

# Acute Skeletal Muscle Wasting and Dysfunction Predict Physical Disability at Hospital Discharge in Patients With Critical Illness

Kirby P. Mayer (✉ [kirby.mayer@uky.edu](mailto:kirby.mayer@uky.edu))

University of Kentucky College of Health Sciences <https://orcid.org/0000-0003-3844-3846>

Melissa L. Thompson Bastin

University of Kentucky

Ashley A. Montgomery-Yates

University of Kentucky

Amy M. Pastva

University of Kentucky

Esther E. Dupont-Versteegden

University of Kentucky

Selina M. Parry

University of Melbourne

Peter E Morris

University of Kentucky

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## Research

**Keywords:** critical illness, muscle wasting, ICU-acquired weakness, physical function, acute respiratory failure, sepsis, muscle atrophy, muscle power

**Posted Date:** August 17th, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-57908/v1>

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**Version of Record:** A version of this preprint was published on November 4th, 2020. See the published version at <https://doi.org/10.1186/s13054-020-03355-x>.

# Abstract

**Background:** Patients surviving critical illness develop muscle weakness and impairments in physical function, however, the relationship between early skeletal muscle dysfunction and physical function at hospital discharge remains unclear. The primary purpose of this study was to determine if changes in muscle size, strength and power assessed in the intensive care unit (ICU) predict physical function at hospital discharge.

**Methods:** Study design is a single-center, prospective, observational study in patients admitted to the medicine or cardiothoracic ICU with diagnosis of sepsis or acute respiratory failure. Rectus femoris (RF) and tibialis anterior (TA) muscle ultrasound images were obtained day one of ICU admission, repeated serially and assessed for muscle cross-sectional area (CSA), layer thickness (mT), and echointensity (EI). Muscle strength, as measured by Medical Research Council-sum score, and muscle power (lower-extremity leg-press) were assessed prior to ICU discharge. Physical function was assessed with performance on 5-times sit-to-stand (5STS) at hospital discharge.

**Results:** Forty-one patients with median age of 61 years (IQR 55-68), 56% male, and sequential organ failure assessment score of  $8.1 \pm 4.8$  were enrolled. RF muscle CSA decreased significantly a median percent change of 18.5% from day 1 to 7 ( $F = 26.6, p = 0.0253$ ). RF EI increased at a mean percent change of  $10.5 \pm 21\%$  in the first 7 days ( $F = 3.28, p = 0.081$ ). At hospital discharge 25.7% of patients (9/35) met criteria for ICU-acquired weakness. Change in RF EI in first 7 days of ICU admission and muscle power measured prior to ICU were strong predictors of ICU-AW at hospital discharge (AUC = 0.912). Muscle power at ICU discharge, age and ICU length of stay were predictive of performance on 5STS at hospital discharge.

**Conclusion:** ICU-assessed muscle dysfunction is a predictor of physical disability at hospital discharge in patients surviving critical illness.

## Background

Patients surviving critical illness have significant skeletal muscle dysfunction, including weakness and atrophy.<sup>1,2</sup> Up to two-thirds of patients admitted for critical illness will be diagnosed with Intensive Care Unit-Acquired Weakness (ICU-AW),<sup>3</sup> leading to deficits in physical function.<sup>4,5</sup> As a result, survivors have long-term physical disability leading to difficulty performing activities of daily living (ADL), such as standing up from a chair, and deficits in these basic ADLs are highly associated with poor Health Related-Quality of Life (HRQoL).<sup>6,7</sup> Observational and single-center randomized controlled trials demonstrate that physical rehabilitation provided in the ICU may positively influence short- and long-term patient outcomes, including enhanced muscle strength, reduced mechanical ventilation duration, and improved HRQoL.<sup>8-10</sup> Additionally, clinical practice guidelines support physical rehabilitation for mitigating the detrimental effects of immobilization periods that occur during critical illness.<sup>11,12</sup> However, recent ICU-based physical rehabilitation randomized controlled trials (RCTs) fail to demonstrate robust immediate or long-

term functional benefits.<sup>13-18</sup> One potential explanation for these results is subject heterogeneity.<sup>19</sup> Also, rehabilitation trials rarely implement or stratify interventions based on muscular dysfunction leading to “one-size fits-all” interventions.

Muscle strength and muscle power are vital components of muscular function. Muscle power is differentiated from muscle strength in that power accounts for velocity (distance/time) of force production, while muscle strength is the ability to generate maximal muscle force only.<sup>20</sup> Muscle power is crucial for daily activities that require velocity to overcome distance or gravity, such as standing up from a chair or from a toilet.<sup>21,22</sup> However, muscle power is not a current focus in ICU or hospital rehabilitation. Assessment of muscle power is novel in this population and deficits in power suffered during critical illness may help explain persistence of physical impairments.

Early classification of muscle dysfunction, including the degree of deficits, is important for appropriate allocation of rehabilitation interventions, but difficult due to the heterogeneity and severity of acute critical illness.<sup>23</sup> Muscle ultrasound has gained significant traction as a tool to assess and track changes in skeletal muscle potentially improving classification of patients who may be at risk for muscular or physical impairments. However, data surrounding muscle ultrasound are conflicting. A recent study demonstrated that muscle size measured at day 7 of ICU admission was not predictive of ICU-AW,<sup>24</sup> while an observational study in a cohort of 22 critically-ill patients demonstrated that muscle size and quality were associated with physical function at ICU discharge.<sup>25</sup> Additionally, earlier and greater change in muscle size measured by ultrasound were associated with in-hospital mortality, mechanical ventilation (MV) duration, and ICU-AW.<sup>26</sup> Conflicting evidence may be attributed to the heterogeneity in patient populations and potentially discrepancies in user approach leading to variations in practice and human operator error.<sup>27</sup> Currently, there is a need to determine if muscle dysfunction assessed in ICU is related to or predictive of ICU-AW and physical function at hospital discharge. The primary purpose of this study was to determine if muscle dysfunction assessed by changes in muscle size, quality and power are associated with or predicts physical function at hospital discharge.

## Methods

### Ethical Considerations

This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and approved by the Institutional Review Board at the University of Kentucky. Research subjects or legally authorized representative provided written informed consent before participating in the study. Consent was obtained from a legally authorized representative for patients unable to give consent due to sedation, mentation, and/or consciousness, re-consent was obtained once patient was awake, stable, and could provide informed consent themselves.

*Study Design:* A prospective, longitudinal observational study was conducted with adult patients admitted to Medicine ICU (MICU) or the Cardiothoracic ICU (CTICU) and enrollment occurred from November 15,

2018, to July 15, 2019. Eligibility criteria were: 18 years of age or older with a primary or secondary diagnosis of acute respiratory failure (ARF) or sepsis of any origin that were anticipated to spend more than 3 days in the MICU/CTICU and survive the current hospitalization and enrolled within 48 hours of admission. Patients were excluded from enrollment if they had baseline cognitive impairments, were non-ambulatory prior to hospitalization, had a pre-existing neurologic or neuromuscular disorder, new traumatic injury with lower-extremity fracture, one or more amputations of lower-extremity, were pregnant, admitted for substance abuse or were otherwise inappropriate for study procedures as determined by the primary attending physician. Patients with morbid obesity (body-mass index (BMI) > 45 kg/m<sup>2</sup>) were excluded to reduce distortion of ultrasound images.

*Muscle Size and Echointensity:* The Sonosite IViz (FUJIFILM SonoSite Inc. Bothell, WA) portable ultrasound with 8.5-MHz linear transducer was used to assess the right rectus femoris (RF) and the right tibialis anterior (TA) muscle on ICU days 1, 3, 5, and 7. Ultrasound device settings were kept constant for subjects across time-points with the same sonographer (KM, physical therapist, PhD, > 4 years of muscle ultrasound experience) acquiring all images.<sup>28</sup> The methods for image acquisition and analysis of RF and TA were previously reported<sup>1,29</sup> and have good to excellent reliability<sup>28,30-32</sup>. Minimal probe compression and depth of 5.9 cm were utilized to obtain three images at all timepoints of both muscles with RF muscle imaged at 2/3 distance from Anterior Superior Iliac Spine (ASIS) to superior patella border and TA muscle imaged at 1/3 distance from lateral tibial plateau to inferior border of the lateral malleolus. Images were saved on the device hard-drive and transferred to computer for analysis using ImageJ software (NIH, Bethesda, MD). The average value of three consecutive images was used in analyses.<sup>25,27</sup> Each ultrasound image was analyzed for quantification of muscle cross-sectional area (CSA) and thickness (mT), and for muscle quality (Echogenicity- EI)<sup>28</sup> with two approaches: CSA, mT and EI on ICU day one of admission to ICU (baseline) and parameters as percentage change from ICU day 1 to day 7.

## **Muscle strength, power and physical function**

Prior to volitional assessments, patient had to be oriented (determined as ability to complete 3 of 4 domains of name, birthday, location, and date) and demonstrate ability to follow commands by scoring  $\geq 3/5$  on DeJonghe criteria.<sup>33</sup>

### **Muscular strength**

Muscle strength was assessed using three different techniques at ICU and hospital discharge

- 1) The Medical Research Council sum score (MRC-SS) is a measure of global peripheral limb muscle strength that is standard of care for diagnosing ICU-AW.<sup>33-35</sup>
- 2) Muscle strength force production and the rate of force development of the knee extensors and ankle dorsiflexion strength were recorded using a hand-held dynamometry (HHD) (Lafayette Manual Muscle Test System Model-01165, Lafayette Company, Lafayette, IN).<sup>36</sup>

3) Hand-grip strength were assessed using the Jamar Hydraulic dynamometer (Sammons Preston Rolyan, Bolingbrook, IL, USA).<sup>37</sup>

## **Muscle Power**

Muscle power was assessed prior to ICU discharge and hospital discharge with a linear potentiometer (HUMAC-360, CSMi, Stoughton, MA) to record the velocity and peak-velocity of a unilateral lower-extremity press using a Shuttle MiniPress (Shuttle Systems, Bellingham, WA) while sitting in hospital bed or seated in hospital chair. Subjects performed three repetitions of the leg press at two pre-determined levels of resistance, 2 lbs and 10% of bodyweight. Patients were permitted to perform three repetitions for familiarization prior to formal testing.

## **Physical functional outcomes**

The primary physical function outcome of interest was performance of 5-times sit to stand test (5x STS) at hospital discharge since it is a fundamental component of mobility and an independent measure of muscle strength and power.<sup>38</sup> The Short Performance Physical Battery (SPPB)<sup>39,40</sup>, six-minute walk distance (6MWD)<sup>41,42</sup> and clinical frailty scale (CFS) were assessed at hospital discharge. The Physical Function in the ICU Test (PFIT-s) was performed by staff physical therapists according to routine care which includes performing the test once prior to ICU discharge.<sup>43,44</sup>

## **Clinical Variables**

Baseline demographics (age, sex, BMI), Charlson Comorbidity Index (CCI), and critical illness data including ICU admission diagnosis, Sequential Organ Failure Assessment (SOFA), hours of mechanical ventilation (MV), ICU and hospital length of stay (LOS), time to first rehabilitation session, number of rehabilitation sessions, sedation (yes/no), use of inotropes and vasopressors (yes/no), and mortality (defined as in-hospital mortality plus transfer to inpatient hospice) were assessed.

A priori sample size calculation: Puthuchery et al previously reported a sample size of 32 patients to detect a 10% reduction in RF muscle CSA over first ten days of ICU admission.<sup>1</sup> Parry et al utilized a pragmatic sample size (n = 20) to demonstrate a 25% reduction in RF muscle CSA in first seven days<sup>25</sup>. Therefore, we utilized a pragmatic sample of 40 patients for this study.

## **Statistical Analysis**

Data were assessed using descriptive statistics including mean and standard deviation (SD) or median and interquartile range (IQR), histograms, and Shapiro-Wilk test for normality. Ultrasound data were examined for change over time using a linear mixed-model approach. The relationships between muscle ultrasound parameters, muscle power, muscle strength, demographics, clinical, and physical function data were assessed with Spearman Rho tests. A multivariate logistic regression model was created to assess the effects of independent variables on development of ICU-AW at hospital discharge. Variables

identified for the model included baseline demographics (age, sex, BMI) and other variables that are purported to be associated with weakness including muscle size and quality, severity of illness, ICU length of stay and muscle power. Stepwise backwards regression at the 0.2 level was used to minimize overfitting. Power assessment (10% BW) at ICU discharge was forced into the model, as this is our primary exploratory predictor variable. Using the same approach, a multivariate linear regression was used to assess the relationship between predictor variables with dependent variable of 5-times sit-to-stand performance at hospital discharge. The models were tested for assumptions of logistic and linear regression as appropriate. Multicollinearity was assessed using variance inflation factor; normality of errors was assessed with the IQR test. We assessed model fit with the Hosmer-Lemeshow and likelihood ratio tests. Heteroskedasticity of residuals was assessed with the Breusch-Pagan/Cook-Weisberg test, and standardized robust errors were used to adjust for heteroscedasticity in the models as appropriate. All other assumptions were met. Data were analyzed and visualized using GraphPad Prism 8.2 (GraphPad Software, San Diego, CA) and regression analyses were performed using Stata (version 14.2, Stata Corp, College Station, Texas, USA). Data are presented as mean and SD or median and IQR.

## Results

Forty-eight patients admitted to MICU and CTICU with median age of 61 (55–68), 56% (n = 27) male, and admission SOFA score of  $8.1 \pm 4.8$  were enrolled in this study. Seven patients were removed due to missing ultrasound images at baseline due to assessor unavailable (n = 1) or images available could not be analyzed due to poor quality (n = 6). Demographic and clinical data of the forty-one patients included in the analyses are presented in Table 1. The time to first ultrasound measurement was median 1.1 days (IQR 0.77–1.4) after ICU admission. Paired ultrasound data were available for 35 patients on day 1 and day 7 of ICU admission and 6 patients had missing images due to assessor unavailable (n = 2) or patient discharged prior to day 7 (n = 4) and thus US data from ICU day 5 was utilized in analyses. Thirty-five patients participated in muscle strength, power, and physical functional testing at hospital discharge. One patient's time-point was missed by researcher and 5 patients died or transferred to inpatient hospice before discharge (**Supplemental Fig. 1**).

Table 1  
Patient demographics and critical illness data

Parameter	(n = 41)
Age (years), median [IQR]	61 [55–68]
Male, n (%)	23 (56)
BMI (kg/m <sup>2</sup> ), mean (SD)	29.6 (6.3)
Charlson Comorbidity Index, mean (SD)	5.5 (3.12)
Admitted to Medical ICU, n (%)	30 (73)
Admitted to Cardiothoracic ICU, n (%)	11 (27)
SOFA at ICU admission, mean (SD)	8.1 (4.8)
ICU LOS days, median [IQR]	8 [4–13]
Hospital LOS days, median [IQR]	11.2 [8–19]
MV, n (%)	30 (73)
MV days, median [IQR]	3.4 [1–7.7]
Sedation, n (%)	24 (59)
CRRT, n (%)	5 (12)
Inotropes and pressor, n (%)	25 (61)
Time to first ultrasound measures, days, median [IQR]	1.1 (0.7–1.4)
Time to initial physical therapy session, days, mean (SD)	2.6 (1.84)
Time to initial occupational therapy session, days, mean (SD)	3.2 (2.71)
Number of rehabilitation visits for entire hospital stay, median, [IQR]	6 [4–9.25]
In-hospital mortality, n (%)	5 (12)
IQR = interquartile range; ICU = intensive care unit; BMI = body mass index; SOFA = sequential organ failure assessment; LOS = length of stay; ICU = intensive care unit; MV = mechanical ventilation; CRRT = continuous renal replacement therapy;	

### Muscle ultrasound parameters (n = 41), Fig. 1

Rectus femoris mT at baseline was  $0.98 \pm 0.3$  cm and decreased at median percent change of 20.1% (IQR 12 to 26%) from ICU day 1 to day 7, statistically significant change over time ( $F = 34.89$ ,  $p = 0.0316$ ). The mean quadriceps complex mT at baseline was  $2.04 \pm 0.71$  cm and decreased at median percent change of 14.5 (IQR 7–24%) across first seven days ( $F = 21.7$ ,  $p = 0.003$ ). The mean baseline TA mT was  $2.01 \pm 0.36$  cm with median decrease of 9.1% (IQR 5–12%) in the first seven days ( $F = 28.3$ ,  $p < 0.001$ ). CSA of

RF muscle at baseline was  $2.99 \pm 0.99 \text{ cm}^2$  and decreased at median percent change of 18.5% (IQR 1% to 23%) in the first 7 days ( $F = 26.6, p = 0.0253$ ). TA CSA at baseline was  $5.3 \pm 0.89 \text{ cm}^2$  with median decreased of 8.1% (IQR 5–15%) in first seven days ( $F = 34.7, p < 0.001$ ). Rectus Femoris EI at baseline was  $91 \pm 24.9$  and increased at a median percent change of 10.5% (IQR – 5–20%) in the first seven days ( $F = 3.28, p = 0.081$ ). Tibialis Anterior EI was  $82.7 \pm 21.2$  at baseline and increased at median percent change of 15.4% (IQR 7–28%) within the first 7 days (IQR 7 to 27,  $F = 6.73, p = 0.002$ ).

### **Muscle Power**

Twenty-six patients completed muscle power in the ICU with mean  $8.0 \pm 2.9 \text{ W}$  for 2 lbs resistance and  $44.8 \pm 22.6 \text{ W}$  for 10% of body weight test (Table 2). Muscle power increased from ICU to hospital discharge at a median percent change of 35% (IQR 15–55%) for 2 lbs resistance and 27% (IQR 7–48%) for 10% of BW resistance. Muscle power assessment at 2 lbs and 10% of BW were highly correlated, and therefore only muscle power at 10% of BW was utilized in statistical analysis.

Table 2  
Muscle Ultrasound, strength, power and physical function

Muscle parameter	Day 1	Day 7
<b>Ultrasound Parameters</b>	n = 41	n = 41
TA mT (cm)	2.01 (0.36)	1.82 (0.31)
TA CSA (cmPP <sup>2</sup> PP)	5.28 (0.89)	4.71 (0.95)
TA EI (0-255)	82.7 (21.2)	96.7 (22.6)
RF mT (cm)	0.98 (0.3)	0.81 (0.27)
RF + VI mT (cm)	2.04 (0.71)	1.77 (0.62)
RF CSA (cmPP <sup>2</sup> PP)	2.99 (0.99)	2.47 (0.88)
RF EI (0-255)	90.7 (24.9)	99.1 (27.6)
	<b>ICU Discharge</b>	<b>Hospital Discharge</b>
<b>Muscle Power (W)</b>	n = 26	n = 33
2 lbs	8.0 (2.89)	9.6 (3.5)
10% bodyweight	44.8 (22.6)	58.7 (30.6)
<b>Muscle Strength</b>	47.1 (7.3) (n = 31)	51.4 (5.7) (n = 35)
MRC-ss (0–60)	16.9 (5.3) (n = 24)	19.8 (6.9) (n = 31)
RF HHD force (kg)	3.8 (1.1) (n = 24) <sup>e</sup>	3.6 (1.1) (n = 31) <sup>g</sup>
RF HHD RFD (seconds)	14.5 (5.2) (n = 24) <sup>e</sup>	15.6 (5.4) (n = 31) <sup>g</sup>
TA HHD (kg)	3.9 (1.2) (n = 24) <sup>e</sup>	3.7 (1.2) (n = 31) <sup>g</sup>
TA HHD RFD (seconds)	18.2 (9.1) (n = 26) <sup>b</sup>	21.7 (10.0) (n = 32)
Handgrip (kg)		
<b>Physical Function</b>	4.7 (3.9) (n = 26) <sup>b</sup>	5.9 (4.0) (n = 35) <sup>f</sup>
SPPB	0.49 (0.18) (n = 19)	0.56 (0.27) (n = 31) <sup>g</sup>
4-m gait speed (m/s)	14.8 (5.6) (n = 13)	18.9 (14.5) (n = 28)
5x STS (seconds)	1.96 (1.4) (n = 19) <sup>i</sup>	2.3 (1.2) (n = 31) <sup>g</sup>
Balance	265 (182) (n = 26) <sup>b</sup>	455 (424) (n = 35) <sup>f</sup>
6 MWT distance (feet)	6.1 (1.5) (n = 36)	5.3 (1.7) (n = 36)
CFS		

Muscle parameter	Day 1	Day 7
		<p>TA = tibialis anterior muscle; RF = rectus femoris muscle; CSA = cross-sectional area, mT = muscle layer thickness; EI = echointensity; MRC-ss = medical research council-sum score; VI = vastus intermedius muscle; HHD = handheld dynamometer; RFD = rate of force development; SPPB = short performance physical battery; 5x STS = five-times sit-to-stand test; 6 MWT = six-minute walk test; W = watts; CFS = clinical frailty scale;</p>
		<p>a 10 patients unable to complete test: 4 patients unable to follow commands/poor cognition; 3 patients had &lt;3/5 strength; 2 were missed by assessor; and 1 patient was unable to maintain oxygen saturations &gt;10% of baseline with simple movement in bed;  b 3 unable to complete: 2 patients with &lt; 3/5 strength and 1 patient unable to complete test: missed by assessor  c 5 patients unable to complete: 4 patients unable to follow commands/poor cognition, 1 patient declined due to pain  d 12 patients unable to complete test: patients reported in footnote b plus 2 patients fatigued after initial testing and physically were unable to perform HHD testing  e 1 patient declined due to pain  f 5 patients unable to complete: 2 with &lt; 3/5 strength, 2 deferred to pain/fatigue, 1 patient missed by assessor  g 4 patients unable to complete: 2 with &lt; 3/5 strength, 1 deferred to pain/fatigue, 1 patient missed by assessor  h 17 patients unable to complete test: patients reported in footnote b plus 7 patients unable to stand for balance or walk 4m without physical assistance  i 23 patients unable to complete test: patients reported in footnote b plus 13 patients unable to stand from chair in time allotted or without assistance  j 8 patients unable to complete: 2 with &lt; 3/5 strength, 2 deferred to pain/fatigue, 1 patient missed by assessor, 3 patients could not performed without assistance</p>

**Relationship between muscle power, strength and physical function at hospital discharge (n = 35)**

At hospital discharge the mean MRC-ss was 52.4 (5.7) with 25.7% (9/35) meeting criteria for ICU-AW (< 48/60). Hand-grip strength was 21.7 ± 10 kg and RF muscle strength measured by HHD was 19.8 ± 6.9 kg with 3.6 ± 1.1 seconds to peak force production (Table 2). Patients scored an average 5.9 ± 4 on SPPB, with 0.56 ± 0.3 m/s gait speed and 18.9 ± 14 seconds to complete 5-times sit-to-stand test (Table 2). RF EI on day 1 of ICU admission was associated with performance on 5x STS (rs = 0.462, 0.013), ICU-AW (rs = 0.337, p = 0.048), and CFS score (0.460, 0.003) at hospital discharge (Table 3). Muscle power measured prior or at ICU discharge was significantly related to ICU-AW and CFS at hospital discharge (Table 3).

Table 3

Correlations demographics, clinical data, and muscle parameters measured ICU with physical function at hospital discharge. Ultrasound images analyzed as baseline (day of ICU admission) and change in TA from day 1 to day 7 (delta). Spearman rho tests presented as correlation coefficient.

Variable	Physical Function and Frailty at Hospital Discharge				
	5x STS	ICU-AW	4-m gait speed	6 MWT	CFS
Age	0.822, < 0.001	0.269, 0.118	-0.629, < 0.001	-0.596, < 0.001	0.554, < 0.001
BMI	0.386, 0.042	-0.285, 0.097	-0.355, 0.054	-0.210, 0.219	0.093, 0.567
CCI	0.369, 0.053	0.137, 0.431	-0.269, 0.151	-0.359, 0.032	0.340, 0.032
SOFA	-0.352, -0.066	0.400, 0.017	0.262, 0.162	0.144, 0.401	-0.219, 0.174
ICU LOS	-0.262, 0.178	0.348, 0.041	0.324, 0.081	0.028, 0.872	0.155, 0.339
Hospital LOS	-0.323, 0.094	0.440, 0.008	0.433, 0.017	0.061, 0.722	-0.026, 0.872
RF mT	-0.145, 0.461	-0.308, 0.072	0.002, 0.993	0.059, 0.732	-0.152, 0.349
Delta RF mT	-0.178, 0.366	-0.272, 0.114	-0.082, 0.667	-0.079, 0.646	0.047, 0.775
RF CSA	-0.230, 0.248	-0.239, 0.166	0.131, 0.491	0.211, 0.217	-0.239, 0.138
Delta RF CSA	0.123, 0.532	-0.181, 0.297	-0.261, 0.163	-0.105, 0.541	-0.003, 0.983
RF EI	0.462, 0.013	0.337, 0.048	-0.324, 0.081	-0.295, 0.080	0.460, 0.003
Delta RF EI	-0.306, 0.110	-0.214, 0.218	0.280, 0.134	0.190, 0.268	-0.139, 0.392
PFIT-s*	-0.447, 0.019	-0.640, < 0.001	0.255, 0.191	0.648, < 0.001	-0.763, < 0.001

\* measured at ICU discharge, "Delta" represents the percentage change in muscle mT, CSA, and EI from day 1 to day 7

CCI = Charlson Comorbidity Index; SOFA = sequential organ failure assessment; MRC-ss = Medical Research Council Sum Score; RF = rectus femoris muscle; HHD = handheld dynamometry; SPPB = short performance physical battery; 5x STS = five time sit-to-stand test; 6 MWT = six minute walk test; mT = muscle layer thickness; CSA = cross-sectional; EI = echo-intensity

Variable	Physical Function and Frailty at Hospital Discharge				
	5x STS	ICU-AW	4-m gait speed	6 MWT	CFS
MRC-ss*	-0.409, 0.047	-0.626, < 0.001	0.071, 0.731	0.429, 0.018	-0.478, 0.006
Handgrip*	-0.416, 0.001	-0.649, < 0.001	0.167, 0.447	0.365, 0.073	-0.489, 0.011
RF HHD*	-0.396, 0.076	-0.597, 0.003	0.122, 0.589	0.443, 0.034	-0.551, 0.005
Muscle Power (10% BW)*	-0.386, 0.076	-0.541, 0.005	0.164, 0.456	0.384, 0.058	-0.622, 0.001
* measured at ICU discharge, "Delta" represents the percentage change in muscle mT, CSA, and EI from day 1 to day 7					
CCI = Charlson Comorbidity Index; SOFA = sequential organ failure assessment; MRC-ss = Medical Research Council Sum Score; RF = rectus femoris muscle; HHD = handheld dynamometry; SPPB = short performance physical battery; 5x STS = five time sit-to-stand test; 6 MWT = six minute walk test; mT = muscle layer thickness; CSA = cross-sectional; EI = echo-intensity					

## Prediction Modeling

Multivariate logistic regression predicted diagnosis of ICU-AW by < 48/60 on MRC-ss with muscle power, change in rectus femoris CSA and EI, and sex as predictor variables. Muscle power and change in RF EI in first 7 days of ICU admission were the strongest predictors of ICU-AW (Table 4, **Area Under Curve = 0.912, Supplemental Fig. 2**). Multivariate linear regression demonstrated that muscle power, age and ICU LOS are significant predictors of muscle 5x STS performance (Table 4). Muscle power measured prior to ICU discharge was a strong independent predictor of sit-to-stand at hospital discharge.

Table 4

Multivariate Logistic Regression predicting ICU-AW at hospital discharge and Multivariate Linear Regression predicting sit-to-stand performance at hospital discharge

<b>Dependent variable: diagnosis of ICU-AW at hospital discharge</b>					
<b>Model p = 0.003 R<sup>2</sup> = 0.51, VIF = 1</b>	<b>Odds Ratio</b>	<b>Standard Error</b>	<b>z</b>	<b>P&gt; z </b>	<b>[95% Conf. Interval]</b>
Power 10% BW in ICU	0.033	0.04	-2.02	0.044	0.85, 0.99
Change in RF CSA days 1 to 7	< 0.001	0.0001	-1.33	0.182	8.12e-13, 197.7
Change in RF EI days 1 to 7	4.40	0.0003	-1.78	0.074	5.76e-12, 3.36
Male	0.53	1.25	1.56	0.787	0.005, 54.3
<b>Dependent variable: performance on 5x STS test at hospital discharge</b>					
<b>Model p = 0.04, R<sup>2</sup> = 0.55, VIF 1.11</b>	<b>β-Coefficient</b>	<b>Standard Error</b>	<b>t</b>	<b>P&gt; t </b>	<b>[95% Conf. Interval]</b>
Power 10% BW in ICU	-0.282	0.124	-2.26	0.036	-0.543, -0.020
Age	0.534	0.173	3.09	0.006	0.171, 0.897
ICU LOS	-0.091	0.033	-2.76	0.013	-0.161, -0.0217
BW = bodyweight; RF = rectus femoris; CSA = cross-sectional area, EI = echo-intensity; ICU = intensive care unit; LOS = length of stay					

## Discussion

The results of this study demonstrate that muscle ultrasound parameters, specifically RF EI, and lower extremity muscle power measured in the ICU are significant predictors of physical function at hospital discharge. Assessment of muscle dysfunction by ultrasound and muscle power in the early course of critical illness, when combined with age and ICU LOS, may improve classification and prognostication of patients in the ICU at risk for weakness and physical dysfunction. Identifying the risk of physical impairments in critically-ill patients upon admission or within the first few days in the ICU is important to improve clinical-decision making for therapeutic interventions. Timely assessment of muscle dysfunction promotes an increased understanding of type and severity of muscle dysfunction, which can improve prognostication and may lead to a more specific dosage of rehabilitation interventions and/or pharmacologic intervention to mitigate current or continued function decline. Furthermore, muscle power is a novel concept that is rarely assessed in patients with and in those patients that have survived critical illness, but should be incorporated in routine practice since power is a clinically important determinant physical function.

Muscle power is not a current focus in critical care rehabilitation, but is a key component of functional mobility<sup>21</sup> and is important because it accounts for velocity (time and distance) to perform task. Muscle

power may present a novel therapeutic target with focus on an individualized training for patients with deficits. In older individuals, muscle power has been shown to decline earlier and at a steeper rate than muscle strength,<sup>45,46</sup> and therefore power training is a modality purported to mitigate the effects of sarcopenia.<sup>47</sup> Critical illness muscle dysfunction certainly has different underlying mechanisms of muscle atrophy when compared to mechanisms of age-related muscle mass loss. The concepts of muscle power training, however, may be beneficial in both populations. Additionally, more than half of ICU admissions in the USA are older individuals (> 65 years of age)<sup>48</sup> and thus suggest muscle power is an important construct in muscle and physical dysfunction for those critically ill. Changes in muscle power may be explained by a selective decrease in type-II muscle fibers, which are most important for power production. Data from muscle biopsies in patients with critical illness demonstrate that type-II fibers may have smaller CSA and potentially decrease at more predominant rate than type-I fibers patients requiring mechanical ventilation.<sup>49,50</sup> Additionally, selective loss of type-II muscle fibers and a fiber-type shift from fast (type-II) to slow (type-I) in critically ill patients is supported in models of sepsis<sup>51</sup> and cancer cachexia.<sup>52,53</sup> Data from muscle power assessment in this study had moderate to strong correlations with rectus femoris muscle size and quality, and physical function. Rectus femoris muscle has a high composition of type IIA and IIX muscle fibers<sup>54</sup> and thus support the connection between changes in size, quality, and power in this study and subsequently reduced physical function. Muscle power increased from ICU to hospital discharge, which may suggest time-points in the ICU may be influenced by limited voluntary muscle contraction when patients are acutely ill.

Lower-extremity muscle power measured in this cohort had similar correlations with physical function when compare to muscle strength assessments. The ability to generate force, quickly to overcome gravity to stand from seated position requires lower-extremity muscle power.<sup>55</sup> Previous data suggest that older patients and those with longer mechanical ventilation will have delayed time to achieve independence with sit-to-stand transfer.<sup>56</sup> Thus, 5x STS was selected as the primary physical function outcome of interest since it has strong construct validity with muscle strength and power, an important measure of functional mobility.<sup>57,58</sup> Muscle power measured at hospital discharge in this cohort was significantly reduced compared to previously reported data from healthy, age matched controls (reductions up to 52%, *manuscript accepted with minor revisions*). Muscle power should be explored in future studies to understand long-term recovery.

Results of the current study confirm the rapid and significant deterioration in skeletal muscle size and quality in patients admitted to the ICU for critical illness that have been reported in prior published work.<sup>1,25,59,60</sup> We demonstrated decrease in RF muscle CSA of 19% in first week of critical illness, slightly higher than prior data ranging from decreases 12.5–17%.<sup>1,25,61</sup> It should be noted that baseline RF muscle size (mT and CSA) was lower when compared to previous studies.<sup>25,60</sup> This may be explained by differences in landmarking, variability in sonographer compression technique, and, more likely, differences in study populations. Specifically, the inclusion of patients in the cardiothoracic ICU with heart or lung failure with potential for chronic wasting and frailty may explain part of the differences in

baseline rectus femoris muscle size. Differences in techniques and heterogeneous populations confirm the need to develop standardized approaches when performing muscle ultrasound in the ICU.<sup>27</sup> EI, a marker of muscle quality,<sup>62</sup> increased across these same time-points by 10.5%, which is similar to prior published data (+ 9.6%).<sup>25</sup> These changes are purported to be clinically meaningful deteriorations in the muscle structure potentially related to myofiber necrosis.<sup>62,63</sup>

Muscle ultrasound is a non-invasive and relatively inexpensive tool that can be implemented early during critical illness to potentially expedite classification of muscle dysfunction. Early diagnosis and classification of patients at risk for physical impairments may improve outcomes by promoting earlier allocation or greater intensity (number of visits) of physical rehabilitation. Current diagnosis of ICU-AW is typically delayed until the patient can volitionally engage in the MRC-ss.<sup>34,64</sup> Therefore, ultrasound used early in the time-course of critical illness when patients are not yet able to volitionally engage may improve assessment of muscle dysfunction. Data from this study demonstrate that deterioration in rectus femoris muscle quality are moderately and significantly correlated to ICU-AW, physical function and clinical frailty scale at hospital discharge. Therefore, this study provides preliminary data to suggest that quantification of muscle size and quality with ultrasound imaging can improve classification.

The primary limitation of this study is the small sample size limiting the strength of correlations and the strength of the modeling or prediction analyses. Multivariate logistic and linear regression were performed as exploratory analyses but should be interpreted with caution due to the study being under-powered. A secondary limitation is some missing data due to assessor availability or the patient unable to complete tests due to pain, lack of cognitive function or change in care to hospice or comfort care.

## Conclusion

In this study we showed that changes in muscle size, quality and power in the ICU are significantly related to physical function in patients with critical illness. Muscle power could be an important measure to be considered in the clinical assessment of patients with and those patients that have survived critical illness.

## Declarations

**Ethics approval and consent to participate:** This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and approved by the Institutional Review Board at the University of Kentucky. Research subjects or legally authorized representative provided written informed consent before participating in the study. Consent was obtained from a legally authorized representative for patients unable to give consent due to sedation, mentation, and/or consciousness, re-consent was obtained once patient was awake, stable, and could provide informed consent themselves.

**Consent for publication:** Not applicable

**Availability of data and materials:** The minimal data are included in this published article. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Competing interests:** The authors declare that they have no competing interests

**Funding:** Dr. Mayer was supported in part by a Promotion of Doctoral Studies (PODS) – Level II Scholarship from the Foundation for Physical Therapy Research.

Dr Selina Parry is currently supported by an NHMRC Early Career Fellowship (1111640).

**Authors' contributions:** KPM, SMP, PEM, EEDV contributed to all phases of the research study and manuscript writing. MTB performed and assisted with data management and data analyses. AMY and AMP provided scientific oversight and assisted with editing. All authors read and approved the final manuscript.

**Acknowledgements:** Dr. Mayer would like to acknowledge Jamie Sturgill, PhD, Evan Cassity, MS and Sherif Sheif, MBBCh for their support and technical assistance with IRB polices and research methodology.

## Disclosures

No authors of this study have any relevant financial or other conflict-of-interests related to the content of this project for disclosure.

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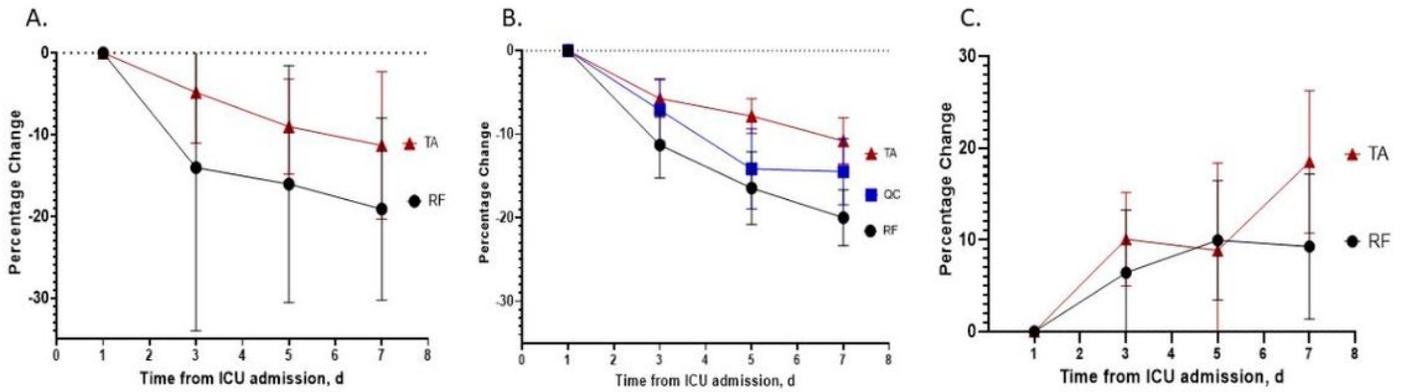
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## Figures



**Figure 1**

Change in rectus femoris and tibialis anterior muscle size and quality in first seven days of ICU stay. Panel A) percent change of muscle layer thickness; Panel B) percent change of muscle cross sectional area C) Percent change of echo intensity from day 1 to 7 d = days, RF = rectus femoris muscle; QC = quadriceps complex muscles; TA = tibialis anterior muscle

## Supplementary Files

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