Comparison of ultrasound-derived muscle thickness with computed tomography muscle cross-sectional area on admission to the intensive care unit : A pilot cross-sectional study

Lambell, Kate J., Tierney, Audrey C., Wang, Jessica C., Nanjayya, Vinodh, Forsyth, Adrienne, Goh, Gerard S., Vicendese, Don, Ridley, Emma J., Parry, Selina M., Mourtzakis, Marina and King, Susannah J.

A comparison of ultrasound-derived muscle thickness with computed tomography muscle cross-sectional area on admission to the intensive care unit: A pilot cross-sectional study

Kate J Lambell, MNutrDiet[1,2], Audrey C Tierney, PhD[2,3], Jessica C Wang, MD[4,5], Vinodh Nanjayya, MD[5,6], Adrienne Forsyth, PhD[2], Gerard S Goh, MD[7,8], Don Vicendese, PhD[9], Emma J Ridley, PhD[1,6], Selina M Parry, PhD[10], Marina Mourtzakis, PhD[11] and Susannah J King, PhD[1,2]

[1]Nutrition Department, Alfred Health, Melbourne, Australia

[2]Department of Dietetics, Nutrition and Sport, La Trobe University, Melbourne, Australia

[3]Faculty of Education and Health Implementation Science and Technology Cluster, University of Limerick, Ireland

[4]Department of Critical Care Medicine, University of Calgary, Calgary, Canada

[5]Intensive Care Unit, The Alfred, Melbourne, Australia

[6]Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, Australia

[7]Department of Radiology, The Alfred, Melbourne, Australia

[8]Department of Surgery, Monash University, Melbourne, Australia

[9]Department of Mathematics and Statistics, La Trobe University, Melbourne, Australia

[10]Department of Physiotherapy, The University of Melbourne, Melbourne, Australia

[11]Department of Kinesiology, University of Waterloo, Waterloo, Canada

Corresponding Author

K. J. Lambell, MNutrDiet, APD, Nutrition Department, Lower Ground Floor, Main Ward Block, The Alfred, 55 Commercial Road, Melbourne, VIC 3004, Australia.

Email: k.lambell@latrobe.edu.au

Financial disclosure

K. J. Lambell is supported by an Australian Government Research Training Scholarship.

Conflicts of interest

None declared.

Word count

4956 words

Abstract

Introduction: The development of bedside methods to assess muscularity is an essential research priority for monitoring nutritional status and predicting functional recovery in critical care. We aimed to compare ultrasound-derived muscle thickness at five landmarks with computed tomography (CT) muscle area at intensive care unit (ICU) admission. Secondary aims were to 1) combine muscle thicknesses and baseline covariates to evaluate correlation with CT muscle area and 2) assess the ability of the best-performing ultrasound model to identify patients with low CT muscle area.

Methods: Adult patients who had a CT scan at the third lumbar area <72hours after ICU admission were prospectively recruited. Where possible, muscle thickness was measured at the mid-upper arm, forearm, abdomen, and thighs. Low CT muscle area was determined using published cut-points. Pearson's correlation compared ultrasound-derived muscle thickness and CT muscle area. Linear regression was used to develop ultrasound prediction models. Bland-Altman analyses compared ultrasound-predicted and CT-measured muscle area.

Results: Fifty ICU patients were enrolled (mean±SD 52±20years, BMI 28±5kg/m^2). Ultrasound-derived muscle thickness at each landmark correlated with CT muscle area (P<0.001). The sum of muscle thickness at mid-upper arm and bilateral thighs, including age, sex, and Charlson Comorbidity Index, improved the correlation with CT muscle area (r =0.85, P<0.001). Mean difference between ultrasound-predicted and CT-measured muscle area was -2cm^2 (95% limits of agreement -40cm^2 to +36cm^2). The best-performing ultrasound model demonstrated good ability to identify 14 patients with low CT muscle area (area under curve 0.79).

Conclusion: Ultrasound shows potential for assessing muscularity on ICU admission (Clinicaltrials.gov NCT03019913).

Keywords
Critical illness, intensive care unit, ultrasound, computed tomography, skeletal muscle mass, body composition

Clinical relevancy statement

Currently, there is no routinely available bedside tool that is considered reliable and accurate for objectively assessing whole-body muscularity in the intensive care unit (ICU) setting. The primary aim of this prospective study was to evaluate the relationship between muscularity assessed by bedside ultrasound with a reference method (single-slice computed tomography (CT) image analysis) on admission to the ICU. The sum of ultrasound-derived muscle thickness at the mid-upper arm and thighs was strongly correlated to CT muscle area. These results demonstrate the potential for ultrasound to assess muscularity on admission to the ICU.

Background

Low muscularity on ICU admission has been associated with increased length of stay and mortality and therefore may be an important predictor of outcome.[1-3] The quantification of muscle mass is pivotal in the assessment of nutritional status whereby muscle atrophy is strongly related to malnutrition.[4] Further, body composition analysis is important to consider for the determination of nutrition requirements (with fat-free mass being the largest driver of metabolic rate) and for monitoring the effectiveness of nutrition interventions aimed at attenuating muscle wasting.[5]

Despite the importance of assessing muscularity in acute illness, there is currently no method that is considered accurate, reliable and feasible in the ICU setting.[6] Reference methods for body composition analysis, such as dual-energy X-ray absorptiometry (DXA) and CT image analysis, are costly, often inaccessible, involve radiation (CT), and are impractical for use in critically ill patients, often requiring patients to be transported out of the ICU for measurement.[7] Ultrasound is an emerging tool for the assessment of muscularity in the ICU setting largely because it is safe, non-invasive, portable and readily available in most ICUs.[8] There are only limited data evaluating the utility of ultrasound as a measure of muscularity in critically ill patients, finding a moderate correlation between ultrasound-derived quadriceps muscle thickness and CT muscle cross-sectional area (CSA) using maximal compression ultrasound technique.[9] In healthy volunteers, ultrasound protocols incorporating measurements of the upper and lower limbs and using minimal compression technique have reported a strong agreement with fat-free mass assessed by DXA.[10,11]

Therefore, we aimed to compare ultrasound-derived muscle thickness at five different anatomical landmarks with muscularity assessed by a reference method that is accessible in a sub-group of critically ill patients on ICU admission (CT muscle cross-sectional area at the third lumbar, L3, area). Our secondary aims were to 1) evaluate if combining muscle thickness at different landmarks and readily available patient information, could strengthen the correlation with CT muscle area and 2) to assess the ability of the best-performing ultrasound model to accurately classify patients with low CT muscle area.

Methods

Patients

This was a prospective observational study conducted in a single center between 23rd January 2017 and 25th March 2019 after approval from the Research and Ethics Committees at The Alfred Hospital and La Trobe University. The study was registered *a priori* on clinicaltrials.gov (NCT03019913). Patients were screened on pre-determined weekdays when investigators were available, and met inclusion criteria if they were aged ≥18 years and had a CT scan including the L3 area performed for clinical purposes ≤24 hours before or ≤72 hours after ICU admission. Exclusion criteria were: The CT scan was unanalyzable, death was imminent, anticipated ICU stay was <24 hours, pregnancy, it was impractical and/or not possible to perform the ultrasound protocol (including imaging at least two or more muscle groups, including at least one thigh) or it was not possible to obtain consent.

Patients with a BMI of >40kg/m^2 were also excluded, with being outside the range for previously assessed utility of a similar ultrasound protocol in the ICU setting.[12]

Written and informed consent was obtained from the eligible patient and/or their legal medical decision-maker. For all patients the following demographic and clinical data were collected: age, sex, weight, height, Charlson Comorbidity Index[13], Acute Physiologic and Chronic Health Evaluation (APACHE) II[14] and III[15] scores, admission diagnosis (trauma, medical or surgical), ICU and hospital LOS and in-hospital mortality. Body mass index (BMI) (kg/m^2) was calculated using estimated or reported weight and height on ICU admission and BMI category was determined using the WHO BMI cut-off values (underweight <18.5kg/m^2, normal weight =18.5-24.9kg/m^2, overweight =25-29.9kg/m^2, obese ≥30kg/m^2).[16]

CT image analysis

During the screening process, investigators visualized skeletal muscle area at L3, and where necessary, a consultant radiologist (GG) confirmed the quality of the scan was adequate for analysis. Patients were excluded if the muscle borders were indistinguishable; there was interference of artifact and/or if whole muscle group(s) were not visible due to positioning during CT scanning.

CT scans were uploaded onto the licensed software, SliceOmatic version 5.0 (TomoVision, Montreal, QC, Canada) for analysis by investigator KJL, who identified L3, and the CT slice for analysis. Skeletal muscle boundaries were recognized based on Hounsfield Units (–29 to +150 for muscle).[17] Abdominal skeletal muscle CSA (cm^2), herein termed *CT muscle area*, was automatically computed by the software by summing the skeletal muscle tissue pixels and multiplying by the surface area of each pixel.

Intrarater reliability for CT image analysis was performed by the primary investigator (KJL) re-landmarking and re-analyzing scans from ten study patients at least six months after initial analysis. Interrater reliability was performed by having a second trained investigator (LM) landmark and analyze scans from ten study patients.

Ultrasound

Trained investigators (KJL or JCW) performed the one-off evaluation of muscularity by ultrasound as soon as possible after patient enrolment. The sites chosen to compare to CT muscle area included muscle thickness of the right mid-upper arm and forearm (left side if right not available), abdominal, and bilateral thighs (details below). The sites were chosen because they are readily accessible while a patient is supine. Further, the measurement protocols for determining muscle thickness at the upper and lower limbs have been reported as reliable in the ICU setting and associated with whole-body muscularity in healthy volunteers.[10,11,18-20] It was hypothesized that including ultrasound assessment of a muscle group at the L3 region may strengthen agreement between the two methods, and therefore rectus abdominis muscle thickness was included.

A portable B-mode ultrasound device (Philips® Sparq, Philips Ultrasound, Bothell, WA, USA) with a multi-frequency linear array transducer (4-12 MHz) was used. Patients were supine with the head of the bed at approximately 30 degrees (usual positioning in our ICU). Water-soluble transmission gel was applied to the transducer and using minimal compression, the transducer was held perpendicular to the skin at the mark on the skin and depth was adjusted to visualize the relevant bone (or the inner muscle fascia layers for the abdomen). Three still images were taken at each landmark; saved and uploaded to the NIH Image J software for analysis (Version 1.52, US National Institutes of Health, Maryland, USA). The previously published measurement protocols for each site are described below:

Mid-upper arm[12,19]:
A mark was made on the skin at the midway point between the tip of the acromion and the olecranon process. The thickness of the bicep flexor compartment was imaged with the elbow extended and forearm supinated and resting on the bed. Muscle thickness was measured from the subcutaneous adipose tissue-muscle interface to the muscle-bone interface of the humerus.

Forearm[21]:

A point was marked at 30% proximal between the ulnar styloid process and the head of the radius. With the hand supinated and forearm relaxed on the bed, the image was taken. Ulna muscle thickness was measured as the distance between the subcutaneous adipose tissue–muscle interface and muscle–bone interface of the ulna.

Abdominal[21]:

A mark was made 3 cm to the right of the umbilicus. The probe was rotated, and the image saved as the rectus abdominis muscle was positioned horizontally on the screen. Muscle thickness was measured from the distance between the upper and lower inner muscle fascia layers (in the center of the image).

Bilateral thighs[18]*:*

With knees extended and relaxed, a point was marked at the anterior superior iliac spine and the upper pole of the patella. A point was then marked at the mid-point and two-thirds point between these landmarks. Muscle thickness was measured from the subcutaneous adipose tissue–muscle interface to the muscle–bone interface of the femur at both points on both thighs.

For each site, the average result of the three still images was used for analysis. For each thigh, the value used for analysis was an average of muscle thickness at the mid- and two-thirds point. The bilateral thigh thickness value was taken as the average across both thighs (i.e. right mid-point + right two-thirds + left mid-point + left two-thirds/4). For upper arm, forearm and thigh, muscle thickness (cm) was multiplied by limb length (distance between each bony landmark, e.g. acromion and the olecranon process for upper arm) (cm), and this value used for analysis, as previously described.[10]

A range of reliability testing was performed for ultrasound. Intrarater reliability for the protocol was undertaken by investigator KJL repeating the landmarking and image acquisition in the final ten patients. Intrarater reliability for muscle thickness measurements occurred by KJL re-analyzing images for ten participants at least six months after the initial analysis. Interrater reliability for the ultrasound protocol (landmarking and image acquisition) was assessed in five separate healthy volunteers (due to the nature of the study environment and to limit participant burden). The volunteers were positioned in an ICU bed with the head of the bed at 30 degrees. The first investigator (KJL) performed the protocol, the marks were then removed, and the second investigator (JCW) followed directly after. Interrater reliability for the quantification of muscle thickness measurements occurred by having an independent operator (LB) undertaking a second analysis of images for a randomly selected sub-group of five from the ICU patient cohort.

Statistical Analyses

For this pilot study, a pragmatic sample size of 50 patients was chosen based on predicted eligibility, with the aim of completing recruitment targets within a two-year timeframe to reduce the occurrence of major changes in clinical practices or testing equipment during the recruitment period. Shapiro-Wilk tests were used to assess normality. Data are reported as n (%), mean and standard deviation (±SD) or median and interquartile range [IQR]. Missing data were not imputed.

Differences in mean CT muscle area and ultrasound-derived muscle thickness by sex and age (<65 years versus ≥65 years) were assessed using independent samples t-tests.[9] Pearson's correlation was used to assess the relationship between CT muscle area and ultrasound measures. Baseline covariates thought to influence the level of muscularity (age, sex, BMI, Charlson Comorbidity Index) were individually assessed for their relationship with CT muscle area by univariate linear regressions. Stepwise linear regression was undertaken to identify the ultrasound model with the strongest correlation with CT muscle CSA, including all possible combinations of the sum of ultrasound-derived muscle thickness at each landmark and baseline covariates that had a significant independent association with CT muscle CSA (P <0.001). The best-performing ultrasound model was chosen based on the number of data points (indicating feasibility), the strength of the relationship with CT muscle area, and limits of agreement determined by Bland and Altman analyses (95% limits of agreement for differences between ultrasound-predicted and CT-measured muscle area).[22] To assess the limits of agreement, linear regression analysis was performed for the differences against the averages, with a P value <0.05 indicating proportional bias (a trend to higher or lower values).[7]

Muscularity status (normal or low) was determined using published CT muscle area cut-off values (<170cm^2 for men and <110cm^2 for women) derived from a general ICU population where low CT muscle area was associated with increased mortality.[1] Receiver Operating Characteristic (ROC) Curve analysis was undertaken to assess the specificity and sensitivity of the optimal ultrasound model to accurately classify patients as having normal or low CT muscle area (using ultrasound-predicted CT muscle area generated from the best-performing ultrasound model).

Intraclass correlation coefficient (ICC) and coefficient of variation (CV) were used to assess intrarater and interrater reliability. IBM SPSS version 25 (Armonk, NY) was used for all analysis, and significance was set at P value of <0.05.

Results

A total of 1580 patients were screened, and of the 373 patients who had a CT scan including the L3 area, 323 patients were excluded, and 50 patients were included (Figure 1). Participants were predominantly male (38 (76%)), admitted post trauma (42 (84%)) with a mean age and median APACHE II score of 52±20 years and 12 [9-16] respectively. Other characteristics are detailed in Table 1.

The mean time from ICU admission to performing the ultrasound protocol was 33±12 hours, and from CT scan to the ultrasound protocol was 26±13 hours. The mean CT muscle area was 173±38 cm^2, with males having significantly higher muscle area than females (187±29 cm^2 versus 127±26 cm^2, $P<0.001$), as did those who were younger (<65 versus ≥65 years old) (189±30 cm^2 versus 141±32 cm^2, $P<0.001$) (Table 2).

Of the 50 patients included, ultrasound images were available for the following number of patients at each site: 48 for mid-upper arm, 39 for forearm, 39 for abdominal, 49 for one thigh and 37 for bilateral thighs. The mean muscle thicknesses for the individual sites and according to sex and age category are outlined in Table 2. Reasons for missing ultrasound data, which largely relate to traumatic injuries, are presented in Table 3. There were a small number of patients where arm measurements on the right side were not accessible due to pain or traumatic injury and the left side was used (four for mid-upper arm and three for forearm).

Reliability of measurement protocols

The method of CT image analysis showed good reliability with intrarater testing revealing a CV=0.7% and ICC=0.998 and interrater testing CV=0.8% and ICC=0.995. For the ultrasound protocol, due to the study environment (first few days of ICU admission) and requirement for clinical procedures, it was only possible to repeat the protocol in six patients (not ten as planned). The ultrasound protocol also showed good reliability for 1) re-landmarking and image acquisition (intrarater CV=2.8% and ICC=0.966, and interrater CV=3.8%, and

ICC=0.997), and 2) MT measurements (intrarater CV=2.2% and ICC=0.998, and interrater CV=3.6% and ICC=0.992).

Comparison between ultrasound-derived muscle thickness and CT muscle area

There was a significant positive relationship between ultrasound-derived muscle thickness at each anatomical landmark and CT muscle area (mid-upper arm r=0.79, forearm r=0.68, one thigh r=0.70, both thighs r=0.75, abdominal r=0.68; P<0.001). The sum of muscle thickness at the mid-upper arm and bilateral thighs (or one thigh if not able to image both thighs) was the ultrasound protocol which had the most complete data (n=47) and a strong positive relationship to CT muscle area (r=0.82, P <0.001) (Figure 2A), and underwent further evaluation incorporating baseline covariates as outlined below. Supplementary Table S1 provides a summary of the correlations between ultrasound muscle thickness measurements at each landmark (and combination) and CT muscle area.

Incorporation of baseline covariates

Baseline covariates with a significant independent association with CT muscle area were age (r=0.53, P<0.001), sex (r=0.66, P<0.001), and Charlson Comorbidity Index (r=0.54, P<0.001). BMI did not have a significant association with CT muscle area (r=0.23, P=0.104) and was therefore not included in further modeling. Incorporating age, sex, and Charlson Comorbidity Index to the ultrasound protocol further strengthened the relationship with CT muscle area (r=0.85, P<0.001), and this combination was labeled the best-performing ultrasound model (Figure 2B). The mean difference between CT-measured and ultrasound-predicted CT muscle area generated from the best-performing ultrasound model was -2cm^2 (95% limits of agreement -40 to 36cm^2), with no proportional bias (P=0.102), see Figure 3.

Identification of participants with low muscularity

Fourteen participants (10 men and 4 women) were identified as having low CT muscle area.[1] Using ultrasound-predicted CT muscle area derived from the best-performing ultrasound model (n=47), 85% of patients were correctly classified as having normal or low CT muscle area, with 79% sensitivity and 94% specificity. The positive predictive and negative predictive values were 82% and 86%, respectively. The best-performing ultrasound model had good ability to identify patients with low CT muscle area (area under the curve (AUC) = 0.79 [95% CI 0.65-0.92]) (Figure 4).

Discussion

To our knowledge, this is the first study to compare muscularity assessed by ultrasound at multiple anatomical sites with a reference method for muscle assessment in critically ill patients. We compared ultrasound-derived muscle thickness measured at the mid-upper arm and thighs on ICU admission with CT muscle area at the L3 region, finding a strong correlation. The addition of age, sex, and Charlson Comorbidity Index, strengthened the relationship, and accounted for 70% of the variance in muscle assessed by CT image analysis. The mean bias between measured and ultrasound-predicted CT muscle area was -2cm^2 with limits of agreement from +36 to -40cm^2. There is currently no consensus on what is considered acceptable performance in terms of prediction of muscularity at the individual level, but our data provides a reference point for comparison with subsequent studies.

Whilst most of the ICU literature using ultrasound has focused on describing changes in muscle thickness and/or muscle CSA at ICU admission[23,24] and using it as a tool to monitor the responsiveness of nutrition interventions[25,26], there is a paucity of literature evaluating the accuracy of ultrasound measurements of muscularity compared to reference methods in the critical care setting. This is primarily due to the challenges of performing traditional body composition methods in critical care. When other reference methods are unavailable or inaccessible, CT image analysis at the L3 area is considered to be a useful method; however due to cost and radiation exposure, scan acquisition is generally restricted to clinical diagnostic indications and therefore the study populations in ICU using this method are likely to represent only a subset of the broader mixed ICU population. This further highlights the need for the validation of bedside tools that can measure body composition in a wide range of critically ill patients.

Most frequently in the ICU literature, muscle ultrasonography has focused on the quadriceps group, which is proposed to have more considerable implications on physical and clinical outcomes compared to other muscle groups.[8] However, the findings from the current study demonstrate that ultrasound measurement of the thigh alone may not provide the most optimal representation of whole-body muscularity. These results are supported by a recent study by Paris et al, in 96 healthy volunteers, where ultrasound-derived muscle thickness of bilateral quadriceps alone had a strong relationship to appendicular lean tissue mass assessed by DXA (R^2=0.72), but was further improved by adding anterior mid-upper arm muscle thickness and covariates age and sex (R^2=0.92).[10] Further, critically ill patients lose muscle at differing rates from different areas of the body and therefore when considering a tool to measure the effectiveness of interventions aimed to attenuate whole-body muscle wasting (such as nutrition delivery) it may be important to consider the assessment of muscle groups at both the upper and lower limbs.[27,28]

Low muscularity and malnutrition have been associated with a range of adverse clinical outcomes in the acute setting, and patients identified as malnourished may benefit from more intensive nutrition therapy.[29,30] The diagnosis of malnutrition using criteria set out in the recent Global Leadership Initiative on Malnutrition (GLIM) recommendations[4] and in the widely used subjective global assessment (SGA) tool are challenging in the ICU setting[31], specifically, because these assessments rely on obtaining an accurate weight and weight history. These are frequently affected by fluid overload and an inability to obtain a history from the patient early in the ICU admission. Additionally, the remaining part of the SGA tool involves dietary history and subjective physical assessment of muscle and fat wasting, the latter of which is also recommended by GLIM when reference body composition methods are not available and may also be affected by edema and obesity. These challenges were demonstrated in 56 ICU patients, who also had a CT Scan at the L3 area.[32] All were classified as normally nourished by a dietitian using SGA, but despite this classification, 56% had low muscularity on CT image analysis.[32] Therefore, it is highly relevant for the assessment of nutritional status to consider the ability of an objective bedside method to classify a patient as having low or normal muscularity accurately. This is supported by the GLIM recommendations, where the identification of depleted muscle stores is included as a criterion for the diagnosis of malnutrition.[4] The ultrasound model described in this study demonstrated a good ability to accurately classify the 14 patients with low CT muscle area (AUC 0.79). Although the sample size was small, this finding highlights that ultrasound may be a useful tool to identify patients with muscle wasting who may be malnourished on ICU admission and to quantitatively monitor muscularity during the ICU and hospital stay.

There are no internationally recognized cut-off values for classifying patients with low muscularity using ultrasound-derived muscle thickness. Recently, in the study aforementioned, Paris et al. developed cut-points for ultrasound muscle thickness at the thigh and anterior mid-upper arm, to classify individuals into three groups (low, moderate, and high) for risk of low lean tissue mass.[10] Given the present study used a similar protocol, these cut-points may warrant further investigation, to determine if they have relevance to functional and clinical outcomes in ICU patients.

This study has strengths and limitations, which need to be considered. A strength is the high acquisition rate for ultrasound of the upper arm and thighs even in a cohort of largely trauma patients, demonstrating its feasibility as a bedside body composition method on ICU admission. This study was performed in a single centre, which fosters consistency in the application of ultrasound technique in order to test its capabilities to reliably assess muscularity. Further, the ultrasound protocol was efficient to perform (less than 30mins) and trainable for non-medical professionals, which highlights the potential for widespread use of the method. Limitations include the modest sample size. Caution should be exercised in generalizing the results to the broader ICU population, given the high representation of trauma patients in our sample (due to the inclusion requirement for patient having a CT scan). It remains unknown whether CT muscle area determined by a single slice at the L3 area is representative of whole-body muscle in ICU patients.

Conclusion

Ultrasound has the potential to assess muscularity and to identify patients with low muscle mass on ICU admission. Although the results from this study need extension in other settings and tracking over time, we have demonstrated a strong relationship between muscularity assessed with a widely available and applicable ultrasound method and a reference method. Future research priorities include investigating how muscle status, assessed by ultrasound on ICU admission, relates to important functional and clinical outcomes.

Supporting Information

jpen1822-sup-0001-tableS1.pdf

Acknowledgements

We thank the staff and participants from The Alfred ICU for their cooperation and support for the study. We also thank Ibolya Nyulasi, Lisa Murnane (LM) and Louise Becroft (LB) (The Alfred Nutrition Department) for their support and help with interrater reliability testing; and Mike Paris and staff at The University of Waterloo who helped with ultrasound and CT image analysis training.

References

1. Weijs PJ, Looijaard WG, Dekker IM, et al. Low skeletal muscle area is a risk factor for mortality in mechanically ventilated critically ill patients. *Critical Care.* 2014;18(2):R12.
2. Moisey LL, Mourtzakis M, Cotton BA, et al. Skeletal muscle predicts ventilator-free days, ICU-free days, and mortality in elderly ICU patients. *Crit Care.* 2013;17(5):R206.
3. Shibahashi K, Sugiyama K, Kashiura M, Hamabe Y. Decreasing skeletal muscle as a risk factor for mortality in elderly patients with sepsis: a retrospective cohort study. *J Intensive Care.* 2017;5:8.
4. Jensen GL, Cederholm T, Correia M, et al. GLIM Criteria for the Diagnosis of Malnutrition: A Consensus Report From the Global Clinical Nutrition Community. *JPEN J Parenter Enteral Nutr.* 2019;43(1):32-40.

5. Prado CM, Heymsfield SB. Lean tissue imaging: a new era for nutritional assessment and intervention. *JPEN J Parenter Enteral Nutr.* 2014;38(8):940-953.

6. Sheean P, Gonzalez MC, Prado CM, McKeever L, Hall AM, Braunschweig CA. American Society for Parenteral and Enteral Nutrition Clinical Guidelines: The Validity of Body Composition Assessment in Clinical Populations. *JPEN J Parenter Enteral Nutr.* 2020;44(1):12-43.

7. Earthman CP. Body Composition Tools for Assessment of Adult Malnutrition at the Bedside: A Tutorial on Research Considerations and Clinical Applications. *JPEN J Parenter Enteral Nutr.* 2015;39(7):787-822.

8. Mourtzakis M, Parry S, Connolly B, Puthucheary Z. Skeletal Muscle Ultrasound in Critical Care: A Tool in Need of Translation. *Ann Am Thorac Soc.* 2017;14(10):1495-1503.

9. 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(2):171-180.

10. Paris MT, Lafleur B, Dubin JA, Mourtzakis M. Development of a bedside viable ultrasound protocol to quantify appendicular lean tissue mass. *J Cachexia Sarcopenia Muscle.* 2017;8(5):713-726.

11. Abe T, Kondo M, Kawakami Y, Fukunaga T. Prediction equations for body composition of Japanese adults by B-mode ultrasound. *Am J Hum Biol.* 1994;6(2):161-170.

12. Campbell IT, Watt T, Withers D, et al. Muscle thickness, measured with ultrasound, may be an indicator of lean tissue wasting in multiple organ failure in the presence of edema. *Am J Clin Nutr.* 1995;62(3):533-539.

13. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40(5):373-383.

14. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med.* 1985;13(10):818-829.

15. Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest.* 1991;100(6):1619-1636.

16. Body mass index - BMI. Available at: http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi. Accessed July 18th, 2019.

17. Heymsfield SB, Smith R, Aulet M, et al. Appendicular skeletal muscle mass: measurement by dual-photon absorptiometry. *Am J Clin Nutr.* 1990;52(2):214-218.

18. Tillquist M, Kutsogiannis DJ, Wischmeyer PE, et al. Bedside ultrasound is a practical and reliable measurement tool for assessing quadriceps muscle layer thickness. *JPEN J Parenter Enteral Nutr.* 2014;38(7):886-890.

19. Hadda V, Kumar R, Hussain T, et al. Reliability of ultrasonographic arm muscle thickness measurement by various levels of health care providers in ICU. *Clin Nutr ESPEN.* 2018;24:78-81.

20. Fivez T, Hendrickx A, Van Herpe T, et al. An Analysis of Reliability and Accuracy of Muscle Thickness Ultrasonography in Critically Ill Children and Adults. *JPEN J Parenter Enteral Nutr.* 2016;40(7):944-949.

21. Abe T, Fujita E, Thiebaud RS, Loenneke JP, Akamine T. Ultrasound-Derived Forearm Muscle Thickness Is a Powerful Predictor for Estimating DXA-Derived Appendicular Lean Mass in Japanese Older Adults. *Ultrasound Med Biol.* 2016;42(9):2341-2344.

22. Bland JM, Altman DG. Measuring agreement in method comparison studies. *Stat Methods Med Res.* 1999;8(2):135-160.

23. Puthucheary ZA, Rawal J, McPhail M, et al. Acute skeletal muscle wasting in critical illness. *JAMA.* 2013;310(15):1591-1600.

24. Parry SM, El-Ansary D, Cartwright MS, et al. Ultrasonography in the intensive care setting can be used to detect changes in the quality and quantity of muscle and is related to muscle strength and function. *J Crit Care.* 2015;30(5):1151 e1159-1114.

25. Ferrie S, Allman-Farinelli M, Daley M, Smith K. Protein Requirements in the Critically Ill: A Randomized Controlled Trial Using Parenteral Nutrition. *JPEN J Parenter Enteral Nutr.* 2016;40(6):795-805.

26. Fetterplace K, Deane AM, Tierney A, et al. Targeted Full Energy and Protein Delivery in Critically Ill Patients: A Pilot Randomized Controlled Trial (FEED Trial). *JPEN J Parenter Enteral Nutr.* 2018;42(8):1252-1262.

27. Lambell KJ, King SJ, Forsyth AK, Tierney AC. Association of Energy and Protein Delivery on Skeletal Muscle Mass Changes in Critically Ill Adults: A Systematic Review. *JPEN J Parenter Enteral Nutr.* 2018.

28. Nakanishi N, Oto J, Tsutsumi R, Iuchi M, Onodera M, Nishimura M. Upper and lower limb muscle atrophy in critically ill patients: an observational ultrasonography study. *Intensive Care Med.* 2018;44(2):263-264.

29. Schuetz P, Fehr R, Baechli V, et al. Individualised nutritional support in medical inpatients at nutritional risk: a randomised clinical trial. *Lancet.* 2019;393(10188):2312-2321.

30. Lew CCH, Yandell R, Fraser RJL, Chua AP, Chong MFF, Miller M. Association Between Malnutrition and Clinical Outcomes in the Intensive Care Unit: A Systematic Review [Formula: see text]. *JPEN J Parenter Enteral Nutr.* 2017;41(5):744-758.

31. Baker JP, Detsky AS, Whitwell J, Langer B, Jeejeebhoy KN. A comparison of the predictive value of nutritional assessment techniques. *Hum Nutr Clin Nutr.* 1982;36(3):233-241.

32. Sheean PM, Peterson SJ, Gomez Perez S, et al. The prevalence of sarcopenia in patients with respiratory failure classified as normally nourished using computed tomography and subjective global assessment. *JPEN J Parenter Enteral Nutr.* 2014;38(7):873-879.

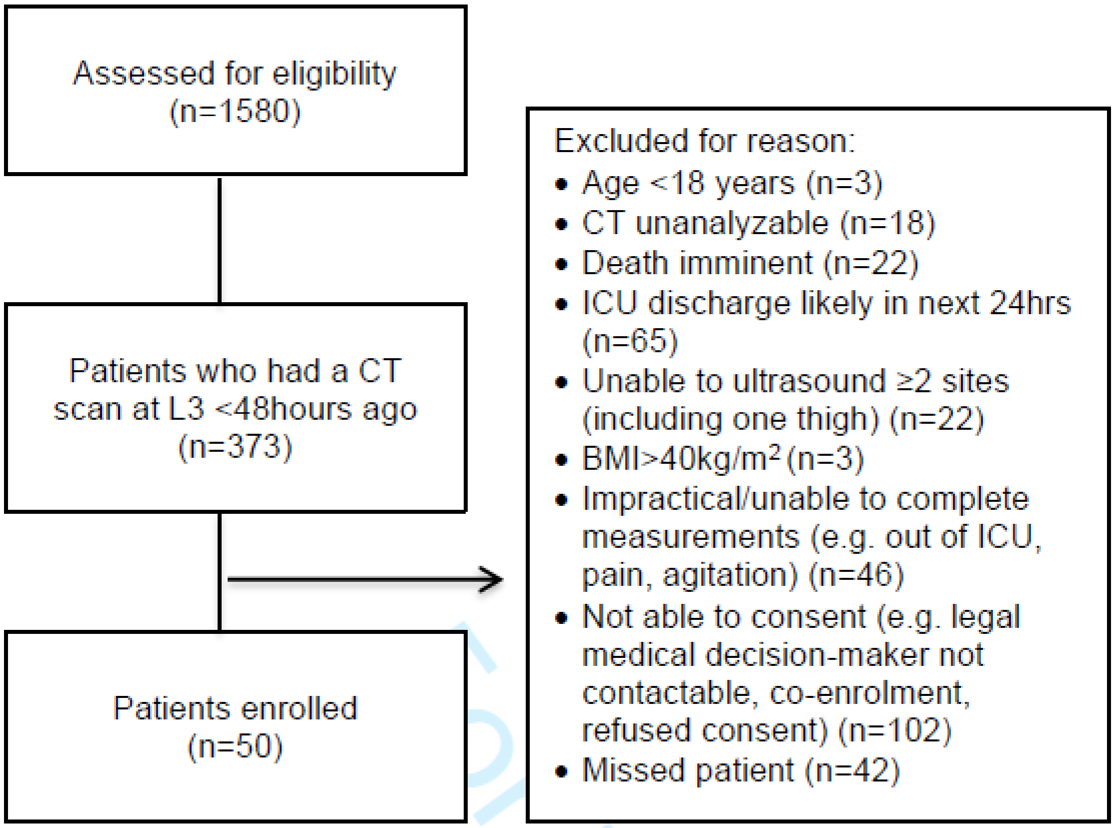

Figure 1. xxxxxxxxxxxxx

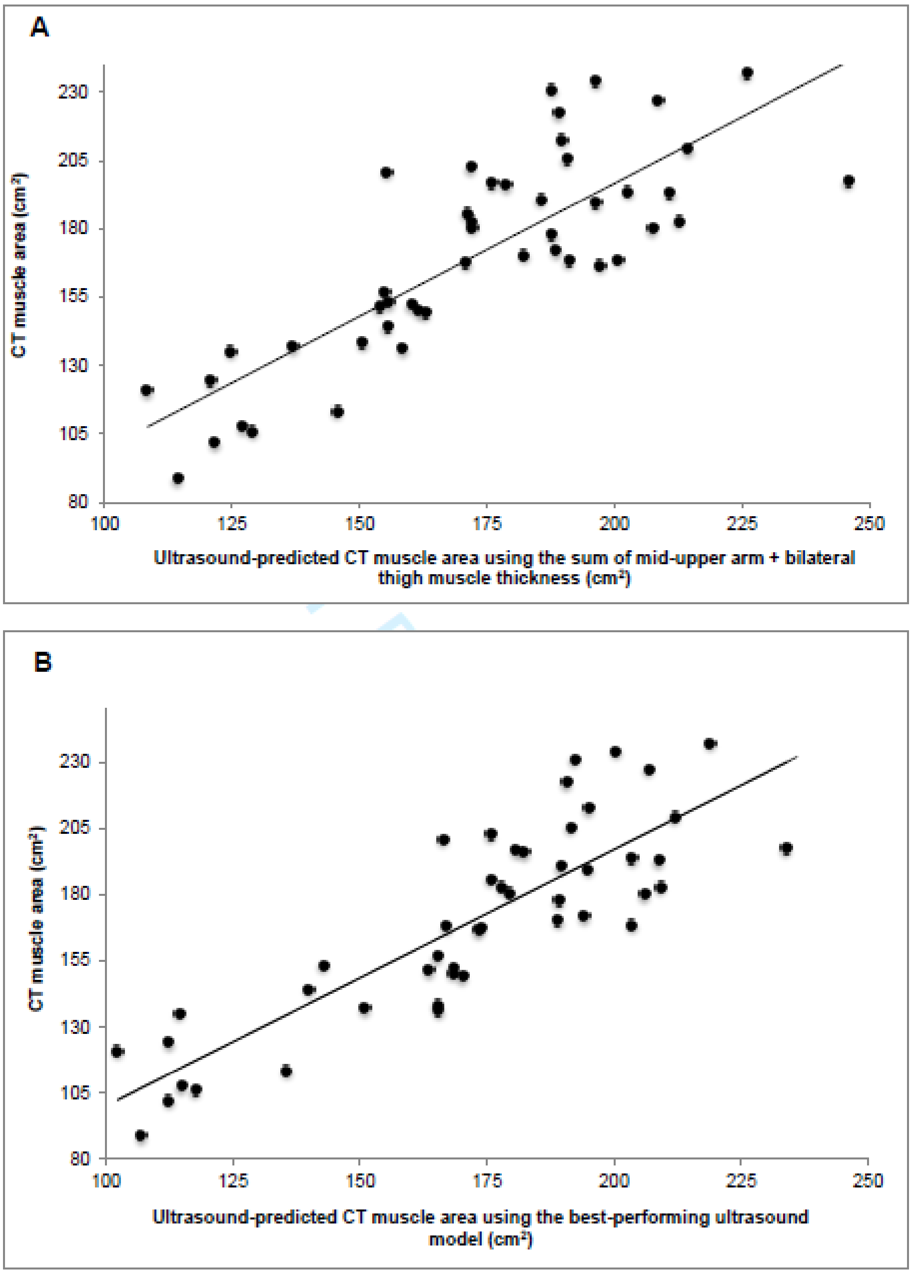

Figure 2. xxxxxxxxxxxxx

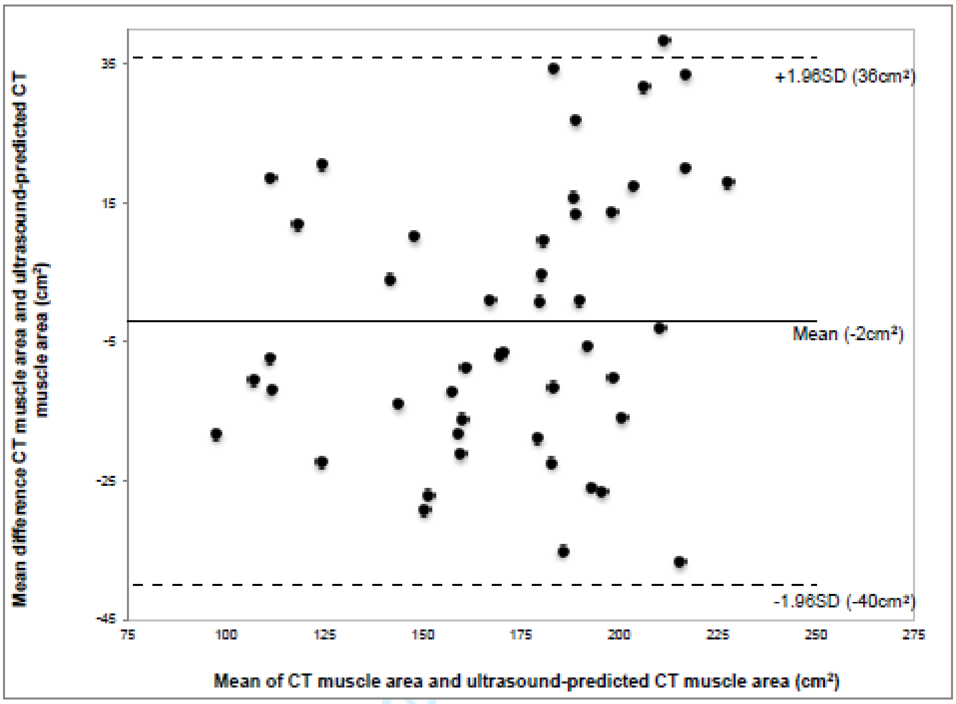

Figure 3. xxxxxxxxxxxxx

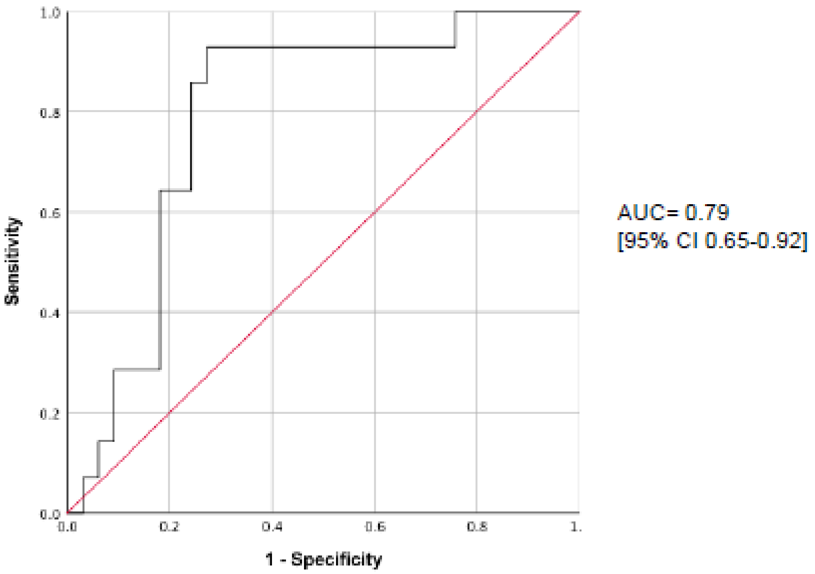

Figure 4. xxxxxxxxxxxxx

Table 1. Patient clinical and demographic characteristics[a]

Characteristics	All Patients (n=50)
Age (years)	52 ± 20 (21 – 88)
Age category	
<65 years	33 (66)
≥65 years	17 (34)
Sex	
Male	38 (76)
Female	12 (34)
APACHE II	12 [9-16] (2 - 36)
APACHE III	45 [35-65] (17 - 139)
Height (m)	1.72 ± 0.09 (1.50 - 1.98)
Weight (kg)	82 ± 15 (50 - 120)
BMI (kg/m^2)	28 ± 5 (18 - 38)
Underweight	1 (2)
Normal weight	15 (30)
Overweight	18 (36)
Obese	16 (32)
Charlson Co-morbidity Index	2 ± 2 (0 - 6)
Admission reason	
Trauma	42 (84)

Multi trauma (excluding head)	29 (69)
Multi trauma (including head)	4 (10)
Traumatic brain injury	9 (21)
Medical	7 (14)
Surgical	1 (2)
Patients MV	31 (62)
ICU LOS (days)	5 [2-11] (1 – 36)
Hospital LOS (days)	16 [11-24] (3 - 61)
Hospital mortality	4 (8)

[a]Values are reported as n; mean±SD(range), median [Q1 to Q3](range), or n(%)

APACHE, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation

Table 2. Characteristics of CT muscle area and ultrasound-derived muscle thickness at each landmark and by sex and age group

Variable	**All** (n, mean±SD)		**Male**		**Female**		***P* value**	**Young (<65 years)**		**Older (≥65 years)**		***P* value**
CT muscle CSA (cm^2)	50	172.9 ± 38.2	38	187.3 ± 29.2	12	127.4 ± 26.0	0.001	33	189.1 ± 30.5	17	141.5 ± 32.2	0.001
Mid-upper arm (cm^2)[a]	48	109.2 ± 27.8	36	119.2 ± 23.0	12	79.3 ± 17.9	0.001	31	119.4 ± 25.3	17	90.4 ± 22.3	0.001
Forearm (cm^2)[a]	39	112.4 ± 23.2	30	119.1 ± 21.6	9	90.1 ± 11.3	0.001	25	120.2 ± 20.1	14	98.6 ± 21.0	0.004
One thigh (cm^2)[a]	49	155.1 ± 49.2	37	169.8 ± 38.0	12	109.7 ± 53.2	0.003	32	176.4 ± 37.5	17	114.9 ± 43.7	0.001
Bilateral thighs (cm^2)[a,b]	49	154.8 ± 47.9	37	169.0 ± 37.0	12	111.2 ± 52.6	0.003	32	177.4 ± 35.2	17	112.3 ± 39.2	0.001
Abdomin	39	1.0 ±	33	1.1 ±	6	0.7 ±	0.0	26	1.2 ±	13	0.7 ±	0.0

al (cm)		0.3		0.3		0.4	03		0.3		0.3	01

[a]Muscle thickness (cm) multiplied by limb length (cm), [b] Average muscle thickness of bilateral thighs (or muscle thickness for one thigh if images not available for both)

CSA, Cross-sectional area; CT, Computed Tomography

Table 3. Reasons for missing ultrasound data

Reason for missing data	Thigh (n=13)	Mid-upper arm (n=2)	Forearm (n=11)	Abdominal (n=11)
Traumatic injury	6	2	2	
Lines/dressings			6	1
Wounds	1			8
Unanalysable image	2		3	1
Other	4			1