Title: Assessment of skeletal muscle mass in critically ill patients: considerations for the utility of computed tomography imaging and ultrasonography

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ABSTRACT

Purpose of review: Low muscularity and skeletal muscle atrophy are commonly exhibited in critically ill patients and has major implications on patient outcomes. Typically, in the intensive care unit (ICU), body composition is assessed through anthropometrics or bioelectrical impedance analysis, but these modalities cannot specifically quantify skeletal muscle; thus, we evaluate the merits and challenges of using computed tomography (CT) and ultrasonography to specifically measure skeletal muscle in the ICU.

Recent findings: CT-based cut-points have been used to identify critically ill patients with low muscle mass, and low muscularity associates with poor clinical outcomes and function. Ultrasonography is emerging as a useful tool to quantify skeletal muscle loss and degradation in architecture, as well as prospectively track changes in these parameters over time. Rates of muscle atrophy and changes in muscle architecture has been quantified by ultrasonography and associated with poor clinical outcomes, but identification of critically ill patients with low muscularity is still in its infancy.

Summary: CT imaging and ultrasonography require additional comprehensive validations against accurate measures of whole body muscle mass. As these validations begin to emerge, there will be a need to translate this knowledge into a simple tool that clinicians can apply as part of routine care.

INTRODUCTION

Skeletal muscle is a compartment of lean body mass and is a highly plastic tissue. Loss of muscle mass is prevalent amongst critically ill patients [1, 2] and may have important implications on metabolic and clinical outcomes [1, 3]. Research in the intensive care unit (ICU) has typically utilized body mass index (BMI), anthropometric measures (such as circumferences) and bioelectrical impedance analysis (BIA) to measure or predict body size or fat-free mass. While these tools may be clinically accessible, expedient and relatively inexpensive, they only provide surrogate measures of muscle mass. It is important to distinguish skeletal muscle from other tissues because changes in skeletal muscle can independently alter glucose and cytokine regulation [4, 5] and may also have unique implications on clinical outcomes including survival [3, 6**], ICU length of stay [3] and physical function post-ICU [7].

Lean body mass is comprised of skeletal muscle, liver, other internal organs and connective tissues; each of these tissues may distinctly change during critical illness and may mask muscle atrophy. For example, if the liver or spleen exhibited an increase in size, this may mask the loss of muscle if measures of whole body lean tissue or total body weight were used as surrogates. To understand the exclusive role of skeletal muscle in ICU patients and its relation to clinical outcomes, modalities that specifically quantify skeletal muscle are needed. Two such technologies, computed tomography (CT) imaging and ultrasonography, which have traditionally been used for diagnostic purposes or clinical follow-up, are now opportunistically utilized for specific quantification of skeletal muscle. CT imaging and ultrasonography can accommodate some of the unique challenges that ICU patients typically present. For example, moving a patient is highly challenging as the patient may be heavily sedated, may require strict

immobilization and have several lines inserted. Retrospectively analyzing CT scans (taken as part of routine care) or using highly accessible ultrasound equipment may accommodate these challenges to provide measures of skeletal muscle. However, interpretation of results from patients in the ICU using any modality requires care given: variability in hydration status, challenges in acquiring height and limb length (for normalizing muscle cross-sectional area (CSA) in CT scans or muscle thickness or area in ultrasound), bias in the type of patients that have CT scans, as well as the extent that edema confounds muscle measures. In this narrative review, we briefly discuss the importance of measuring skeletal muscle mass in ICU patients and address its value to clinical research as well as clinical practice. Subsequently, we will critically examine the utility, merits and challenges of CT imaging and ultrasonography as body composition technologies in the ICU.

IMPORTANCE OF MEASURING SKELETAL MUSCLE IN THE ICU

In ICU patients, bedrest, immobilization, systemic inflammation, reduced peripheral blood flow, reduced protein intake and ICU-based insulin resistance contribute to muscle atrophy. Critically ill patients can lose 17-30% of their muscle within the first 10 days of ICU admission [2, 8**]. The magnitude of muscle atrophy may be amplified in patients with multi-organ failure (16% loss in the first 7 days of ICU) compared with single-organ failure (3% loss in the first 7 days of ICU) [2]. Skeletal muscle is central to cytokine regulation [5] and it contributes 85% of total body glucose clearance [4]. Thus, loss of muscle mass and detrimental changes in its metabolic function may further contribute to ICU-related complications that may increase rates of mortality, ICU length of stay and duration of mechanical ventilation. Precise and specific

technologies are needed to document these changes in muscularity, help identify patients with low muscle mass and to associate these changes in muscularity with clinical, metabolic and/or functional outcomes. Functional impairments, that may be partly attributed to muscle loss, are reported up to 5 years following ICU discharge [7], resulting in reduced functional independence. With a growing demographic of older adults, the effects of muscle atrophy on survival, managing co-morbidities and independent living are essential to consider. We have previously shown that, at ICU admission, 71% of older patients (>65 years old) have low muscularity (often described as sarcopenia in aging populations) [3]. This sarcopenic group of patients was at greater risk for mortality, reduced ventilation-free days as well as ICU-free days.

Studies that have demonstrated associations between muscularity and survival, ICU length of stay, duration of mechanical ventilation and other clinical outcomes have typically used either CT imaging or ultrasonography for muscle quantifications. Several efforts and ideas have been put forth towards maintaining or attenuating muscle loss and function in critically ill individuals through nutrition [9], exercise/rehabilitation [10], pharmaceuticals [11] or some combination of strategies [12]. In order to assess the success or failure of these therapeutic interventions, CT imaging and ultrasonography may offer precise and accurate measures of skeletal muscle to identify individuals with low muscularity and detect longitudinal changes in muscle mass.

CT IMAGING: UTILITY IN ICU RESEARCH

Single cross-sectional slices using CT and magnetic resonance imaging (MRI), at different regions of the body, have been validated as accurate and precise predictions of whole body skeletal muscle and fat mass in healthy populations [13, 14]. The 3rd

lumbar vertebra is commonly used as a bony landmark in most studies as it relates well to whole body skeletal muscle mass in healthy populations [14]. This consistent landmark also permits longitudinal assessment of muscle change. Specialized software (including Image J and Sliceomatic) can be used to distinguish specific tissues using Grey Level Image or Hounsfield unit (HU) thresholds, where skeletal muscle is defined as -29 to +150 [3]. CSA is calculated by summing pixels for the muscle regions and multiplying this value by the pixel surface area (Figure 1). Intra- and inter-analyst variability is typically <2% [3, 15, 16]. Various regression equations have been developed to predict whole body muscle mass; however, these have been developed in healthy [14] and in cancer populations [15]. These predictions should be used with caution as their applicability in ICU patients has not been confirmed.

Given the similarities in methodological approaches between CT and MRI and that the majority of studies used CT imaging to describe ICU patients, the remainder of this section will only refer to CT imaging. Cut-points for identifying patients with low muscularity have been developed using diverse approaches in different clinical populations [6**, 15]. Despite the diversity in approaches to derive these cut-points, 50-60% of ICU patients have low muscularity, comparable with other clinical populations (Table 1). In an aged ICU population, the prevalence is notably greater reaching upwards of ~70% of the population [3]; however, more work is needed in other ICU settings to confirm the universality of this finding. It is also remarkable that for decades we have relied on BMI for identifying malnourished individuals in the ICU, when in fact, there are few patients that are classified as underweight based on this tool [3, 15, 16, 17, 18, 19, 20] (Table 1 and Figure 1). Weijs et al. (2014) are the only research group who have developed ICU-specific cut-points for low muscularity and have related these

cut-points to mortality. While these results are valuable, they need to be confirmed in other ICU sites across different geographic and cultural settings. Also, the ICU-specific cut-points developed by Weijs et al (2014) are not normalized to height, which typically accounts for variation in body size. Given the challenges in acquiring accurate height measures in the ICU, future studies need to consider the value in normalizing CT images to height.

There has been emerging data demonstrating associations between HU, which generally represent skeletal muscle density, and clinical outcomes in non-ICU populations [16, 18, 21]. Martin et al. (2013) demonstrated that low muscle HU was independently prognostic of survival; furthermore, they showed that muscle attenuation may be different for individuals who are overweight or obese compared with those who are normal or underweight, based on BMI. These are not only important findings for the cancer field, but may be applicable in our ICU work.

Various clinical populations have translated and applied these methods to quantify muscle CSA at a given point in the disease trajectory [6**, 15], detect changes in muscle [17, 22] as well as relate muscle quantifications with clinical outcomes [3, 6**, 16, 18]. As such, the use of CT and MRI has emerged as a common modality for assessing muscularity in ICU.

METHODOLOGICAL CONSIDERATIONS FOR CT ANALYSIS

CT analysis has provided a unique approach for acquiring body composition measures on a population that typically presents with various practical and biological challenges. Where other body composition modalities may only have the capacity to provide total lean body mass, CT provides specific and precise, compartmentalized

results for diverse lean and fat tissue depots. Single slice scans can be used to predict whole body muscle mass and to identify patients with low muscularity in healthy and cancer populations but little is known about this relationship in ICU populations. To properly validate L3 scans, whole body CT or MRI scans are needed; this would be expensive depending on the sample size and, if using CT imaging, it would expose patients to a substantial dose of radiation. As such, we use L3 assuming that the relationship that has been demonstrated against whole body scans in healthy has not changed with ICU patients. Also, the vast majority of studies that have retrospectively evaluated CT images and scans are rarely requested for body composition purposes. Moreover, scan analysis was primarily conducted using software that requires training and time for analysis. While CT imaging has provided us with a phenomenal approach to understanding prevalence and changes in muscle, it may not be feasible in clinical practice. New, simplified approaches are needed to provide accurate predictions of skeletal muscle quantifications for use in clinical practice.

THE UTILITY OF ULTRASOUND: AN EMERGING TOOL FOR QUANTIFYING SKELETAL MUSCLE

Ultrasound, as a technique to characterize muscle, is still in its infancy, especially in terms of its application in the ICU. Here, we summarize merits and challenges of ultrasound work in the ICU (for in-depth reviews of ultrasound in the ICU the reader is referred to [23*, 24**, 25*, 26*]). We also draw some literature from other populations, but caution the translatability to the ICU.

Skeletal muscle is estimated using ultrasound by imaging one or more anatomical site(s) to obtain the corresponding muscle thicknesses and populating

previously developed prediction equations [27*]. In critically ill patients, numerous recent investigations have utilized ultrasound to quantify muscle thickness or CSA [1, 2, 8**, 28] and either compared these to healthy reference groups or tracked the changes in muscle architecture over time. The majority of studies demonstrated decreased thickness or CSA compared to baseline measures (17-30 % over 10 days) [2, 8**]; however, this loss of skeletal muscle thickness is not seen in all investigations [28]. To our knowledge, the application of these methods has not been validated against whole body skeletal muscle measures using an accurate body composition modality in ICU patients. Proper validation studies may help explain such discrepancies in results. Importantly, validation studies will strengthen our ability to identify individuals with low muscularity and assess the ability to attenuate muscle loss using nutritional and rehabilitative therapies.

Ultrasonography may be useful in measuring degradation in quadriceps muscle quantity and quality (i.e. architectural features) during the ICU trajectory, which together, may be strongly associated with function after ICU discharge. One year following acute hospitalization of patients with chronic respiratory disease, individuals who were in the lowest quartile for rectus femoris CSA at admission had greater rates of hospital readmission and mortality compared to those in the 3rd, 2nd and 1st quartiles [29*]. In an ICU population, loss of rectus femoris CSA has been shown to be associated with degree of organ failure and inflammation [2]. Parry et al. (2015) demonstrated moderately strong associations between muscle architecture of the quadriceps with measures of strength and physical function at ICU discharge. However, moderate or strong correlations are not consistently reported with ultrasound measures [30*]. These discrepancies may be attributed to population characteristics, severity of illness, diverse

methodological approaches in using ultrasound and / or differences in assessing function (physical function in intensive care test scored vs. manual muscle testing).

Echogenicity is emerging as an important ultrasound-based measure of muscle quality. It is a measure of the greyscale of the ultrasound image, and it can be visually assessed (Heckmatt score) [31] or quantitatively analyzed using free computer software (ImageJ). In non-critically ill populations, it has been evaluated as a surrogate measure of fat and fibrotic infiltration [32*] and is independently associated with reduced strength and physical function [33, 34]. Using Heckmatt scores in critically ill populations, echogenicity increased from day 4-14 of ICU stay, and was increased compared to healthy controls at all time points [31]. Parry et al. (2015) showed a 12-25% increase in echogenicity of the quadriceps after 10 days in an ICU, which was associated with worsening physical function. Puthucheary et al. (2015) also demonstrated increased echogenicity from baseline to day 10 in patients who developed muscular necrosis, suggesting that echogenicity may provide additional physiological and metabolic insight other than just architectural changes in muscle [35**].

While echogenicity may be a valuable feature, echogenicity cannot be directly compared across different ultrasound equipment and protocols. Zaidman and colleagues have been developing a method known as calibrated muscle backscatter, which may provide a common approach for measuring echogenicity with the use of a common phantom [36]. Although much work is still required in establishing this interesting parameter, echogenicity in conjunction with measures of skeletal muscle thickness or CSA may provide a comprehensive approach to characterize muscle architecture and function in critically ill patients.

Currently, an optimal protocol for measuring muscle thickness or CSA with ultrasound has not been established, limiting comparability between studies. A standardized protocol that can be used in the ICU for identifying individuals with low muscularity and tracking longitudinal changes in muscle is needed to compare results between independent research groups and provide consistency in multi-centre investigations. There are several steps in ultrasonography of skeletal muscle that can add error to estimates and must be taken into account when developing a protocol (including but not limited to patient positioning, landmarking, pressure applied by the probe, and caliper placement on the image).

CONCLUSIONS AND FUTURE DIRECTIONS

Although the use of CT and ultrasound modalities as body composition tools has increased dramatically over the last 10 years, more work is needed to ensure the validity of these measures in predicting whole body muscularity and in interpreting associations between these body composition measures and clinical or functional outcomes. Both CT and ultrasonography have exciting potential applications, but ICU-specific cut-points that identify individuals with low muscle mass are needed for both modalities. Growing interest is observed in the use of these modalities for assessing the quality of the muscle using muscle attenuation (or HU) for CT or echogenicity for ultrasound. These parameters may provide additional insight that will allow us to better understand changes in muscle quality and their effects on patient outcomes.

An integrative approach between basic and applied sciences along with clinical research is essential to investigating the feasibility and practicality of these modalities in the ICU. As validation studies begin to emerge, there will be a need to take what has

been learned and translate that knowledge into a widely acceptable and practical assessment tool that can be easily incorporated into routine care in the ICU.

KEY POINTS

- Computed tomography and ultrasonography are promising modalities to quantify skeletal muscle mass in critically ill populations, but validation studies are lacking to ensure the validity of these measures in estimating whole body skeletal muscle mass.
- To enhance the application of ultrasonography, a standardized protocol to quantify muscle thickness or cross-sectional area that can be widely adopted is required; development of this universal protocol will increase the comparability of results across multiple studies and consistency within multi-centre studies.
- Computed tomography has important applications in the identification of individuals with low muscularity, but further work is specifically warranted on the development of ICU specific cut-points and how they relate to clinical outcomes.
- Measures of muscular architecture obtained by ultrasonography associate with clinical and functional outcomes, but developing normalized cut-points to expediently and accurately identify patients with low muscle integrity and low muscularity would greatly enhance its utility.

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Conflicts of Interest: None

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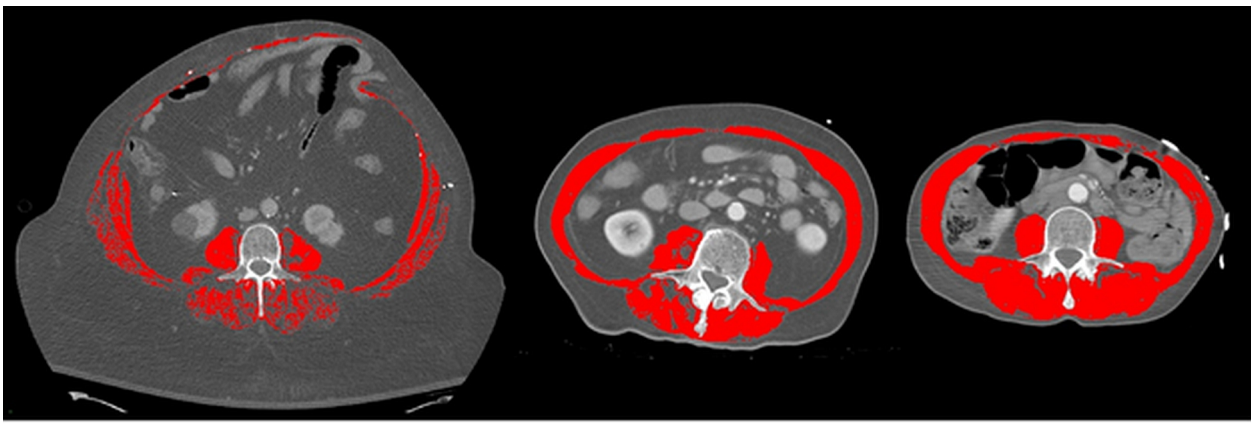
Figure Titles:

Figure 1. Comparison of axial computed tomography scans of the 3rd lumbar vertebra for female patients who are all considered to have low muscularity (<38.9 cm^2/m^2 [15] or 110 cm^2 [6**]) despite large variation in body mass index values. Red – muscle cross-sectional area defined by Hounsfield units of -29 to +150.

Table 1. Comparison of BMI and prevalence of low muscularity based on abdominal CT analysis in various clinical populations.

Reference	Patient Type	% Low Muscularity	% Underweight	% Overweight/Obese
Moisey et al Critical Care 2013 [3]	Elderly at ICU admission (n=149)	71	9	47
Mourtzakis et al APNM 2008 [15]	Lung & Colorectal Cancer (n=51)	56	4	56
Martin et al JCO 2013 [16]	Lung & GI Cancer (n=1473)	53% in females; 31% in men	12	52
Di Sebastiano et al BJN 2013 [17]	Pancreatic Cancer (n=50)	48	10	32
Tandon et al Liver Transpl 2012 [18]	Liver Cirrhosis (n=142)	41	6	50
Montano-Loza et al Clin Gastroenterol Hepatol 2012 [19]	Liver Cirrhosis (n=112)	40	1	67
Baracos et al AJCN 2010 [20]	Lung Cancer (n=441)	47	8	50

Underweight classified as a BMI of <18.5 kg/m^2 and overweight/obese classified as a BMI of ≥ 25.0.



67 years old
BMI 40.1 kg/m^2

87 years old
BMI 23.5 kg/m^2

73 years old
BMI 16.7 kg/m^2