Muscle area loss in critically ill COVID-19 patients during the first two weeks of ICU admission

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Abstract

Introduction

Critically ill patients commonly experience significant muscle area loss, up to around 18% within ten days. The dynamics of muscle area changes during ICU stays and after discharge in COVID-19 patients are not well understood, and conventional risk factors may vary in this population.

Methods

In this retrospective Dutch cohort study at Amsterdam University Medical Centre, individuals diagnosed with COVID-19 from March 2020 to April 2022 were enrolled from the Amsterdam UMC COVID-19 Biobank. Muscle area at level Th12 was measured using thoracic CT scans conducted due to evolving COVID-19 understanding. A multiple regression analysis in SPSS with key variables (sex, age, BMI category, APACHE IV score) explored associations with muscle area loss during the first 10–18 days of ICU admission.

Results

The study included 34 patients; 26.5% were female. Body weight distribution: 2.9% underweight, 32.4% normal weight, 47.1% overweight, and 17.6% obese. Average age at ICU admission was 61.9 years (SD 11.7). Mean muscle area at admission was 93.3 cm^2 (SD 18.9), with an average loss of 10.3 cm^2 (SD 6.68) during the first 10–18 days of ICU admission, representing 11.0% reduction. All four variables added not statistically significantly to the prediction ($p = 0.360$). None of the four variables significantly predicted muscle area loss, $p < 0.05$.

Conclusion

Critically ill COVID-19 patients suffer muscle wasting and have a mean muscle area loss of 10.3 cm^2 during the first two weeks of ICU admission, representing 11.0% reduction. This study found no statistically significant predictions of muscle area loss during the first two weeks of ICU admission based on sex, age, BMI category or APACHE IV score.

Keywords

Muscle area loss, COVID-19, intensive care unit, critically ill, sex, age, BMI, APACHE IV.

Words: 266

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1. Introduction

Coronavirus disease 2019 (COVID-19) can result in hypoxemic respiratory failure and acute respiratory distress syndrome (ARDS). ARDS is frequently complicated by prolonged mechanical ventilation and intensive care unit (ICU)-acquired weakness (ICU-AW), which is characterized by severe muscle wasting (1–3). Critically ill patients often experience a substantial loss in muscle area, reaching up to approximately 18% within a ten-day period (1,4,5). Patients with a reduced muscle area upon admission have a higher risk of complications, including extended weaning from invasive mechanical ventilation, prolonged ICU stay and increased mortality (6–8).

Computed tomography (CT) scans are used to measure body components through the segmentation of CT images by using segmentation tools (7,9,10). The increase in the use of CT scans for regularly examination of COVID-19 patients, as suggested by global guidelines (11,12), has made it possible to monitor skeletal muscle area. Existing literature indicates that L3 is the optimal vertebral level for evaluating total skeletal muscle mass (13,14). However, in the context of the COVID-19 pandemic, thoracic CT scans have been employed to monitor disease progression (11,15). Notably, literature suggests that Th12 serves as a feasible alternative for measuring skeletal muscle area (16,17).

Several risk factors contribute to muscle area loss in general ICU cases. These encompass age, weight, comorbidities, illness severity, organ failure, drug exposure and immobility (1,18). Notably, the association between Acute Physiology and Chronic Health Evaluation (APACHE) score and ICU-induced muscle area loss suggests that the severity of illness, as assessed by the APACHE II score, is closely linked to the overall physiological stress experienced by patients in the ICU (19). Currently, there is a more recent derivative of the APACHE II score known as the APACHE IV score (20). Additionally, De Jonghe et al. found that being female independently predicts ICU-acquired paresis, but the reasons for this are unclear (21). It could be due to physiological differences in body composition, muscle strength, and energy metabolism (22,23). Weijs et al. suggests that a higher BMI is resulting in lower mortality in ICU ventilated patients (7), also known as the obesity paradox (24). Conversely, Sprockel Díaz et al. demonstrated that there is not an association between obesity and risk of inpatients transfer to intensive care or death of ICU patients due to COVID-19 (25).

In the context of COVID-19, the risk factors for muscle area loss include pre-existing health conditions, sepsis, organ failure, mechanical ventilation, immobilization, neuromuscular blockade, corticosteroid administration and glycaemic control (3,26). The alterations of muscle area during ICU stays and post-ICU discharge in COVID-19 patients remain poorly understood, and conventional risk factors may manifest differently in this specific patient population.

A investigation into alterations in skeletal muscle area in COVID-19 patients within the ICU becomes important to potentially predict higher risk of complications, including extended weaning from invasive mechanical ventilation, prolonged ICU stay and increased mortality.
The aim of this retrospective cohort study is to understand the demographic characteristics and explore how sex, age, BMI category and APACHE IV score are related to changes in skeletal muscle area during the first two weeks of ICU admission for critically ill COVID-19 patients.

2. Methods

2.1 Subjects

In this retrospective Dutch cohort study, conducted at a single centre, critically ill patients diagnosed with COVID-19 and admitted to the Amsterdam University Medical Centre, Amsterdam, the Netherlands, within the period from March 2020 to April 2022, were enrolled from the Amsterdam UMC COVID-19 Biobank.

A total of 277 patients were selected for this study. Inclusion criteria encompassed confirmed COVID-19 infection through polymerase chain reaction, an age of 18 years or older, ICU admission, a minimum of 48 hours of invasive ventilation, and the availability of at least two thoracic CT scans during the hospitalization, with a time gap of at least five days between scans.

A predetermined subset of patients was identified for this current investigation. The criteria for inclusion in this subgroup were as follows: the initial thoracic CT scan conducted within 0–4 days after admission to the ICU, coupled with a subsequent CT scan performed during 10–18 days after the first scan. The flowchart detailing patient inclusions is available in Figure 1.

2.2 Design

Patient data were extracted from an existing directory structure by one investigator. The raw data was initially acquired by one of the supervisors and certain modifications were implemented during the analysis to rectify inaccuracies, as documented in the syntax.

Th12, located closest to the more common L3 assessment method, provides a measure of the skeletal muscle area by analysing cross-sectional images featuring both transverse processes. In this study, the muscle area at level Th12 was used, because there were no abdominal CT scans available. Thoracic CT scans were conducted during that timeframe, for clinical reasons to monitor the evolution of COVID-19 in the lungs.

The required sample size was determined through estimation, aiming for a statistical power of 0.80, necessitating the inclusion of 83 patients. The power of this study was 0.35. The sample size determination and power calculation can be found in Appendix A.

The study does not adhere to the regulations outlined in the Medical Research Involving Human Subjects Act (WMO). The relevant committee approved that this study is a non-WMO required study.

2.3 Measurements

This study outlined four variables, namely: sex, age (in years), BMI category (categorized into four groups: < 18.5, 18.5-25.0, 25.1-30.0, > 30.0 in kilograms per m^2) and APACHE IV score to quantify illness severity. The main outcome was the measurement of muscle area at the level of Th12 in cm^2. Muscle area quantification in cm^2 was executed by a sole radiologist with experience in this method.

2.4 Statistical analysis

Temporal gaps between CT scans were computed using IBM SPSS Statistics version 28.0.1.1 (SPSS) (27) through the *'Date and Time wizard'*. The initial CT scan occurred within 0–4 days following admission to the ICU, with subsequent scans taking place during the first 10–18 days after the first CT scan. RStudio version 4.2.1 (28) was employed to code BMI and APACHE IV score. Values closest to the ICU admission date were chosen.

In SPSS (27), the descriptive statistics were used to compute the variables: sex, age, BMI category, APACHE IV score and muscle area loss during the first 10–18 days of ICU admission. For continuous variables, mean values with standard deviation were calculated. The decision to utilize mean values is informed by the sample size of 34 patients. In smaller samples, the median is often considered due to its resistance to extreme values. However, in this case, the mean is chosen to provide a more informative measure of central tendency (29). Age and BMI category, being ordinal variables, are presented using percentages in Table 1. Quantitative variables are presented as means ± standard deviation (SD). Notably, the dataset exhibited no missing data or dropouts.

To explore potential associations among key variables—sex, age, BMI category, APACHE IV score—with muscle area loss among COVID-19 patients 10–18 days post-ICU admission, a multiple regression analysis was performed using SPSS (27). The value of $p < 0.05$ was considered to be statistically significant. The validity of the model was contingent upon meeting all eight assumptions outlined below, ensuring robustness in the interpretation of the data (30).

The analysis adheres to the first assumption, as the variable 'muscle area loss during the first 10–18 days of ICU admission' is established as dependent. The second assumption is also met, given the presence of two or more independent variables in the dataset, comprising both continuous (age and APACHE IV score) and ordinal (sex and BMI category) variables.

The third assumption is met by ensuring the independence of observations, validated through the Durbin-Watson statistic (2.280) in SPSS (27). The fourth assumption is fulfilled due to the presence of both a linear relationship between the dependent variable and each independent variable, as well as a collective linear relationship between the dependent variable and the set of independent variables.

Homoscedasticity is confirmed by the White test ($p = 0.699$) in SPSS (27), meeting the criteria for the fifth assumption. The sixth assumption is met, as there is no evidence of multicollinearity in the data. The seventh assumption is met, as no significant outliers, high leverage points or highly influential points were identified.

Lastly, a normal P-P plot meets the eighth and final assumption, confirming that the residuals (errors) are normally distributed. Collectively, these assessments contribute to the robustness and validity of the multiple regression analysis.

3. Results

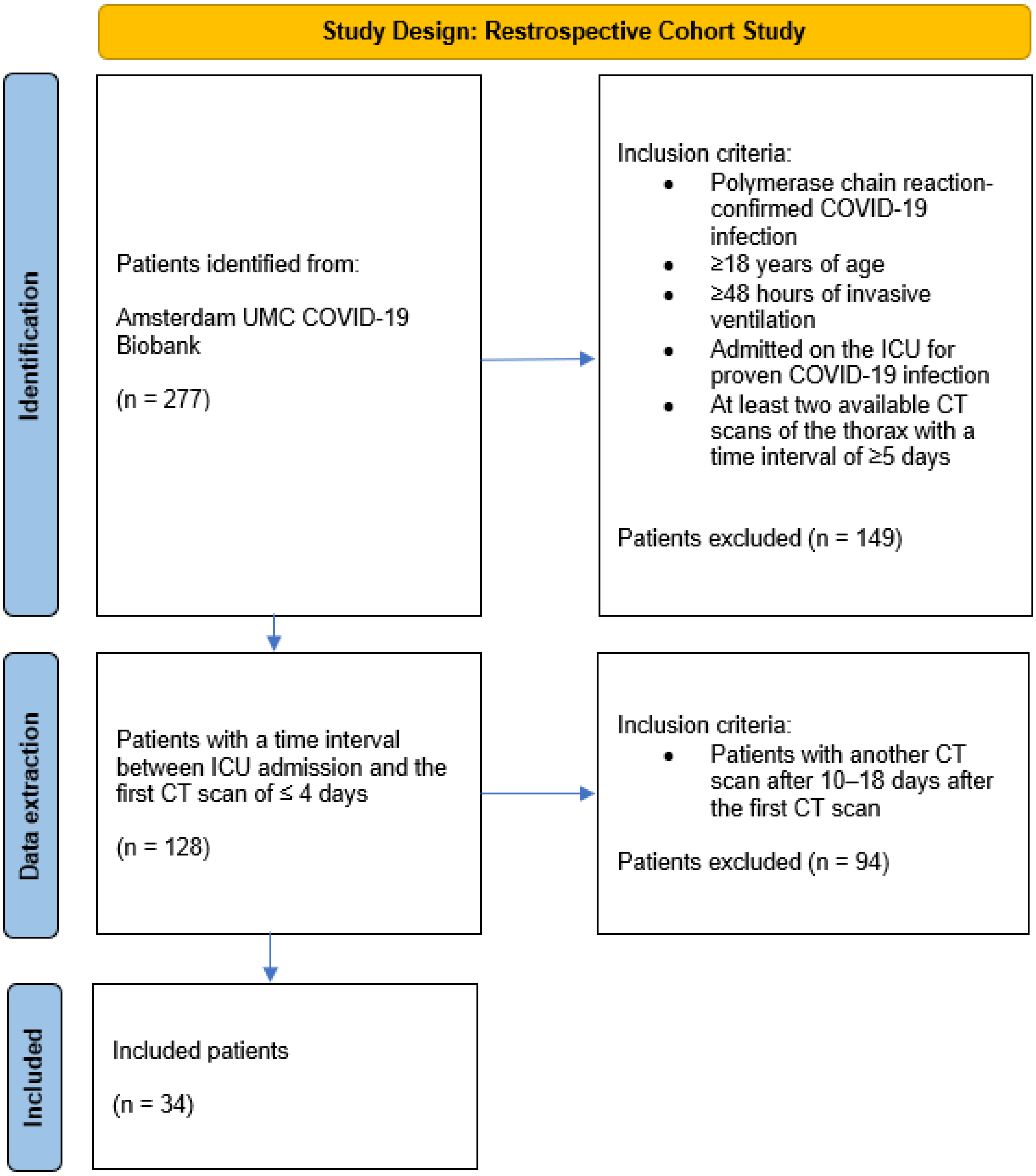

Figure 1: Flowchart of inclusion of patients.

3.1 Inclusion of patients

Figure 1 presents a comprehensive flowchart illustrating the patient inclusion process. A total of 277 patients meeting the specified inclusion criteria were identified from the Amsterdam UMC COVID-19 Biobank. Subsequently, a subset of 128 patients was selected based on a time interval between ICU admission and the first CT scan, falling within the 0–4 days range. Ultimately, 34 patients were included in the study, as this subgroup underwent a subsequent CT scan during the first 10–18 days after the initial scan.

Table 1: Patient characteristics of COVID-19 patients administered to the ICU.

Clinical feature	**Total (n = 34)**	**n (%)**	**Minimum**	**Maximum**	**Mean**	**Standard deviation**
Sex						
	Female	9 (26.5)				
	Male	25 (73.5)				
Age (years)			27	78	61.9	11.7
Height (cm)			160	190	176.0	8.08
Weight (kg)			46.3	115.0	83.3	11.8
BMI (kg/m^2)			17.2	37.3	26.9	3.54
BMI category (kg/m^2)						
	Underweight (< 18.5)	1 (2.9)				
	Normal weight (18.5-25.0)	11 (32.4)				
	Overweight (25.1-30.0)	16 (47.1)				
	Obese (> 30.0)	6 (17.6)				
APACHE IV score			27	111	64.8	18.6
Muscle area at admission (cm^2)			55.8	131.6	93.3	18.9
Muscle area loss during the first 10–18 days of ICU admission (cm^2)			-3.8	19.9	10.3	6.68

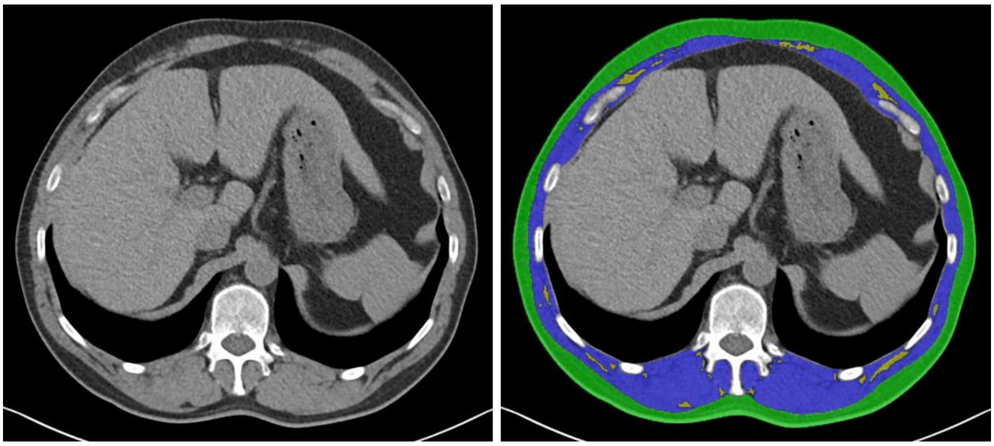

Figure 2: Example of a segmented CT image at the level of thoracic vertebra 12. Segmented tissues are coded with different colours: subcutaneous fat = green, skeletal muscle = blue/purple, intermuscular adipose tissue = yellow.

3.2 Patient characteristics

Table 1 presents the demographic characteristics of the 34 COVID-19 patients included in the study. Among them, nine patients (26.5%) were female. The distribution of body weight categories among the patients was as follows: one patient with underweight (2.9%), 11 patients with normal weight (32.4%), 16 patients with overweight (47.1%), and six patients with obesity (17.6%). The average age at ICU admission was 61.9 years (SD 11.7).

3.21 Muscle area loss

The mean muscle area upon ICU admission measured 93.3 cm^2 (SD 18.9), with an average loss of 10.3 cm^2 (SD 6.68) during the first 10–18 days of ICU admission, representing an 11.0% reduction. Both are shown in Table 1. Figure 2 shows an example of a segmented CT image at the level of Th12.

3.4 Analysis

Table 2: Variables table of the multiple regression.*

Model	Unstandardized B	Coefficients Std. Error	Sig.
(Constant)	15.7	9.739	0.118
Sex	0.635	2.620	0.810
Age (years)	-0.171	0.100	0.097
BMI category (kg/m^2)	0.250	1.531	0.871
APACHE IV score	0.063	0.063	0.327

**Dependent variable: Muscle area loss during the first 10–18 days of ICU admission (cm^2).*

3.41 Multiple regression

A multiple regression was run to predict muscle area loss during the first 10–18 days of ICU admission from sex, age, BMI category and APACHE IV score. All variables are shown in Table 2. All four variables added not statistically significantly to the prediction ($p = 0.360$). None of the four variables significantly predicted muscle area loss, $p < 0.05$. Unstandardized B can be used to establish a formula to predict muscle area loss.

3.42 APACHE IV score

Figure 3 shows a scatter plot describing muscle area loss during the first 10–18 days of ICU admission (cm^2) by APACHE IV score. The other scatter plots for each variable can be found in Appendix B.

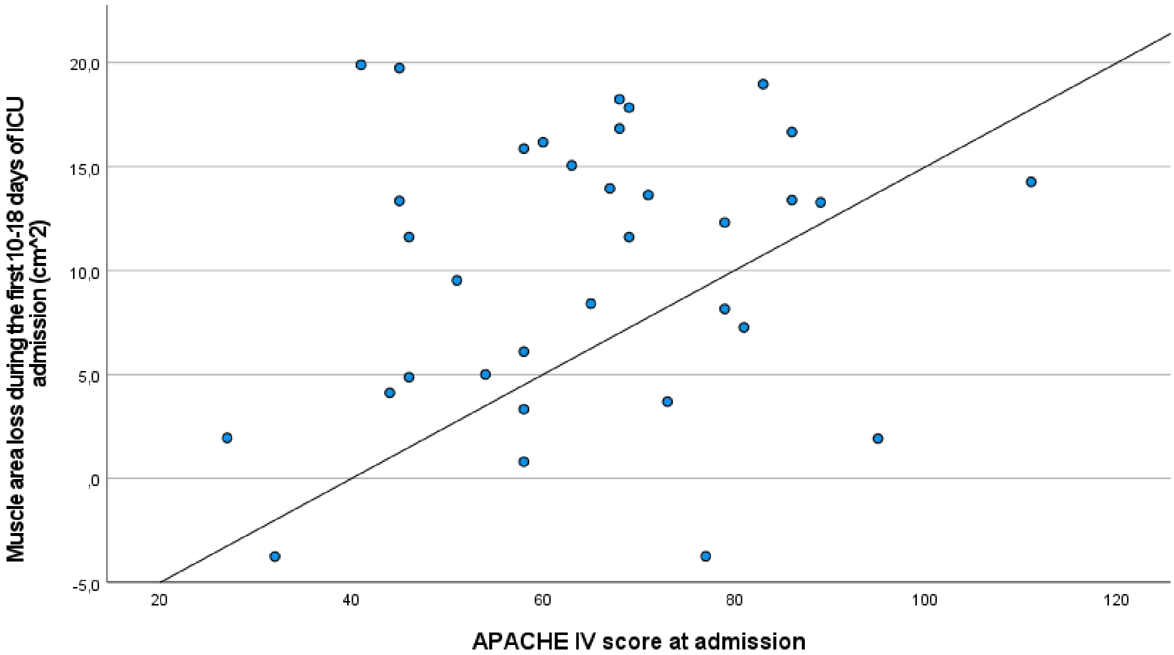

Figure 3: Scatter plot of muscle area loss during the first 10–18 days of ICU admission (cm^2) by APACHE IV score at admission. The line is illustrated, but lacks statistical significance, excluding its validity or meaningful interpretation.

4. Discussion

The mean muscle area loss during the first two weeks of ICU admission was 10.3 cm^2 (SD 6.68), representing 11.0% reduction. All four variables (sex, age, BMI category, and APACHE IV score) did not demonstrate reliable predictors for muscle area loss during the first two weeks of ICU admission.

Conventional risk factors may manifest differently in the COVID-19 population. In contrast to Weijs et al.'s findings that females exhibited significantly lower muscle area, this study did not identify a significant difference in muscle area between females and males (7). In this study, only 9 female and 25 male patients were included, whereas Weijs et al. included 94 females and 146 male patients (7). The distribution between men and women in the original data (n = 277) was 85 women and 192 men (30.7% women and 69.3% men), indicating that the distribution in the ICU remains approximately comparable with this smaller study sample size. Due to the limited number of female patients in this study, it is challenging to definitively conclude that there is no significant difference in muscle area loss between women and men.

It is important to consider that both age and BMI are factors to account for when diagnosing low muscle area (31). In this study, age did not appear as a dependable predictive factor for muscle area loss. Although, age did have a p-value closest to $p = 0.05$ ($p = 0.097$). This implies that, with a larger sample size, age might emerge as a significant predictor of muscle area reduction, suggesting a propensity for increased muscle area loss with aging. De Hoogt et al. highlighted age as an independent predictor of in-hospital mortality (18). However, their investigation did not specifically explore the impact of age on muscle area loss.

A slight majority of the study population was overweight (47.1%). However, BMI category did not demonstrate statistical significance in predicting muscle area loss in this study. Notably, Sjögren et al. observed in a substantial cohort of Swedish ICU patients with COVID-19 that a high BMI was associated with an elevated risk of death and prolonged ICU stay (32). Conversely, Weijs et al. suggests that a higher BMI is resulting in lower mortality in ICU ventilated patients (7), while Sprockel Díaz et al. demonstrated that there is not an association between obesity and risk of inpatients transfer to intensive care or death of ICU patients due to COVID-19 (25). Stating that the literature has not reached a consensus on this matter and that this study also does not provide clarity due to the low sample size of patients and an inadequate distribution across various BMI categories. For example, there is only one patient in the underweight category. A more balanced distribution in each BMI category is necessary to gain better insights into this issue.

In this study, the APACHE IV score did not show statistical significance in predicting muscle area loss. It is worth noting that Yang et al. reported a significant association between muscle area loss in the ICU and the APACHE II score, and can be considered comparable to the newly derived APACHE IV score (19,33). In this study, comorbidities were not considered, which could potentially influence disease severity and consequently the APACHE IV score. Figure 3 shows a scatter plot describing muscle area loss by APACHE IV score. As this variable lacks statistical significance in the results, any interpretation of the scatterplot remains speculative. However, there appears to be a linear trend, suggesting that higher APACHE IV scores may correspond to increased muscle area loss. Additionally, due to the low sample size, clear implications cannot be firmly drawn. This speculation could be explored further in subsequent research with a larger sample size.

This study's strength lies in the well-fitted multiple regression analysis for the dataset, as all eight assumptions were met (30). The homogeneity of the group and the amount of available CT scans further contribute to the robustness of the data.

One limitation of this study is its low power (0.35), originating from the inclusion of only 34 patients meeting the specified criteria. The initial power analysis, outlined in Appendix A, had calculated a requirement of 83 patients for achieving a power of 0.80. The limited number of patients could potentially explain why none of the variables reached statistical significance in predicting muscle area loss during the first 10–18 days of ICU admission. As a retrospective study relying on pre-existing data, conducting a prospective study with a second CT scan for each patient at 14 days post-ICU admission would enhance the robustness of the findings. While Núñez-Seisdedos et al. and Schmidt et al. conducted a prospective cohort study, considered an ideal approach, their investigation explored other variables, including the use and duration of neuromuscular blockers, the duration of mechanical ventilation, and the administration of corticosteroids (34,35). Furthermore, both studies did not use CT image segmentation to define skeletal muscle area as in this study, but instead focused solely on ICU-AW through bedside manual muscle testing (34,35).

Additionally, this study did not investigate other potential factors contributing to muscle area loss, such as the impact of corticosteroids, muscle relaxants, exercise or comorbidities. These variables could play a significant role in influencing muscle area loss (4,34,35). This can be investigated in future research.

In this study, only nine female patients (26.5%) were included. This sample size of included female patients may not adequately reflect the potential differences between females and males, as Weijs et al. showed with 94 female and 146 male patients included in their study (7). With a larger sample of female patients in this study, it becomes easier to determine if there is a potential difference in muscle area loss between women and men. This study acknowledges a limitation in this regard. If future research utilizes similar methods, it is advisable to strive for more balanced sex groups to enhance the quality of the study. Handling this challenge is crucial, because studies show COVID-19 is more severe in men than women (36).

Collaborative efforts across various university medical centres to establish a shared dataset would strengthen the robustness of future investigations. Additionally, ensuring a well-balanced distribution of variables such as sex, age, BMI category, and APACHE IV score is crucial. Subsequent research could explore comorbidities, corticosteroid use, muscle relaxants, and the duration of mechanical ventilation, with a prospective design being the optimal approach for more accurately predicting the amount of muscle area loss in critically ill COVID-19 patients. In future studies, there exists an opportunity for in exploration into potential mechanisms contributing to muscle area loss. This prospect is highlighted by a recent publication in *Nature Communications* by Appelman et al., which reported the possible mechanism underlying the long COVID related muscle wasting (37).

Critically ill COVID-19 patients suffer muscle wasting and have a mean muscle area loss of 10.3 cm^2 during the first two weeks of ICU admission, representing 11.0% reduction. This study found no statistically significant predictions of muscle area loss during the first two weeks of ICU admission based on sex, age, BMI category or APACHE IV score.

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6. Appendix

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Appendix A: Sample size determination and power calculation

In this study, statistical power calculations for the multiple regression analysis were conducted using a dedicated tool, specifically designed for linear regression and ANOVA (F distribution) (38). This tool assisted in determining the appropriate sample size considering factors such as the number of predictors and effect sizes.

Table A1: Illustrates the sample size determination, indicating that a sample size of 83 patients would be required to achieve a power of 0.80 (38).

Type	Regression	*Regression or ANOVA*
α	0.05	*Significant level (0-1), maximum chance allowed rejecting H_0 while H_0 is correct (Type 1 Error)*
n:	83	*The sample size*
Predictors	4	*The number of independent variables (X)*
Effect size	Medium	*Leave empty if you know the effect type and the effect size value*
Effect type	f	*The expected effect size – f or R-squared or η-squared*
Effect size value	0.39	*The expected effect that the test should detect*
Digits	2	*Amount of digits*

The power would be 0.80 with an estimated sample size of 83 patients.

Table A2: Illustrates the power calculation for this study, indicating that this cohort with 34 patients achieves a power of 0.35 (38).

Type	Regression	*Regression or ANOVA*
α	0.05	*Significant level (0-1), maximum chance allowed rejecting H_0 while H_0 is correct (Type 1 Error)*
n:	34	*The sample size*
Predictors	4	*The number of independent variables (X)*
Effect size	Medium	*Leave empty if you know the effect type and the effect size value*
Effect type	f	*The expected effect size – f or R-squared or η-squared*
Effect size value	0.39	*The expected effect that the test should detect*
Digits	2	*Amount of digits*

The power in this cohort study is 0.35 with a sample size of 34 patients.

Appendix B: Box and scatter plots for each variable, conducted in SPSS (27)

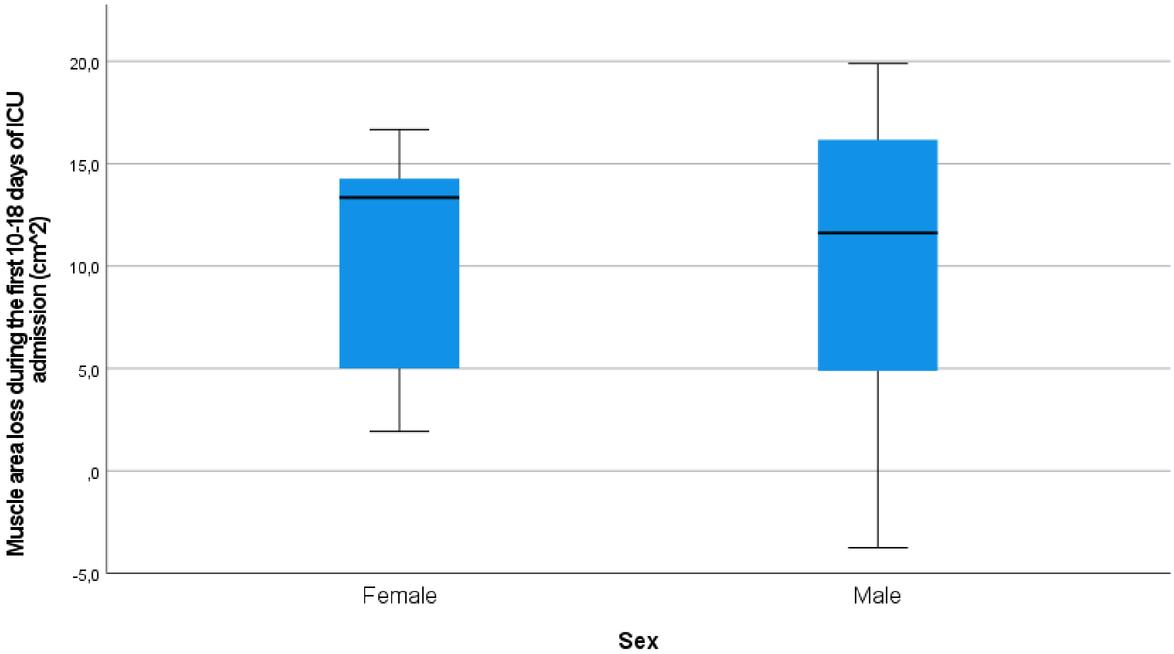

Figure A3: Simple boxplot of muscle area loss during the first 10–18 days of ICU admission (cm^2) by sex.

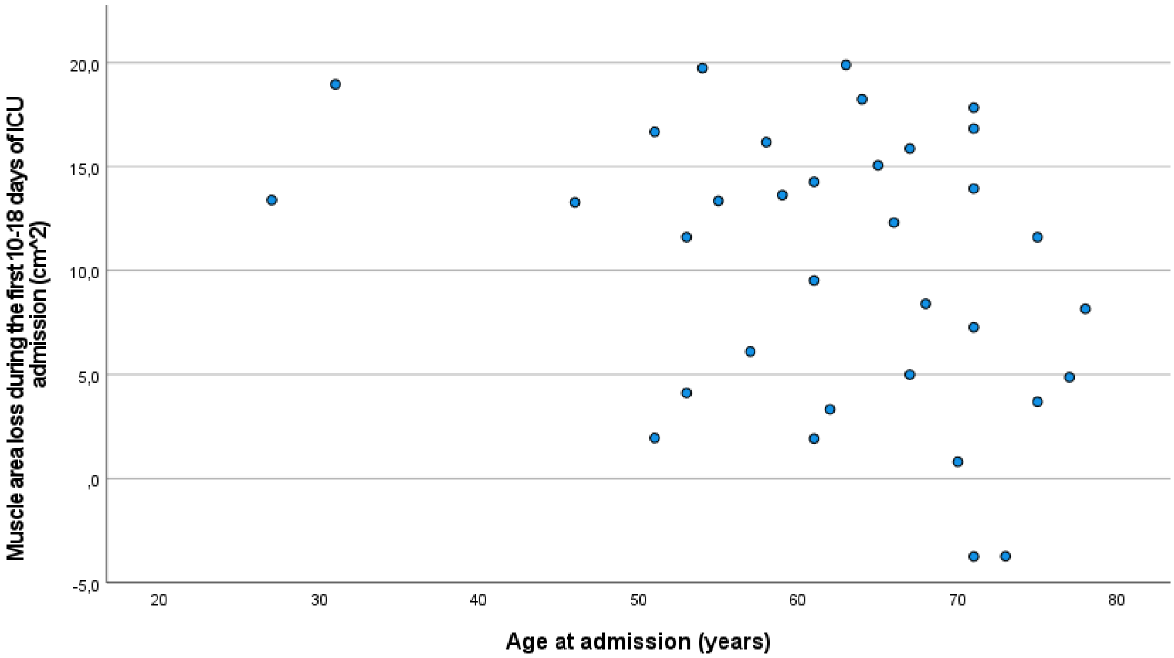

Figure A4: Scatter plot of muscle area during the first 10–18 days of ICU admission (cm^2) by age at admission (years).

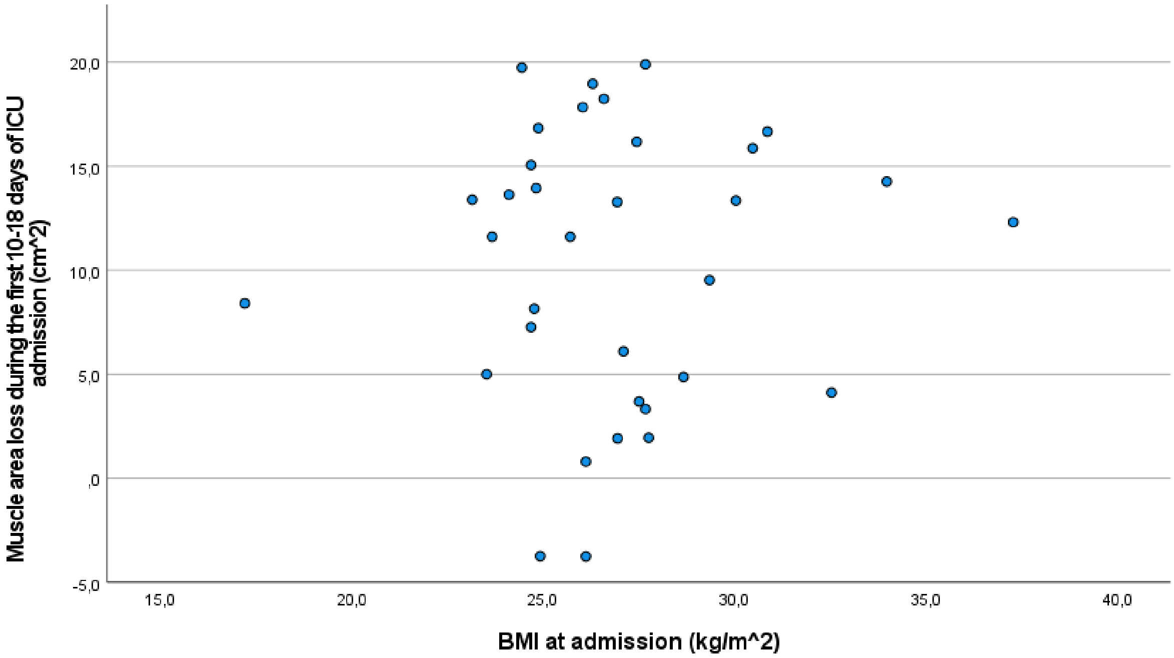

Figure A5: Scatter plot of muscle area loss during the first 10–18 days of ICU admission (cm^2) by BMI at admission (kg/m^2).

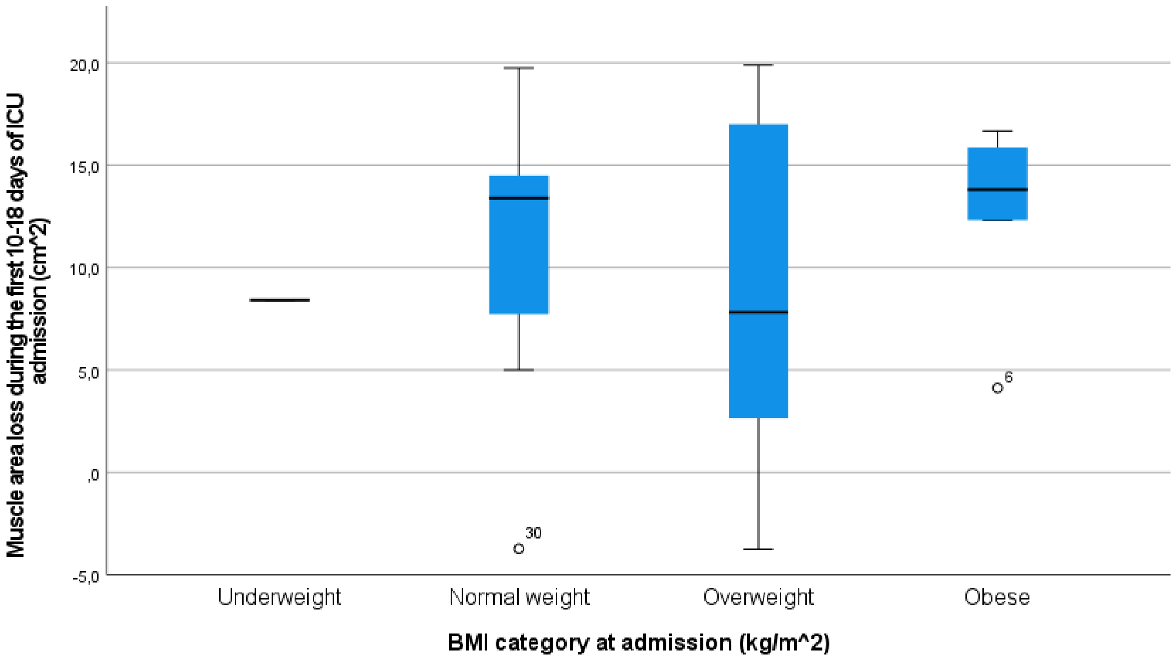

Figure A6: Simple boxplot of muscle area loss during the first 10–18 days of ICU admission (cm^2) by BMI category at admission (kg/m^2).