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Evaluating muscle mass in survivors of ARDS: a 1-year multi-center longitudinal study

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Abstract

Objective—Rapid muscle wasting occurs during acute respiratory failure, resulting in muscle weakness and functional impairments. This study examines survivors' body composition in the year after acute respiratory distress syndrome (ARDS) and tests associations of patient characteristics, hospital exposures, and survivors' strength and physical functioning with whole body percent lean mass.

Design—Prospective cohort study with 6- and 12-month follow-up

Setting—National study enrolling patients from 5 study centers

Patients—ARDS survivors (N=120)

Interventions—None

Measurements and Main Results—Lean and fat mass from dual energy X-ray absorptiometry (DXA). On average, survivors gained whole body total mass (+1.4kg, 0.1, 2.7) and fat mass (+1.2 kg, 0.2, 2.2), and maintained lean mass (+0.2kg, −0.4, 0.8) between 6 and 12 months. Proportionally, percent fat mass increased and percent lean mass decreased for the whole body, trunk, and legs ($p<0.05$). Greater whole body percent lean mass was associated with younger age, male sex and lower baseline body-mass index, but not other patient characteristics or ICU/hospital exposures. Greater percent lean mass was also significantly associated with gait speed and 6-minute walk distance, but not volitional strength or self-reported functional status.

Conclusions—In the first year after ARDS, patients gained fat mass and maintained lean mass. We found no association of whole body percent lean mass with commonly-hypothesized hospital risk factors. Direct measurement of body composition and performance-based functional measures may be helpful for understanding functional recovery in ICU survivors.

Keywords

DXA; anthropometry; lean mass; ARDS; longitudinal studies

INTRODUCTION

In patients with acute respiratory failure, including acute respiratory distress syndrome (ARDS), substantial muscle wasting occurs within the first week of intensive care unit (ICU) admission.[1] By hospital discharge, ARDS survivors are often severely wasted, with an 18% mean loss in body weight.[2] Although baseline body weight typically returns by 12 months, functional impairments often persist, which patients attribute to muscle wasting and weakness.[2] There is limited data on body composition for survivors to understand these relationships and, in particular, whether “lean mass” (which is largely comprised of skeletal muscle) during recovery is linked to patient characteristics, hospital exposures or physical outcomes.

Dual energy X-ray absorptiometry (DXA) is a precise reference-standard method for evaluating whole body lean mass and appendicular lean mass. These measures, with coefficient of variations of 1%, [3–5] reflect overall skeletal muscle mass and may be used to indicate sarcopenia. DXA is used to evaluate bone mineral density of ICU survivors in assessing fracture risk [6]; however, DXA has not been reported as a post-discharge measure of lean mass. [7] This study uses DXA to describe body composition of survivors in the first year after ARDS. We also examined associations of whole body percent lean mass with relevant baseline characteristics and ICU/hospital exposures, along with concurrent measures of strength and physical functioning, to identify potential markers and outcomes of proportional muscle mass during recovery.

MATERIALS and METHODS

Study Population

Data were from the ARDS Network (ARDSNet) Long-Term Outcome Study (ALTOS), a national multi-center prospective study that evaluated survivors at 6 and 12 months after ARDS, defined as receiving positive-pressure mechanical ventilation through an endotracheal tube, with a PaO₂/FiO₂ < 300 mm Hg and bilateral infiltrates on chest radiography consistent with pulmonary edema, without evidence of left atrial hypertension. [8] Participants were enrolled from four ARDSNet clinical trials evaluating ICU-based therapies for ARDS. [9–12] Between August 2007 and September 2013, ALTOS patients were enrolled from 41 hospitals at 12 ARDSNet study centers within 48 hours of ARDS onset and 72 hours of initiation of mechanical ventilation. Major exclusion criteria include: pre-existing severe malnutrition (BMI < 18.5 or loss of > 30% total body weight in prior 6 months), lung, liver, or neuromuscular diseases; or limitations in life support at time of study eligibility (additional details in online Methods Supplement). [9–12] Patients were excluded from prospective follow-up in ALTOS if they were < 18 years old, homeless, non-English speaking, or had potential cognitive impairment prior to admission (based on medical records or patient/proxy report). An ancillary study was funded (R01HL091760-02S1) to obtain DXA assessments at five ALTOS study centers (N=5, 15, 30, 31, 39) that conducted in-person assessments. Consent for these DXA assessments were provided as part of written informed consent. Institutional review boards at Johns Hopkins University and participating study centers approved the study.

Measurements

Dual energy X-ray absorptiometry—The primary outcome is DXA-based whole body percent lean mass (whole body lean mass divided by whole body total mass), which largely reflects skeletal muscle mass. However, we also describe DXA measures for different body regions, allowing for more comprehensive evaluation of overall vs. regional changes in the body. DXA scans were performed 6- and 12-months after onset of ARDS; 120 survivors had 1 scan, 97 at 6 months, 91 at 12 months, and 68 at both time points. Four centers used Hologic Discovery A (Bedford, MA); one used Lunar Prodigy (Milwaukee, WI) DXA machines. DXA findings from one of the Hologic sites were converted to NHANES Pre-Apex 3.4 values [13] to provide comparable data analyzed by the same software algorithms for all Hologic sites. Similarly, we used previously validated cross-conversion equations to

standardize DXA data between GE Lunar Prodigy and Hologic measurements[14] (details provided in online Methods Supplement). If DXA scans of specific body regions were not usable (i.e., amputation), the contralateral body region was used for calculations (10 scans for 8 survivors across follow-ups). If such imputation was not possible, data for that region was not reported and whole-body measures were not calculated (14 scans for 9 survivors across follow-ups). Of 68 patients with scans at both follow-ups, whole body measures at both time points could not be calculated for 5 patients. Appendicular skeletal muscle mass (kg/m^2), a DXA-based measure of skeletal muscle mass, was calculated as the sum of the lean mass in the arms and legs (kg) divided by height squared (m^2). [15] Low appendicular skeletal muscle mass, defined as $<7.26 \text{ kg/m}^2$ in men and $<5.45 \text{ kg/m}^2$ in women, has been used to indicate sarcopenia.[15]

Patient Characteristics—Demographics include age, sex and race. Baseline health status include body-mass index at study enrollment; presence of COPD, rheumatologic, and neurologic comorbidities; Charlson Comorbidity Index[16]; Functional Comorbidity Index[17]; and the retrospectively-administered Short-Form 36 version 2 Physical Function score (SF-36 PF)[18] (normalized with mean=50, SD=10).

ICU/Hospital Exposures—Based on prior literature[1,2,19,20] and investigators' input, ICU/hospital exposures were selected, *a priori*, for evaluation. These included severity of illness (APACHE III score[21]), sepsis as a primary lung injury risk factor, mechanical ventilation duration, percentage of ICU days in coma, average daily percentage of non-failing organ systems (evaluated via the Brussels score[22]) and ICU and hospital length of stay. Medication exposures in the ICU examined include (1) corticosteroids or neuromuscular blockade, with each medication assessed as: ever/never used, total days of use, cumulative dose, and mean daily dose (standard conversion factors used to calculate equivalent doses)[23], and (2) catecholamines, assessed as percentage of ICU days with any use.

Physical Outcomes—Muscle strength, performance-based physical functioning, and self-reported functional status were assessed at each follow-up. Muscle strength was assessed using: (1) manual muscle testing (MMT), scored according to Medical Research Council (MRC) criteria[24] (range: 0 to 60, higher=greater strength, <48 indicate "ICU-acquired weakness"[25]), (2) hand grip strength as percentage of predicted value[26], and (3) maximal inspiratory pressure (MIP), a measure of respiratory muscle strength, as percentage of predicted value[27,28].

Physical functioning was evaluated using 4-meter gait speed (4MGS in meters/sec)[29] and the 6-minute walk test (6MWT in meters)[30], performed and scored according to published standards[31,32]. The 6MWT was performed with variation, when needed, including a single 6MWT at each follow-up (as in prior ARDS research[19]) and using the longest available walking track (e.g., home visits). Self-reported functional measures include: Functional Performance Inventory (FPI)[33], SF-36 PF [18], and the EQ-5D-3L[34] (visual analogue scale; utility score; and individual mobility, self-care, and activities scores).

Statistical Analysis

Descriptive statistics were provided for DXA measures of lean and fat mass at 6 and 12 month follow-up for the whole body and body regions, and by ARDS severity. Change, evaluated as a continuous variable, for DXA measures were tested using paired t-tests in survivors with scans at both time points. To explore potential heterogeneity in body composition changes, continuous change in whole body lean and fat mass were examined using Pearson correlations and scatterplots, for 3 different change groups: survivors with substantial increase (≥ 2 kg), substantial decrease (≤ -2 kg) or had stable (<2 kg) whole body total mass between 6 and 12 months. The 2 kg threshold, an *a priori* decision, was based on knowledge of the range of total body mass in our sample and pre-established estimates of DXA measurement error and variability in measurement protocol.[3,35] Based on the 95% confidence interval of total body mass (80.0–89.5kg) in this sample (see Data Supplement Appendix Table 1), 2 kg represents 2.2–2.5% of mass. Considering that the DXA coefficient of variation is generally $<1\%$ for lean tissue, this estimate provides a conservative approach to distinguishing those who are experiencing substantial tissue change over the 6 month trajectory.

Linear regression models were used to estimate unadjusted and adjusted associations of each ICU/hospital exposure with whole body percent lean mass at 6 months. Baseline demographic and health status variables that were independently and significantly ($p < 0.05$) associated with 6m percent lean mass in a multivariate model were identified and added to the multivariate ICU/Hospital exposure models. Fisher's exact and 2-sample t-tests were used to test for differences in patient characteristics and ICU/hospital exposures between survivors with substantial change and survivors with stable whole body lean mass (kg) to identify any that are linked to whether survivors substantially gained or lost lean mass.

Pearson correlations were used to examine concurrent associations between percent lean mass and physical outcomes for strength and functional status at 6- and 12-month follow-up, and the longitudinal relationships between 6-month percent lean mass with these outcomes at 12 months.

RESULTS

Sample Characteristics

Cohort characteristics and ICU/Hospital exposures are provided in Table 1. Mean BMI at study enrollment was $32 (8) \text{ kg/m}^2$, 52% were obese ($\text{BMI} \geq 30 \text{ kg/m}^2$). All 120 survivors were mechanically ventilated and 75% ($N=90$) were recruited from sites that did not routinely provide early mobilization or rehabilitation services in the ICU. Few survivors had muscle weakness (MRC score <48), with 5% of 97 at 6m and none of 91 at 12m.

Body Composition: BMI and DXA Findings

ARDS survivors had mean BMI of $30 (95\% \text{CI: } 29, 32) \text{ kg/m}^2$ and average whole body total mass of $85 (95\% \text{CI: } 80, 90) \text{ kg}$ at 6 months, with comparable results at 12 months (Data Supplement Appendix Table 1). Whole body percent lean and fat mass did not differ by ARDS severity at either follow-up time point. Among individuals with DXA scans at both

follow-up, average DXA whole body total mass (kg) increased 1.4 (95%CI: 0.1, 2.7) and fat mass increased 1.2 (95%CI: 0.2, 2.2), but lean mass did not differ (0.2, 95%CI: -0.4, 0.8). Interestingly, percent fat mass increased, while percent lean mass decreased for the whole body, trunk, and legs. Among 29 survivors who gained >2 kg in total mass, 24 (83%) gained >2 kg of fat mass while only 9 (31%) gained >2 kg of lean mass (Figure 1). Change in lean mass (kg) was inversely correlated with change in fat mass (kg) for patients with stable weight ($r = -0.85$, 95%CI: -0.93, -0.66, $p < 0.001$, $N = 23$), but not in those who lost >2 kg ($r = -0.10$, 95%CI: -0.66, 0.54, $p = 0.77$, $N = 11$) or gained >2 kg ($r = -0.08$, 95%CI: -0.43, 0.30, $p = 0.68$, $N = 29$).

Association of Patient Characteristics and ICU/Hospital Exposures with Percent Lean Mass at 6-Month

Age, sex and BMI were the only baseline characteristics independently associated with whole body percent lean mass at 6m (Data supplement Appendix Table 2). Survivors who were female, older or had higher BMI at enrollment had lower percent lean mass (all $p < 0.05$).

Of the ICU/hospital exposures examined, none were significantly associated with 6m percent lean mass after accounting for patient age, sex and BMI at enrollment (Table 2); Similar results were found with 12m percent lean mass as the outcome (Data supplement Appendix Table 3). No significant differences in baseline patient characteristics or ICU/hospital exposures were observed between survivors who either gained or lost ≥ 2 kg of whole body lean mass compared to survivors with < 2 kg change (Data supplement Appendix Table 4).

Associations of Percent Lean Mass with Physical Outcomes

In cross-sectional analyses, there were no statistically significant and consistent associations between whole body percent lean mass and the 3 strength measures or self-reported functioning (Table 3). However, percent lean mass was significantly associated with gait speed and walking distance at both follow-ups. Findings were similar for 6-month whole body percent lean mass with these 12-month outcomes.

Median and Inter-quartile range for all continuous study variables are provided in Data Supplement Appendix Table 6.

DISCUSSION

In this multi-center study, we used a rigorous reference methodology, DXA, to evaluate changes in the body composition of ARDS survivors over 12-month follow-up. Approximately 20% of survivors had low appendicular muscle mass, which may indicate sarcopenia. On average, whole body total and fat mass increased significantly by 1.4 and 1.2 kg respectively, while lean mass was stable between 6- and 12-months. However, percent fat mass generally increased while percent lean mass decreased. Of the hypothesized ICU/hospital exposures, none were independently associated with ARDS survivors' percent lean mass at 6m. Age, sex and BMI at enrollment were the only patient characteristics independently associated with percent lean mass. Percent lean mass was associated with

performance-based measures of physical functioning (6MWT and 4MGS), but not with multiple volitional measures of strength and self-reported functional status. These findings suggest that direct measurement of body composition and performance-based functional measures may be helpful for understanding recovery in ICU survivors.

By hospital discharge, ARDS survivors experience substantial loss in body weight, with functional impairments persisting even after a return to baseline body weight.[2] In this study, we present detailed body composition data in the first year of recovery after critical illness, with separate measures for lean and fat mass as well as for regional vs. whole body. Our data goes beyond metrics commonly used in critical care research and clinical practice, such as body weight and BMI, to understand body composition and function during recovery.[2,19,36] Modalities, such as DXA, can provide the precise measures of muscle mass necessary for understanding biological and clinical value of muscle mass recovery. Furthermore, given its low radiation exposure and cost-effectiveness, DXA can be feasibly incorporated in future studies to advance knowledge fundamental to understanding and improving post-ARDS recovery.

In our study, proportional lean mass declined 1%, reflecting gains in fat mass, in this cohort over a 6-month study period. However, these changes may accumulate long-term, especially in absence of targeted nutrition and exercise therapies. Specifically, ongoing periods of bed-rest, as might occur with recurrent acute illness or hospitalizations common in ARDS survivors[37], may increase adiposity. Measures, such as increased mobilization or weight-bearing physical activity in conjunction with proper nutrition, may help increase lean mass to counter fat gains. Although muscle mass did not decrease in this study, the observed increase in adiposity may infiltrate muscle and result in metabolic and physical dysfunction. [38] These factors might explain the slow functional recovery observed for up to 5 years after ARDS.[19,37] Measurement of muscle quality (representing potential changes in metabolic function) using other modalities, such as ultrasound or CT imaging, may be important for understanding the specific relationships between muscle and fat and their impact on muscle function. Progressive understanding of long-term changes in body composition is important for designing and evaluating rehabilitation, nutritional and pharmacological therapies to improve ARDS survivors' physical status.

Younger age, male sex and lower BMI at enrollment were associated with higher percent lean mass at follow-up. Males have inherently higher circulating androgens, which maintain muscle mass or promote muscle hypertrophy, compared to females[39], and regardless of sex, there is a steady decline in muscle mass with age, with or without fat gains[40]. The association of higher proportion lean mass with lower BMI may be due to greater engagement in weight-bearing activity. However, contrary to expectations[1,2,19,20], no ICU/hospital exposures evaluated in our study were independently associated with percent lean mass, which may be related to study timeframe. Moreover, we expected lean mass to decline over the study period, but it was maintained. Previous studies have evaluated these exposures beyond 12 months[2,19,20] and body composition changes following >1 year of ICU survivorship may affect this association. There may be additional explanations for these findings that require future exploration. Specifically, these exposures may have resolved by 6 months or are simply weakly associated with percent lean mass, despite that selected ICU/

hospital exposures[36] and muscle quantity[41–43] has been associated with muscle strength and physical function in prior research. Clarifying the interrelationships of ICU/hospital exposures to muscle strength, percent lean mass, muscle mass and physical functioning, and the longer term changes in body composition, will be important for future studies.

Higher percent lean mass was consistently and positively correlated with both performance-based measures of physical functioning across follow-ups, but not consistently with volitional measures of strength or self-reported functional status. The positive association of higher percent lean mass with performance-based measures may suggest that patients with lower fat mass are more active and therefore, perform better on physical performance tests. It is also possible that percent lean mass, which represents lean mass relative to total body mass, is a relevant indicator for performance on weight-bearing tests, such as 6MWT and 4MGS. For survivors whose absolute lean mass did not change, but fat mass increased, the proportion of total mass represented by muscle mass is lower, reflecting an overall heavier load for muscles that may impair performance on weight-bearing activities. In contrast, the lack of association with non-weight bearing strength measures may be due to the fact that strength is more reflective of absolute muscle mass, rather than the proportion of total mass represented by lean mass, although neither lean nor fat mass for the arms changed in kg or in percent. Other relevant variables that should be examined in future studies may include the metabolic and physiological integrity of the muscle. Alternate non-volitional measures of strength may also be needed.[44] The lack of association of percent lean mass with self-report functional status may reflect that multiple factors, including adaptation, psychological status, and environmental changes, affect this type of outcome measure.[45] Studies evaluating interventions to improve muscle health and promote healthy body composition phenotypes should consider performance-based measures of physical function (which have been associated with important patient-centered outcomes[46]) and identifying other objective measures of strength to assess the intervention effects.

Our study has the following limitations. First, some data of interest were not available in our study. DXA testing was not feasible prior to ARDS or at hospital discharge to interpret recovery trajectory or change from early stages of survivorship. In addition, we did not have DXA data from a comparable control group and detailed data on nutrition, and rehabilitation therapies during hospitalization and follow-up were not available for evaluating these exposures. Second, our sample was drawn from clinical trials with multiple exclusion criteria and DXA was performed in survivors who could attend an in-person follow-up visit. These factors may limit generalizability of study findings. Third, multiple comparisons may increase the risk of type 1 error for significant findings. Finally, some clinically important effects may not have been observed due to our modest sample size or potential measurement error from different DXA equipment used in study sites. Replication of these findings in future studies will be important. However, our study also has important strengths. We present novel and comprehensive longitudinal data on body composition, using a reference standard method, over 1-year follow-up, for a relatively large, multi-center sample of ARDS survivors. Our findings highlight the body composition of survivors during recovery. Since these data were observational and reflect routine care, detailed body composition assessments may be useful as part of comprehensive evaluations of recovery and to assess

effectiveness of nutrition and exercise rehabilitation. Although our study did not aim to identify the causes of survivors' body composition at follow-up, we evaluated associations of percent lean mass with a comprehensive and relevant set of patient and ICU/hospital risk factors, as well as, multiple strength and functional outcomes.

CONCLUSIONS

In their first year after ARDS, survivors gained body weight, but mean percent lean mass decreased while percent fat mass increased. Whole body percent lean mass was not associated with commonly-hypothesized ICU/hospital risk factors, but was associated with patient age, sex and baseline BMI, and with performance-based functional status. These findings suggest that direct measurement of body composition and performance-based functional status may be helpful for understanding the relationship between body composition and functional recovery in ICU survivors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Change in fat and lean mass (kg) for survivors who exhibited weight loss, were weight stable or gained weight from 6 to 12 months based on DXA scans

Notes: 63 subjects had Whole Body DXA results at both follow-ups. Loss (Decrease ≥ 2 kg, N=11), Stable, (Change < 2 kg, N=23), Gain (Increase ≥ 2 kg, N=29). Change in lean mass (kg) and change in fat mass (kg) was not correlated for Loss ($r = -0.10$, 95% CI: -0.66 , 0.54 , $p=0.77$) and Gain ($r = -0.08$, 95% CI: -0.43 , 0.30 , $p=0.68$) groups, but was significant and negatively associated for the Stable group ($r = -0.85$, 95% CI: -0.93 , -0.66 , $p<0.001$)

Table 1

Participant Characteristics

Variables	N=120
Demographics	
Age (years), mean (sd)	50 (15)
Male, n (%)	57 (48)
Race, n (%)	
White	103 (86)
Black	15 (13)
Other	2 (2)
Baseline Health Status	
Charlson Comorbidity Index, mean (sd)	1.2 (1.7)
Functional Comorbidity Index, mean (sd)	1.9 (1.5)
COPD, n (%)	6 (5)
Rheumatologic comorbidity, n (%)	5 (7) ¹
Neurologic comorbidity, n (%)	9 (8)
BMI at enrollment, mean (sd)	32.1 (8.1)
BMI category at enrollment, n (%)	
<18.5 (under-weight)	1 (<1)
18.5 to <25 (normal)	20 (17)
25 to <30 (over-weight)	37 (31)
30 (obese)	62 (52)
SF-36 Physical Function domain score, mean (sd)	44 (13)
ICU and Hospital Encounter Characteristics	
APACHE III score, mean (sd)	86 (28)
PaO ₂ -FiO ₂ ratio ⁴ , n (%) ²	
Mild (200-300)	19 (19)
Moderate (100-200)	57 (58)
Severe (< 100)	23 (23)
Sepsis, primary lung injury risk factor, n (%)	88 (73)
Mechanical ventilation days, mean (sd)	11 (10)
Percentage of ICU days comatose, mean (sd)	19 (18)
Brussels score ³ , average daily percentage of non-failing organ systems, mean (sd)	69 (15)
Ever used corticosteroids in ICU, n (%)	53 (44)
Cumulative dose (prednisone-equivalent ⁵ mg), if any, mean (sd)	813 (1363)
Mean daily dose (prednisone-equivalent ⁵ mg), if any, mean (sd)	107 (168)
Duration of corticosteroids in days, if any, mean (sd)	8 (8)
Ever used neuromuscular blockade, n (%)	30 (25)
Cumulative dose (vecuronium-equivalent ⁵ mg), if any, mean (sd)	260 (453)

Variables	N=120
Mean daily dose (vecuronium-equivalent ⁵ mg), if any, mean (sd)	70 (96)
Duration of neuromuscular blockade in days, if any, mean (sd)	2 (1)
Percentage of ICU days with catecholamine use, mean (sd)	14 (19)
ICU length of stay (days), mean (sd)	15 (11)
Hospital length of stay (days), mean (sd)	22 (15)

¹ Rheumatologic comorbidity data not collected in the SAIL study, percentage based on N=74;

² ARDS severity based on N=99 due to missing values;

³ The Brussels organ failure score was modeled, per patient, as the average daily percentage of non-failing organ systems (cardiac, pulmonary, coagulation, renal and hepatic).

⁴ Measured at study enrollment

⁵ Equivalent doses calculated using standard conversion factors²⁴.

Unadjusted and Adjusted Regression Estimates of ICU/Hospital Exposures with % DXA Whole Body Lean Mass at 6 month

Table 2

Model ¹	Unadjusted Model ²			Adjusted Model ³		
	N	Beta Estimate	p-value	N	Beta Estimate	p-value
ICU and Hospital Exposures						
APACHE III score	87	-0.04	0.28	87	-0.02	0.32
Lung injury from sepsis	89	-4.21	0.03	89	-1.26	0.29
ICU LOS	89	0.08	0.34	89	0.05	0.30
Mechanical ventilation	89	-0.01	0.91	89	0.03	0.60
Percentage of days comatose	82	-0.09	0.08	82	-0.04	0.27
Brussels score, days with organ failure [†]	89	5.47	0.41	89	-0.66	0.87
Hospital LOS	89	0.06	0.39	89	0.03	0.48
Medications Used During ICU						
Percentage of days catecholamines used	89	-0.05	0.32	89	-0.04	0.20
Corticosteroids, cumulative dose						
-Ever	89	-3.04	0.14	89	-1.28	0.29
-Ever*cumulative dose (interaction term)	89	0.001	0.43	89	0.001	0.16
Corticosteroids, mean daily dose						
-Ever	89	-2.51	0.23	89	-0.95	0.44
-Ever*mean daily dose (interaction term)	89	0.001	0.89	89	0.003	0.56
Corticosteroids, duration in days						
-Ever	89	-2.72	0.23	89	-0.52	0.70
-Ever*duration (interaction term)	89	0.04	0.79	89	-0.02	0.85
Neuromuscular blockade, cumulative dose						
-Ever	89	3.31	0.18	89	0.72	0.63
-Ever*cumulative dose (interaction term)	89	-0.01	0.03	89	0.000	0.90
Neuromuscular blockade, mean daily dose						
-Ever	89	3.94	0.14	89	0.97	0.55
-Ever*mean daily dose (interaction term)	89	-0.04	0.04	89	-0.002	0.86

Model ¹	Unadjusted Model ²			Adjusted Model ³		
	N	Beta Estimate	p-value	N	Beta Estimate	p-value
Neuromuscular blockade, duration in days						
–Ever	89	6.50	0.07	89	1.34	0.53
–Ever*duration (interaction term)	89	–2.50	0.04	89	–0.24	0.75

¹The outcome for all models is 6m DXA % whole body lean mass; each row presents results from a separate regression model. For corticosteroids and neuromuscular blockade use, ever-used and the interaction of ever-used with dose/day were included in same regression model.

²For unadjusted models only the specified ICU/Hospital exposure is included.

³Adjusted ICU/Hospital Exposure models each include a specified ICU/Hospital exposure as well as controls for baseline patient variables demonstrating independent association with 6m % whole body lean mass (i.e., age, male sex and BMI, see Appendix Table 1).

⁴The Brussels organ failure score was modeled, per patient, as the average daily percentage of non-failing organ systems (cardiac, pulmonary, coagulation, renal and hepatic).

Table 3

Bivariate Association of DXA % Whole Body Lean Mass with Patient Outcomes

Outcome	Cross-sectional				Longitudinal	
	6 month		12 month		6m DXA with 12m outcome	
	N	Pearson r	N	Pearson r	N	Pearson r
Handgrip, percent predicted	89	0.07	85	-0.15	63	-0.15
MRC muscle strength score	89	0.18	85	0.08	63	0.12
Maximum inspiratory pressure, percent predicted	89	0.35***	83	0.21	61	0.21
Six minute walk distance, meters	85	0.42***	84	0.36***	62	0.45***
Four meter walk test, meters/second	88	0.41***	84	0.27*	62	0.33**
FPI total score	86	0.09	85	-0.06	63	-0.07
FPI body care subscale score	86	0.01	85	-0.07	63	-0.01
FPI maintaining house subscale score	86	0.22*	85	0.07	63	0.06
FPI physical exercise subscale score	86	0.26*	85	0.11	63	0.20
FPI recreation activities subscale score	86	0.07	85	-0.08	63	-0.02
SF-36 Physical Function domain score (normalized)	86	0.28**	84	0.07	62	0.21
EQ-5D mobility question	88	-0.23*	84	-0.03	62	-0.08
EQ-5D self-care question	88	-0.07	84	0.09	62	0.16
EQ-5D activities question	88	-0.05	84	-0.07	62	-0.13
EQ-5D visual analogue score	88	0.01	84	0.03	62	0.09
EQ-5D Utility score	88	0.04	84	-0.03	62	0.10

* =p<0.05,

** =p<0.01,

*** =p<0.001

FPI = Functional Performance Inventory