Incidence of Muscle Wasting in the Critically Ill: A Prospective Observational Cohort Study

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Research

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Abstract

Background: Loss of muscle mass occurs rapidly during critical illness. It can often lead to weakness and fatigue, and it negatively affects quality of life. Despite the importance of understanding the incidence of clinically significant muscle wasting in critically ill patients, there have been few reports on this subject. This study aimed to assess the incidence of and identify risk factors associated with clinically significant loss of muscle mass in this patient population.

Methods: This was a single-center observational study. Informed consent was obtained from all patients. We used ultrasound to determine the rectus femoris cross-sectional area (RFcsa) of each patient on their first and seventh days of treatment in the intensive care unit (ICU). The primary outcome of the study was the incidence of significant muscle wasting, which was defined as a greater or equal to 10% reduction in RFcsa from day 1 to day 7. SOFA score on day 7, length of artificial ventilation, ICU length of stay and twenty-eight-day mortality were evaluated as secondary outcomes. We used a logistic regression model to determine whether patient age, sex, BMI, frailty score, or medical history were significant risk factors for muscle wasting.

Results: We screened an initial cohort of 1,293 patients and recruited 186 as study participants. Ultrasound measurements were completed in 104 patients. Sixty-two of these patients (59.6%) showed ≥10% decreases in RFcsa. Logistic regression analysis identified patient age as the sole risk factor associated with significant muscle wasting. While we detected no statistically significant differences associated with the secondary outcomes, the 28-day mortality rate almost doubled in the group of patients with significant wasting (30.6% *versus* 16.7%; p=0.165).

Conclusions: Clinically significant muscle wasting was frequently observed in our cohort of critically ill adult patients. Patient age was identified as a risk factor for muscle wasting. The results of this study could be used to plan future studies that evaluate strategies to prevent muscle wasting and to improve the outcomes of critically ill patients.

Trial registration: clinicaltrials.gov, NCT 03865095, date of registration: March 6, 2019.

Background

Muscle mass can diminish rapidly during the first two weeks of a critical illness as a result of reduced physical activity, increased protein breakdown, and decreased protein synthesis [1, 2]. Loss of muscle mass has been associated with weakness and fatigue and has a negative impact on the quality of life after recovery from critical illness [3, 4]. To the best of our knowledge, the few published reports focused on the loss of muscle mass in critically ill patients were performed on cohorts with fewer than 25 patients and were not designed to identify risk factors associated with muscle wasting [5, 6]. While one report identified a direct relationship between loss of muscle mass and length of hospitalization in an Intensive Care Unit (ICU), it did not identify any significant risk factors for muscle wasting [7].

One of the critical aspects of identifying the risk factors associated with muscle wasting is the correct assessment of muscle mass. This can be challenging in ICU patients because the procedures commonly used for assessing muscle mass, such as manual muscle testing, nerve conduction studies, dual X-ray absorptiometry, computed tomography or magnetic resonance imaging, are rarely useful in critical care settings. ICU patients typically have limited ability to cooperate and follow commands, require trained staff, require invasive procedures, or require patient transport from the ICU. Several studies have documented the use of ultrasonography to estimate muscle quantity and quality at the bedside and have compared these results to measurements of quadriceps muscle thickness in critical care settings [8-10]. Puthucheary et al. proposed the use of the rectus femoris cross-sectional area (RFcsa) as a replacement for measurements of muscle thickness [11]. In contrast to measurements of muscle atrophy based on muscle thickness, changes in RFcsa are directly correlated with changes in muscle strength in critically ill septic patients [12]. Decreases of ≥10% on ultrasound measurements of RFcsa are considered clinically significant [11, 13]. However, to the best of our knowledge, there are no published data regarding the incidence of significant muscle wasting using this method, despite the importance of this information for devising optimal patient management strategies in the ICU [11, 14]. Thus, this study aimed to (1) assess the incidence of significant loss of muscle mass, defined as a decrease of RFcsa more than or equal to 10% in critically ill adult patients; (2) to assess quantitative changes in muscle mass; and (3) to identify any associated risk factors.

Methods

Study design, setting, and participants

This single-center prospective observational cohort study is registered at ClinicalTrials.gov (NCT03865095).

This study was approved by the Ethics Committee of University Hospital Brno, Czech Republic (reference number 05-130219/EK). Informed consent was obtained from all enrolled patients or an independent physician.

All patients admitted to one of the four ICUs of the Department of Anaesthesiology and Intensive Care Medicine of University Hospital Brno from March 2019 to September 2020 were screened for eligibility for enrollment in this study. Inclusion criteria at ICU admission included ≥18 years of age and the physician's subjective evaluation that the patient would require mechanical ventilation for at least 48 hours. Exclusion criteria included age <18 years, a Clinical Frailty Score >7 prior to admission, a past medical history of neuromuscular disease, amputated lower extremities, prior trauma to the lower extremities involving thighs and inability to cooperate with ultrasound examinations.

Variables, data sources, and measurements

The primary outcome of the study was the quantitative assessment of decreased RFcsa, defined as the percentage reduction in RFcsa based on the results of ultrasound evaluation on day 1 and day 7 of the patient's ICU stay. We considered a decrease in RFcsa >10% to be clinically significant muscle wasting. The secondary outcome of the study was 28-day mortality. We also examined risk factors associated with a clinically significant decrease in RFcsa.

Ultrasound measurements (Vivid S6, GE Healthcare) of RFcsa were performed by the same investigator within the first 24 hours after ICU admission (day 1) and again on day 7 of the patient's ICU stay. The physical point at which the ultrasound measurement was performed was drawn on the patient's skin as a line perpendicular to the long axis of the thigh, three-quarters of the distance between the anterior superior iliac spine and the middle of the upper part of the patella. A linear ultrasound probe with a frequency of 3–9 MHz was placed on the marked line perpendicular to the skin using an excess of gel and minimal pressure. Six images of the rectus femoris muscle cross were collected and stored. An ultrasound machine tool for area measurement was used for RFcsa measurements. The inner side of the fascia of the rectus femoris muscle was manually traced in each image. Following the method described by Turton et al. [15], we omitted the smallest and largest values of RFcsa and calculated the average of the remaining four values. The member of the study team who performed the examination entered the ultrasound measurements into the case report form.

All study-related patient data (age, sex, APACHE II score, SOFA score, Frailty scale value, and ICU Mobility score on admission and day 7) were obtained from medical records and entered into the case report form by a study team member.

Bias and sample size

We cannot rule out selection bias in this study, as one of the primary inclusion criteria (i.e., the physician's personal assessment of the need for 48 hrs of mechanical ventilation) was subjective in nature. The likelihood that a patient would need mechanical ventilation for >48 hours was assessed after discussion between the investigator and the senior ICU physician. This discussion took into account findings from initial diagnostic work-up and the reaction to therapeutic interventions. Because we were unable to locate any previous studies that documented the incidence of significant muscle wasting in critically ill adult patients, we were unable to use previous data to determine the relevant sample size. However, we did note that Bloch et al. [14] reported significant muscle wasting (defined as a decrease in RFcsa of more than 10% at day 7 of an ICU stay) in 55% of patients who had undergone cardiothoracic surgery. Based on these findings, we estimated that 100 patients would provide the appropriate sample size for determining the incidence of significant muscle wasting. Given the possibility that many of enrolled patients might not fully complete the study protocol, we increased the number of participants to 175. To cover potential loss of follow-up, the number of participants was increased to 186.

Statistical analysis

Continuous demographic data and baseline patient characteristics are presented as means with standard deviations (SDs). Continuous outcome characteristics and measurements of RFcsa are presented as means and 95% confidence intervals (CIs) with SDs. Categorical characteristics are summarized using absolute counts and percentages. There were no missing RFcsa measurements, outcome characteristics, demographic, or baseline data for any of the 104 patients we evaluated.

All potential risk factors were examined using both descriptive statistics and forward stepwise selection in a logistic regression model. Risk factors were retained in the model if they had p-value <0.1. A logistic regression model that included change in RFcsa as a dependent binary variable and risk factors that were retained after forward selection as predictors were constructed to estimate odds ratios and 95% Wald CIs.

The relationships between patient characteristics and decreases in RFcsa were examined using Wilcoxon–Mann–Whitney U-tests. The relationship between a decrease in RFcsa and 28-day mortality was evaluated using Fisher's exact test with an alpha level of 0.05. All statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary NC).

Results

Patients

A total of 1,293 patients was screened during the study period. Of these, 186 patients were initially enrolled based on the inclusion and exclusion criteria. An ultrasound examination was performed to document initial RFcsa within 24 hours of ICU admittance. Ultrasound measurements were not performed on day 7 in 82 of these patients due to mortality, transfer to another hospital, and other reasons (Figure 1), providing us with data from 104 patient cases for analysis. Figure 1 presents the flow diagram for this study. The broad admission categories included medical (n=41; 39.4%), surgical (n=3; 2.9%), multiple trauma (n=44; 42.3%), and neurosurgical (n=16; 15.4%). Patient characteristics are outlined in Table 1.

Table 1. Characteristics of the study population.

Parameter	Statistic	Decrease of RFcsa ≥10%		All patients (N = 104)
		Yes (n=62)	No (n=42)	
Sex				
Female	n (%)	24 (38.7%)	14 (33.3%)	38 (36.5%)
Male	n (%)	38 (61.3%)	28 (66.7%)	66 (63.5%)
Age (years)	Mean (SD)	61.0 (17.66)	53.8 (18.75)	58.1 (18.36)
BMI (kg/m^2)	Mean (SD)	27.17 (5.587)	27.24 (4.516)	27.20 (5.158)
Reason for hospitalization				
Medical	n (%)	26 (41.9%)	15 (35.7 %)	41 (39.4 %)
Neurosurgical	n (%)	10 (16.1%)	6 (14.3 %)	16 (15.4 %)
Polytrauma	n (%)	23 (37.1%)	21 (50.0 %)	44 (42.3 %)
Surgical	n (%)	3 (4.8%)		3 (2.9 %)
Clinical Frailty Score				
1	n (%)	6 (9.7%)	3 (7.1%)	9 (8.7%)
2	n (%)	18 (29.0%)	16 (38.1%)	34 (32.7%)
3	n (%)	25 (40.3%)	16 (38.1%)	41 (39.4%)
4	n (%)	10 (16.1%)	5 (11.9%)	15 (14.4%)
5	n (%)	3 (4.8%)		3 (2.9%)
6	n (%)		2 (4.8%)	2 (1.9%)
APACHE II score at hospitalization	Mean (SD)	28.2 (8.36)	26.7 (6.98)	27.6 (7.83)
Enteral nutrition				
Bolus	n (%)	19 (30.6%)	13 (31.0%)	32 (30.8%)
Continuous	n (%)	43 (69.4%)	29 (69.0%)	72 (69.2%)
SOFA score on Day 1	Mean (SD)	10.0 (2.90)	9.1 (2.88)	9.6 (2.91)

APACHE II - Acute Physiology And Chronic Health Evaluation II, BMI – Body Mass Index, SOFA - Sequential Organ Failure Assessment

Measurement of rectus femoris cross-sectional area

The mean RFcsa (95% CI) on day 1 was 2.638 (2.286–2.990) cm^2 for the group of patients with RFcsa measurements that decreased by ≥10% and 2.333 (1.967–2.699) for the group that exhibited a <10% decrease in RFcsa. The mean (95% CI) RFcsa on day 7 was 1.986 (1.683–2.289) cm^2 *versus* 2.355 (2.001–2.710) cm^2 in the groups exhibiting decreases of ≥10% and <10%, respectively. These results are shown in Table 2.

Table 2. Measurement of rectus femoris cross-sectional area (RFcsa)

Parameter	Statistic	Decrease in RFcsa ≥10%	
		Yes (n=62)	No (n=42)
RFcsa on Day 1 (cm^2)	Mean (SD)	2.638 (1.3852)	2.333 (1.1746)
	95% CI	2.286–2.990	1.967–2.699
RFcsa on Day 7 (cm^2)	Mean (SD)	1.986 (1.1929)	2.355 (1.1381)
	95% CI	1.683–2.289	2.001–2.710

Outcomes

We evaluated 104 patients in this study. Sixty-two of these patients (59.6%) exhibited a ≥10% decrease in RFcsa between day 1 and day 7 while in the ICU. The mean (95% CI) SOFA score on day 7 was 6.9 (5.8–7.9) in patients who exhibited a <10% decrease in RFcsa and 7.6 (6.6–8.6) in patients who exhibited ≥10% decreases in RFcsa. The mean duration of artificial ventilation was 12.3 (9.9–14.7) and 11.4 (9.4–13.4) days for patients with decreases in RFcsa of <10% and ≥10%, respectively. The mean length of stay in the ICU was 18.8 (16.6–21.1) and 17.0 (15.1–18.9) days for these two groups, respectively. The mean 28-day mortality was 16.7% in patients that exhibited a <10% decrease in RFcsa and 30.6% in patients that exhibited a ≥10% decrease in RFcsa. Although mortality nearly doubled in the group of patients that exhibited a ≥10% decrease in RFcsa compared to those that exhibited a <10% decrease in RFcsa. None of these differences achieved statistical significance (see *p*-values in Table 3). The outcome data are summarized in Table 3.

Table 3. Outcome characteristics of patients

Parameter	Statistic	Decrease in RFcsa ≥10%		*p*-value*
		Yes (n=62)	No (n=42)	
SOFA score on Day 7	Mean (SD)	7.6 (3.87)	6.9 (3.26)	0.5007
	95% CI	6.6–8.6	5.8–7.9	
Artificial ventilation duration (days)	Mean (SD)	11.4 (7.87)	12.3 (7.73)	0.3457
	95% CI	9.4–13.4	9.9–14.7	
ICU length of stay (days)	Mean (SD)	17.0 (7.51)	18.8 (7.20)	0.1675
	95% CI	15.1–18.9	16.6–21.1	
28-day mortality				
Alive	n (%)	43 (69.4%)	35 (83.3%)	0.1654
Dead	n (%)	19 (30.6%)	7 (16.7%)	

* p-value of Wilcoxon–Mann–Whitney U-test for continuous parameters and Fisher's exact test for mortality

SOFA - Sequential Organ Failure Assessment

Risk factors associated with a ≥10% decrease of RFcsa

All potential risk factors listed in Table 1 were tested for their relationship with RFcsa reduction using forward stepwise selection in a logistic regression model. Patient age was the only parameter identified as a significant risk factor for a ≥10% decrease in RFcsa. The results of this logistic regression analysis are shown in Table 4. The odds ratio suggests that, for each one-year increase in age, the odds that an ICU patient will experience a ≥10% decrease in RFcsa increase by 2%.

Table 4. Significant risk factors for decreases in RFcsa ≥10%

Parameter	Statistic	Value
Age (years)	Odds ratio	1.022
	95% Wald CI	1.000–1.044
	p-value (Wald)	0.0528

Discussion

Key results

Muscle wasting contributes significantly to weakness among patients who have recovered from a critical illness and can have a negative impact on a patient's quality of life [3]. Recent research has focused on identifying adequate techniques of assessment of muscle wasting as well as factors contributing to muscle wasting in critical care settings. Ultrasound measurements of muscle mass are a well-established method for achieving this goal. For example, Mourtzakis et al. [16] reported the outcomes of 11 observational and three interventional studies that used ultrasound measurements to assess muscle wasting in critically ill patients. Ultrasound has specifically been used to assess muscle mass by measuring the RFcsa, which could replace methods that measure muscle thickness [11]. Ultrasound measurements of RFcsa are feasible at the bedside, require no patient cooperation, and show good intra- and interobserver agreement [7, 17].

Previous studies that assessed muscle wasting using RFcsa concluded that a > 9.24% decrease in RFcsa was significant [14, 18]. Observational and interventional studies aimed at the preservation of muscle mass have used a cutoff of a ≥ 10% reduction in RFcsa [11, 13]. To our knowledge, no studies in critical care settings that have used a muscle-wasting criterion of a > 10% reduction in RFcsa as a cut-off for significant muscle wasting have reported its incidence. In this study, the incidence of significant muscle mass wasting was 59.6%, which is similar to the incidence reported in cardiac surgery [14, 18].

While loss of muscle mass has frequently been observed in association with critical illness, the relationship of muscle wasting degree to clinical outcomes remains unclear.

Only a few studies reported the effect of loss of muscle mass on clinical outcomes and none of these studies focused on clinical outcome measures as primary endpoints [13, 18]. Bloch et al. conducted an observational study in high-risk cardiovascular surgery patients and found no statistical differences in the length of ICU or hospital stay between patients with or without muscle wasting, which was defined as reduction of RFcsa > 9.24% [18]. We obtained similar results in this study. The relationship between significant muscle wasting and mortality in adult patients in critical care settings also remains unknown. Our results revealed a nearly two-fold increase in 28-day mortality in patients with significant muscle wasting (30.6% *versus* 16.7% in the groups with ≥ 10% and < 10% decreases in RFcsa, respectively). Although this difference was not statistically significant, the study sample size was not pre-set to evaluate this question.

Patients frequently lose muscle mass in critical care settings; for example, one study showed that patients with multiple organ failure experienced a 15.7% reduction in RFcsa during their first 7 days in the ICU [7]. In our study, the mean decrease in RFcsa over 7 days in all enrolled ICU patients was 14.9%.

Risk factors for muscle wasting remain poorly understood. Puthucheary et al. [7] found that age, bicarbonate level at hospital admission, and the ratio of PaO_2 to FiO_2 were associated with a > 10% decrease in RFcsa measured on day 10 of an ICU stay. In our study, age was identified as a risk factor for a > 10% decrease in RFcsa measured on day 7 of an ICU stay.

Limitations

There were several limitations associated with this study. First, the small sample size precludes a full evaluation of the relationship between the loss of muscle mass and 28-day mortality. Second, the patient cohort surveyed in this study is highly heterogeneous. For example, we enrolled significantly more male than female patients, and our results may therefore not be valid for both sexes. The reasons patients were admitted to the ICU were also not evenly represented, as most patients were admitted for internal complications or trauma, whereas few were admitted for surgical complications. Third, the site where the RFcsa measurement was performed was not standardized across all patients and was instead subjectively chosen by the investigator. Fourth, we did not document the hand dominance of each patient in this cohort. We therefore may have measured RFcsa on the patient's non-dominant side, leading to potential overestimation of muscle wasting. We finally recognize the potential for selection bias, as primary patient selection was based on the investigator's subjective assessment of which individuals were likely to need mechanical ventilation for more than 48 hours after ICU admission.

Conclusion

Significant loss of muscle mass was assessed by ultrasound measurements of RFcsa in 104 critically ill adult patients. Patient age at admission was associated with a risk of developing clinically significant muscle wasting. Mortality rates were two-fold higher in patients with significant muscle wasting (≥ 10% over the first seven days in the ICU) than among those without significant wasting, though this difference in mortality was not statistically significant. The results of this study could be used to plan future studies evaluating strategies to prevent muscle wasting and thus positively affect the outcomes of critically ill patients, e.g., nutrition regimens or physiotherapy.

Abbreviations

APACHE II - Acute Physiology And Chronic Health Evaluation II

BMI – Body Mass Index

CI – confidence interval

ICU – Intensive Care Unit

RFcsa - rectus femoris cross-sectional area

SD - standard deviation

SOFA - Sequential Organ Failure Assessment

Declarations

Ethics approval and consent to participate

The authors confirm this work adhere to ethical guidelines and was approved by the Ethics Committee of University Hospital Brno (Ref. Nr. 05-130219/EK). Informed consent was obtained from all enrolled patients or independent physician.

Consent for publication (include appropriate statements)

Not applicable. No individual patient data are reported.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

OH reports grants and personal fees from MŠMT, during the conduct of the study. KV reports grants and personal fees from MŠMT, during the conduct of the study. MK, RG, TK and RS have nothing to disclose.

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Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by OH, KV, TK, RS and MK. The manuscript was written by OH and RG. All authors read and approved the final manuscript.

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Figures

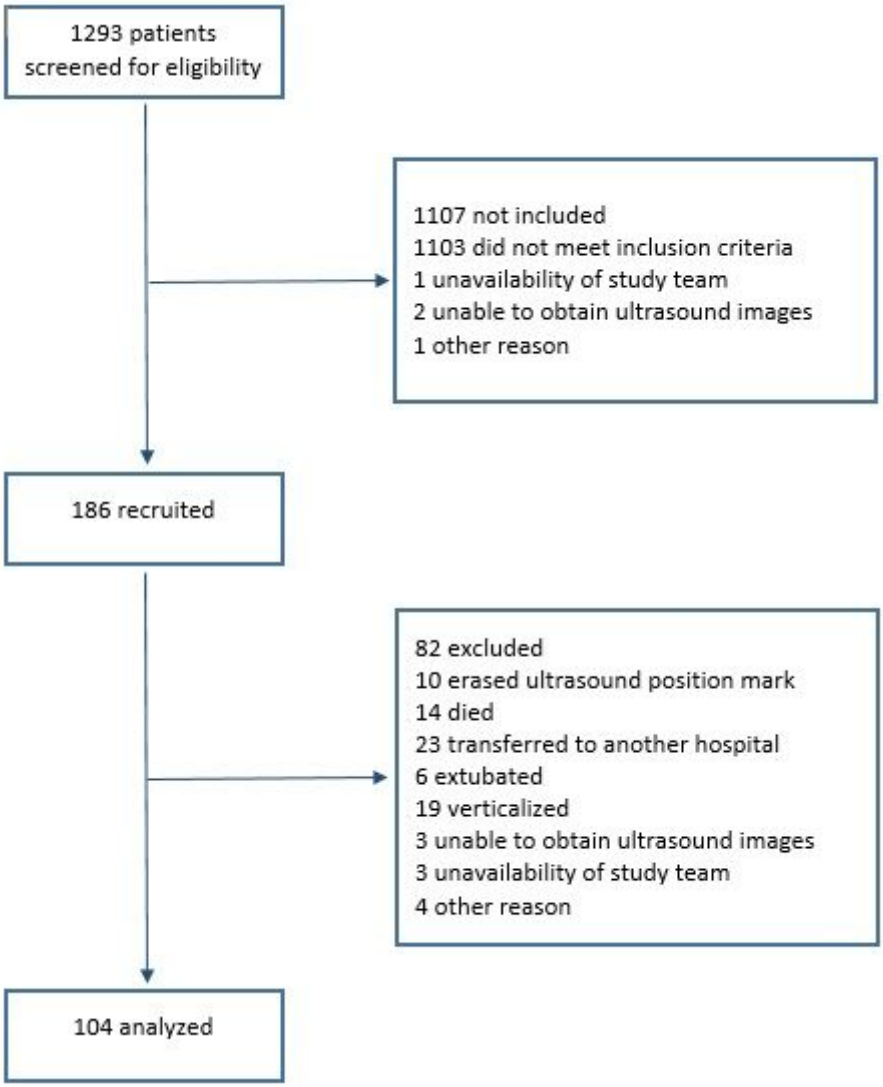

Figure 1

Flow diagram