critically ill patients with COVID-19 and is probably proportional to the coverage of energy and protein requirements. Therefore, it becomes relevant to carry out objective monitoring of muscle mass as well as of nutritional and therapeutic goals from an interdisciplinary perspective in order to mitigate ICU-acquired weakness in critically ill patients with COVID-19.

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Authors' 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

Authors Torres J and Medina-Parra J, have no disclosures to declare in relation to this work. Author Merchan-Chaverra R, has been a speaker for Boydorr Nutrition, Abbott Nutrition, Baxter, Fresenius Kabi, Medtrition, B-braun, and Amarey Nova Medical. Author Cuellar-Fernández Y, has been a speaker for Boydorr nutrition, Alpina, and Abbott Nutrition.

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