Measuring and monitoring lean body mass in critical illness

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Measuring and monitoring lean body mass in critical illness

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Purpose of review
To help guide metabolic support in critical care, an understanding of patients' nutritional status and risk is important. Several methods to monitor lean body mass are increasingly used in the ICU and knowledge about their advantages and limitations is essential.

Recent findings
Computed tomography scan analysis, musculoskeletal ultrasound, and bioelectrical impedance analysis are emerging as powerful clinical tools to monitor lean body mass during ICU stay. Accuracy, expertise, ease of use at the bedside, and costs are important factors, which play a role in determining, which method is most suitable. Exciting new research provides an insight into not only quantitative measurements, but also qualitative measurements of lean body mass, such as infiltration of adipose tissue and intramuscular glycogen storage.

Summary
Methods to monitor lean body mass in the ICU are under constant development, improving upon bedside usability and offering new modalities to measure. This provides clinicians with valuable markers with which to identify patients at high nutritional risk and to evaluate metabolic support during critical illness.

Keywords
bioelectrical impedance analysis, computed tomography, muscle mass, muscle wasting, musculoskeletal ultrasound

INTRODUCTION

An important realization about metabolic support in critically ill patients is that 'one size does not fit all' [1▪]. We need an understanding of a patient's nutritional status and nutritional risk upon ICU admission to help guide metabolic support, as it is the patients with a high risk who will benefit most from metabolic support [2▪]. To this extend, new risk scoring systems have been developed, which incorporate disease severity more than traditional scoring systems [3]. However, defining a patient's nutritional status upon admission remains difficult. Quantifying the amount of lean body mass (LBM) upon admission offers a valuable addition to tailor early nutritional interventions. In this regard, quantifying LBM may be especially helpful in guiding protein dosing, as LBM contains the body's largest protein store. Looking beyond the scope of nutritional support, quantifying LBM might be helpful in dosing of other medication, and provide information on preadmission status, possibly with important consequences for decisions regarding treatment options and treatment limitations [4].

The effects of metabolic support in critically ill patients are difficult to quantify. Outcome parameters used vary from early to late mortality and/or functional outcomes. However, a problem with mortality outcomes is that many factors other than

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KEY POINTS

- We need an understanding of a patient's nutritional status and nutritional risk at ICU admission to help guide metabolic support.
- CT-scan analysis, musculoskeletal ultrasound, and bioelectrical impedance analysis are emerging as clinically useful tools to measure and monitor lean body mass.
- Knowledge about the different methods' advantages and limitations is essential to accurately interpret study results and determine, which method is most suitable in a given situation.
- CT-scan analysis and bioelectrical impedance analysis may provide excellent opportunities for screening and identifying patients at risk.
- Musculoskeletal ultrasound and bioelectrical impedance analysis may be the most suitable for monitoring/follow-up measurements.

metabolic support can contribute to these outcomes. Additionally, in sedated critically ill patients, functional parameters such as hand grip strength are impossible to measure. Again, measuring LBM and monitoring it during admission may provide opportunities.

To help determine a patient's nutritional status and gain insight into the effects of metabolic support; reliable, well tolerated, and quick methods to monitor LBM are needed. Equations to estimate LBM were found not to be accurate in critically ill patients and often overestimate LBM [5▪]. In recent years, the use of computed tomography (CT)-scan analysis, musculoskeletal ultrasound (MKUS), and bioelectrical impedance analysis (BIA) in the ICU has increased and become more widely accepted. Although this development can only be lauded, knowledge about the different methods and insight into their limitations is essential to be able to accurately interpret study results and determine, which method is most suitable in a given situation. We will review current literature and discuss advantages and limitations of the different methods to monitor lean body mass in critical illness.

COMPUTED TOMOGRAPHY

Computed tomography, from the Greek words 'tomos' meaning 'slice' or 'section' and 'graphia' meaning 'describing,' has been used as a diagnostic tool since the beginning of the 1970s. Apart from being a valuable diagnostic tool, which is often used in the ICU, CT scans can be used for analysis of body composition. On the basis of predefined boundaries

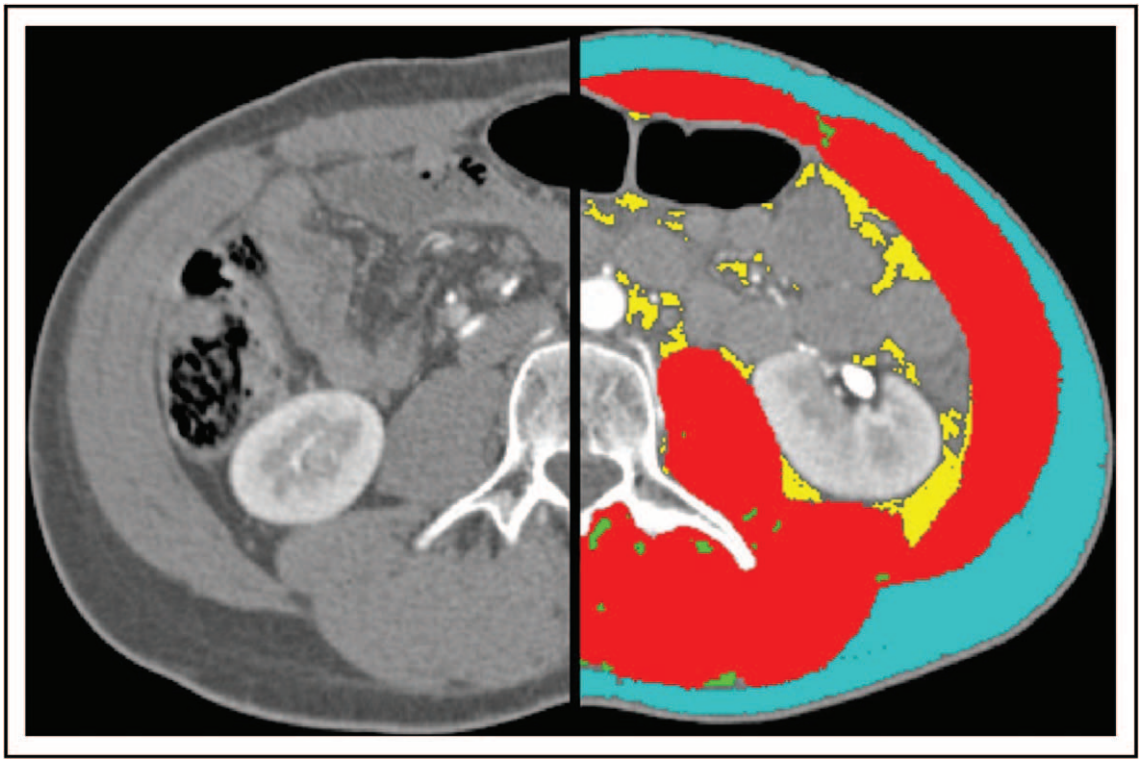

FIGURE 1. Cross-sectional image from abdominal computed tomography scan at the level of the third lumbar vertebra (L3), both unanalyzed (left) and analyzed (right) using SliceOmatic (TomoVision, Magog, Quebec, Canada). Red: muscle, green: intermuscular adipose tissue, yellow: visceral adipose tissue, and blue: subcutaneous adipose tissue.

Table 1. ICU-specific cut-off values related to mortality for computed tomography-scan analysis and bioelectrical impedance analysis

	Measurement	Cut-off value	Study population	Related to	AUC
CT-scan analysis					
Shibahashi *et al.* [14▪▪]	L3 psoas-muscle and paraspinal muscle CSA on day of ICU admission	Women: 39.0 cm^2 Men: 15.2 cm^2	150 elderly (>60y) septic ICU patients	Hospital mortality	Women: 0.72 (0.58–0.88) Men: 0.65 (0.54–0.76)
Weijs *et al.* [11]	L3 total muscle CSA 1 day before to 4 days after ICU admission	Women: 110 cm^2 Men: 170 cm^2	240 mixed ventilated ICU patients with ICU stay of >4 days	Hospital mortality	-
Bioelectrical impedance analysis					
Thibault *et al.* [15▪▪]	Phase angle on day 1 of ICU admission	3.49°	931 mixed ICU patients with expected ICU stay of >48 h	28-day mortality	0.63 (0.58–0.67)
Stapel *et al.* [16▪]	Phase angle <24 h after ICU admission	4.80°	196 mixed ICU patients	90-day mortality	0.70 (0.59–0.80)

Currently, no ICU-specific cut-off values for musculoskeletal ultrasound exist. AUC, area under the receiver-operating characteristic curve; CSA, cross-sectional area; L3, third lumbar vertebra.

on the Hounsfield Unit scale, which can be seen as a grayscale and is a reflection of the scanned tissue's density, muscle and adipose tissue can be identified (Fig. 1).

Multiple software applications are available for detailed measurements with excellent agreement between different applications [6], although most standard radiology applications have a ruler tool, which can be used for linear measurements. Analysis of the muscle cross sectional area (CSA) on a single cross-sectional image at the level of the third vertebra (L3) has been found to be a good reflection of whole body muscle mass in a cadaver validation study [7]. More recently, this process has been made easier as linear measures of the psoas and paraspinal muscles made with a software ruler tool can reliably predict the total CSA at this level [8▪▪]. Early research into body composition using CT scans has focused mostly in oncology patients, who undergo frequent scans as part of routine follow-up, and the first cut-off points for low LBM or sarcopenia were found in this patient population [9]. Recently, however, normal values have been derived from a healthy population of potential kidney donors [10▪], and cut-off points for sarcopenia associated with mortality have been defined for critically ill patients [11].

Applications in critically ill patients

The first studies utilizing CT scans to assess LBM in critically ill patients showed an association between low LBM upon admission and higher mortality rates, less ventilator-free days, less ICU-free days, and less likely discharge to home in elderly trauma patients [12] and a general ICU population [11]. These findings have recently been confirmed in 450 elderly trauma patients where sarcopenia or osteopenia or both, as indicators of frailty, were associated with 1-year mortality [13▪]. Similar results were found in a study in elderly septic patients where low LBM was associated with in-hospital mortality [14▪▪]. This study shows that CT-scan analysis does not need to be a time-consuming process requiring specialized software, as the CSA of only the psoas muscles and paraspinal muscles was delineated, using readily available radiology software. The authors established valuable cut-off values for this method (Table 1). Furthermore, in a sub analysis of a prospective observational study in 231 surgical ICU patients with a CT scan within 5 days after extubation, low LBM was associated with pneumonia, adverse discharge disposition, and 30-day mortality [17▪▪]. Interestingly, CT scans made during ICU stay are, therefore, a clear indication of the detrimental effects of ICU stay itself on LBM. This should be considered coinciding with the pre-ICU status of the critically ill patient. Finally, a study investigated the association of mortality with sarcopenia assessed by different frailty scoring systems as well as CT scans [18]. In univariable analyses, the strongest association to mortality was found in CT scan-derived sarcopenia, whereas frailty scoring systems performed less well. However, it must be noted that no associations were found on multivariable analyses, possibly because of the small sample size.

Apart from the muscle quantity, the quality of muscle may be important. Muscle quality is a measure of a muscle's strength relative to its size (mass/volume). A proxy for the quality of muscle can be gained on CT scans by analyzing the mean density of muscle tissue (expressed in Hounsfield Unit).

Lower muscle density has been associated with increased lipid infiltration in muscle biopsies and poor outcome [19,20]. This has recently been confirmed in ICU patients, where low skeletal muscle density upon ICU admission, independent of muscle quantity, was associated with higher 6-month mortality [21▪].

Limitations

Whenever considering studies that use CT scans for body composition analysis in critically ill patients, several important points must be taken into account. Due to radiation exposure, costs, time, and the risk associated with transporting ICU patients, making a CT scan solely for analysis of LBM is not feasible. Because of these limitations, the use of CT scans for follow-up measurements is not feasible. Additionally, study patients are selected from a patient population in whom an abdominal CT scan made for diagnostic reasons was available. This includes patients with a heterogeneity of diagnoses, but in general these are often the more severely ill patients. The ensuing inclusion bias may cause certain patient groups to be overrepresented or underrepresented in these studies. Finally, all studies are retrospective or secondary analyses of prospective studies, and consequently no conclusions about causality can be made. Although most studies statistically adjust for confounding influences, this confounding can never be fully avoided.

ULTRASOUND

Ultrasound, sound waves that are inaudible to humans with a frequency of above 20 kHz, has been used in medical imaging for over 70 years. More recently, interest has been emerging in the use of ultrasound for body composition analysis. MKUS can be used both in a quantitative and in a qualitative way and is emerging as a potentially powerful clinical assessment tool in a ICU setting [22,23▪▪,24]. An advantage of MKUS is the ability to easily monitor changes, and the ability to look at muscle groups instead of whole-body LBM. Histology and morphology is different within different muscle groups, with direct consequences for wasting patterns [25]. Insight into these different muscle wasting patterns can help guide metabolic support and/or early mobilization in the ICU.

Applications in critically ill patients

Used quantitatively, MKUS has the ability to predict appendicular lean body mass through assessing muscle thickness with a five-site model (upper leg and upper arm), with an excellent relation to whole-body dual-energy X-ray absorptiometry (DXA) [26▪]. Leg muscle thickness has been associated with functional performance and knee extensor strength in older adults [27▪▪]. A decrease of the rectus femoris CSA during the acute phase of critical illness is seen in a high proportion of critically ill patients [28]. In a cohort of septic patients, the occurrence and speed of muscle wasting was extremely high and the change in muscle architecture had a significantly different pattern when compared with patients admitted with traumatic brain injury [25].

MKUS can also determine qualitative aspects of muscle. The intensity with which a sound wave is reflected from muscle tissue, or echo intensity, may be an indication of muscle quality, analogous to muscle density on CT scans. A low-quality muscle produces a brighter or hyperechoic image, which can be caused by fibrosis and adipose tissue infiltration [29,30▪]. Analysis of echo intensity can effectively distinguish healthy versus diseased skeletal muscle, which has been associated with muscle weakness in elderly persons, independent of decreases in muscle mass or muscle thickness [31▪,32].

Echo intensity can also be used to quantify intramuscular glycogen storage. As glycogen is bound to water, and sound waves easily pass through water; a muscle containing more glycogen will produce a darker (hypoechoic) ultrasound image. Specialized software can be used to give an indication of the amount of glycogen present in the muscle. Two studies in trained cyclists comparing this glycogen 'score' to the gold standard of pre-exercise and postexercise muscle biopsy (vastus lateralis and rectus femoris) found high correlations between the two measurements [33,34]. This may help to better understand why critically ill patients undergoing similar mobilization programs may have very different energy requirements and help provide targets for metabolic support [35,36].

A final important characteristic of muscle is its architecture, which contributes greatly to the amount of force it is able to generate. The most important feature in this regard is the pennation angle, the angle between muscle fascicles and the tendon axis (Fig. 2) [37]. This pennation angle can change because of fibrosis, myonecrosis, and (inflammation-related) fluid accumulation in fascial planes [22,24,25]. All of these changes may occur during ICU stay, and the vastus lateralis pennation angle was found to be strongly correlated to the physical function ICU test (PFIT-s) in critically ill patients [22].

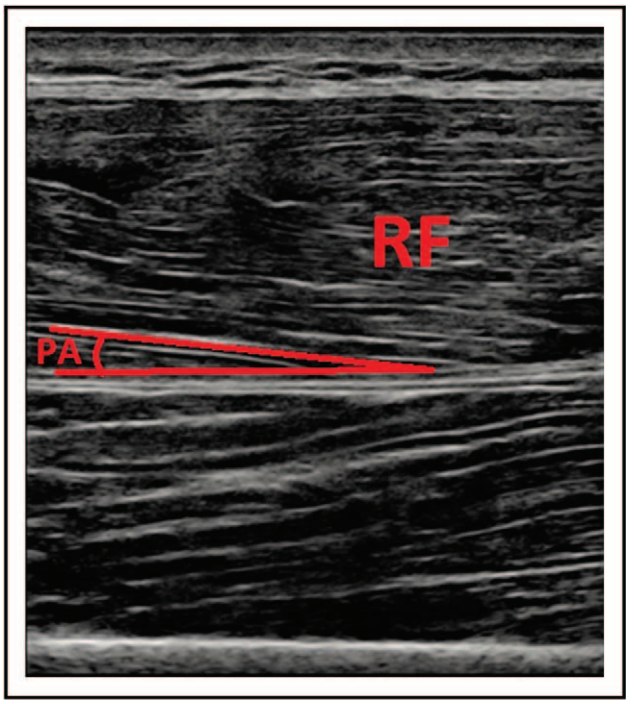

FIGURE 2. Visualization of the pennation angle (the angle between muscle fascicles and the tendon axis) on a long-axis ultrasound image of the rectus femoris muscle. PA, pennation angle.

Limitations

MKUS provides many exciting opportunities to assess and monitor LBM. However, concerns have been raised about interobserver reliability [38▪,39]. Landmarking and the amount of compression used when acquiring the image (full compression to get rid of edema versus no compression at all) are important causes of variability. Furthermore, standardized protocols on where to measure (which muscles, at what point) and what to measure (thickness, CSA, circumference, other measures), and normal values or cut-off values are lacking. In a recent article, Mourtzakis *et al.* [23▪▪] identify important issues to be considered and offer guidance to improve translation into clinical practice.

BIOELECTRICAL IMPEDANCE ANALYSIS

Bioelectrical impedance analysis (BIA) uses an insensible current flowing through the body between electrodes placed on a patient's hands and feet. The body's resistance to this current (R) as well as the delay caused by the body or reactance (X_c) make up a body's total opposition to the current or impedance (Z). From the relationship between R and X_c, the phase angle can be calculated as $\arctan\left(\frac{Xc}{R}\right)*\left(\frac{180^\circ}{\pi}\right)$. The phase angle is considered a measure of general cellular health and is used as a proxy for LBM [40▪].

Through the use of equations incorporating these values with anthropomorphic data, LBM can be estimated. However, these equations are not suitable for critically ill patients; they assume a normal hydration status and accurate anthropomorphic measurements, assumptions, which cannot be met in critically ill patients because of large fluid shifts.

Applications in critically ill patients

Consequently, research in critically ill has focused on 'raw' values R, X_c, and phase angle which can be directly measured, are influenced less by altered hydration status, and are not dependent upon meeting assumptions. In a large international study in a heterogeneous population of 931 ICU patients, lower phase angle on day 1 of admission was associated with higher 28-day mortality [15▪▪]. This was confirmed in a more recent study in 196 critically ill patients also with various diagnoses, where low phase angle within 24 h of admission was associated with higher long-term (90-day) mortality [16▪]. In both studies, a cut-off value was proposed, associated with early (28-day) and late (90-day) mortality, respectively (Table 1). This may help identify patients at nutritional risk at ICU admission.

Limitations

BIA is a simple, easy, and cheap method to gain insight into body composition. Due to the large influence of altered hydration status, BIA values must be interpreted with care while patients are admitted to the ICU. However, early during admission, before large fluid shifts occur, BIA may provide a valuable tool for risk assessment, and after patients are discharged to the ward and hydration status has normalized it can be used as a follow-up marker.

COMPARISON BETWEEN DIFFERENT TECHNIQUES

The different techniques have their own strengths and limitations (Table 2). Although ultrasound and BIA may be relatively inexpensive, well tolerated, and are the most useable on the bedside, concerns exist about the validity and reproducibility of results. Standardized protocols are needed to improve the use in clinical practice. On the other hand, CT-scan analysis may give more reliable results and may be performed in scans made for other reasons, but it is not a feasible tool for longitudinal monitoring and is not readily available in all patients.

Table 2. Comparison of different methods to monitor lean body mass

	CT-scan analysis	Musculoskeletal ultrasound	Bioelectrical impedance analysis
Accuracy	+++ Excellent accuracy	+ Standardized protocols are needed	+ Large influence of hydration status
Information on muscle quality	++ Skeletal muscle density	+++ Different measurements	+ Phase angle (cellular health)
Bedside usability	– Transport to CT-scanner needed	+++ Excellent bedside potential	+++ Excellent bedside potential
Costs	– / +++ If already made for diagnosis	++ Only high initial acquisition costs	++ / +++ Many different options
Harm for patient	– Exposure to radiation	+++ No harm	– / +++ Only in selected patients (pacemaker, implants)

CT, computed tomography.

Results from different methods cannot be used interchangeably, as was stipulated by two recent prospective studies, which evaluated the ability of BIA and ultrasound to identify patients who are sarcopenic on CT scans at ICU admission [40▪,41▪]. Both BIA and ultrasound were performed within 72 h of the CT scan. Both BIA and ultrasound alone were not accurate enough to correctly identify sarcopenic patients. However, after adding age, sex, BMI, Charlson Comorbidity Index (CCI), and admission type to a model, a reasonable area under the curve was found. Therefore, it is important to always deliberate on which technique best suits the current situation, available expertise, and hospital's facilities.

CONCLUSION

To help identify critically ill patients at high nutritional risk at an early stage and to help guide and evaluate metabolic support during ICU admission, measuring and monitoring lean body mass may offer important opportunities. CT-scan analysis, musculoskeletal ultrasound, and bioelectrical impedance analysis are tools, which are increasingly used in the ICU. Interpretation of results must be done with care for the limitations associated with the different methods. Exciting new developments in this area are focused not only on the quantity but also on quality of lean body mass and go as far as to provide an insight into infiltration of adipose tissue and intramuscular glycogen stores. Methods to measure and monitor lean body mass are under constant further development to improve bedside usability and provide clinicians with valuable tools to help guide metabolic support.

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Conflicts of interest

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- ▪▪ of outstanding interest

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Although intrasobserver agreement was excellent between two musculoskeletal ultrasound measurements on day 3 or 4 and on day 10 or 11 of ICU admission, significant differences were found between observers. This study suggests musculoskeletal ultrasound is able to detect muscle wasting, but only if the same investigator performs the measurements.

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40. ▪ Kuchnia A, Earthman C, Teigen L, *et al.* Evaluation of bioelectrical impedance analysis in critically ill patients: results of a multicenter prospective study. JPEN J Parenter Enteral Nutr 2017; 41:1131–1138.

Bioelectrical impedance analysis was performed within 72 h of a CT scan. BIA alone was not accurate in predicting low muscularity on CT-scan analysis. However, after adding other variables to a model a reasonable area under the curve was found.

41. ▪ Paris MT, Mourtzakis M, Day A, *et al.* Validation of bedside ultrasound of muscle layer thickness of the quadriceps in the critically ill patient (VALIDUM Study). JPEN J Parenter Enteral Nutr 2017; 41:171–180.

Musculoskeletal ultrasound was performed within 72 h of an abdominal CT scan. Although it was not accurate in predicting low muscularity on CT-scan analysis, after adding other variables to a model, a reasonable area under the curve was found.