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Original article

Identifying critically ill patients with low muscle mass: Agreement between bioelectrical impedance analysis and computed tomography

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SUMMARY

Background & aims: Low muscle mass and -quality on ICU admission, as assessed by muscle area and -density on CT-scanning at lumbar level 3 (L3), are associated with increased mortality. However, CT-scan analysis is not feasible for standard care. Bioelectrical impedance analysis (BIA) assesses body composition by incorporating the raw measurements resistance, reactance, and phase angle in equations. Our purpose was to compare BIA- and CT-derived muscle mass, to determine whether BIA identified the patients with low skeletal muscle area on CT-scan, and to determine the relation between raw BIA and raw CT measurements.

Methods: This prospective observational study included adult intensive care patients with an abdominal CT-scan. CT-scans were analysed at L3 level for skeletal muscle area (cm^2) and skeletal muscle density (Hounsfield Units). Muscle area was converted to muscle mass (kg) using the Shen equation (MM_{CT}). BIA was performed within 72 h of the CT-scan. BIA-derived muscle mass was calculated by three equations: Talluri ($MM_{Talluri}$), Janssen ($MM_{Janssen}$), and Kyle (MM_{Kyle}). To compare BIA- and CT-derived muscle mass correlations, bias, and limits of agreement were calculated. To test whether BIA identifies low skeletal muscle area on CT-scan, ROC-curves were constructed. Furthermore, raw BIA and CT measurements, were correlated and raw CT-measurements were compared between groups with normal and low phase angle.

Results: 110 patients were included. Mean age 59 $\pm$ 17 years, mean APACHE II score 17 (11–25); 68% male. $MM_{Talluri}$ and $MM_{Janssen}$ were significantly higher (36.0 $\pm$ 9.9 kg and 31.5 $\pm$ 7.8 kg, respectively) and MM_{Kyle} significantly lower (25.2 $\pm$ 5.6 kg) than MM_{CT} (29.2 $\pm$ 6.7 kg). For all BIA-derived muscle mass equations, a proportional bias was apparent with increasing disagreement at higher muscle mass. $MM_{Talluri}$ correlated strongest with CT-derived muscle mass ($r = 0.834$, $p < 0.001$) and had good discriminative capacity to identify patients with low skeletal muscle area on CT-scan (AUC: 0.919 for males; 0.912 for females). Of the raw measurements, phase angle and skeletal muscle density correlated best ($r = 0.701$, $p < 0.001$). CT-derived skeletal muscle area and -density were significantly lower in patients with low compared to normal phase angle.

Abbreviations: APACHE, Acute Physiology And Chronic Health Evaluation; AUC, area under the curve; BIA, Bioelectrical impedance analysis; CI, Confidence Interval; CT, Computed Tomography; FFM, Fat Free Mass; ICU, Intensive Care Unit; L3, Lumbar Level 3; MM, Muscle Mass; ROC, receiver operating characteristics; SD, Standard Deviation; SMA, Skeletal Muscle Area; SMD, Skeletal Muscle Density.

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Conclusions: Although correlated, absolute values of BIA- and CT-derived muscle mass disagree, especially in the high muscle mass range. However, BIA and CT identified the same critically ill population with low skeletal muscle area on CT-scan. Furthermore, low phase angle corresponded to low skeletal muscle area and -density.

Trial registration: ClinicalTrials.gov (NCT02555670).

1. Introduction

Low muscle mass on ICU admission has appeared as an independent predictor of poor outcome, including fewer ventilator free days, longer ICU- and hospital length of stay, and mortality [1–6]. Quantification of muscle mass in critically ill patients is therefore of great relevance.

However, measuring muscle mass in clinical practice is challenging. Reference methods, such as dual-energy X-ray absorptiometry (DXA), whole body magnetic resonance imaging (MRI), or isotope dilution methods are not feasible in the critically ill. Ultrasound is promising [7], but has high interrater variability [8] and needs further validation. Measuring skeletal muscle area on computed tomography (CT)-scans has received increasing attention. The skeletal muscle area (SMA) on a single cross-sectional image at the level of the third lumbar vertebra (L3) has been found to be a good reflection of whole body muscle mass in a cadaver validation study [9]. In addition to muscle mass, muscle quality may be of prognostic significance. Lower skeletal muscle density (SMD) on CT, a marker for decreased muscle quality, has been associated with increased lipid infiltration in muscle biopsies [10] and poor outcome in critically ill patients [11]. However, using CT-scan analysis for measuring muscle mass and -quality has several limitations, including radiation exposure, costs, risks associated with patient transport, and time consumption.

Bioelectrical impedance analysis (BIA) is an easy, non-invasive, portable method to assess body composition. BIA measures the opposition to an alternating current through body compartments (resistance) and the delay in conduction by cell membranes (reactance). The composite marker phase angle (arc tangent of reactance/resistance) reflects the amount and integrity of body cells and predicts patient outcome in a variety of diseases [12–14] including the intensive care population [15,16] and identifies patients with nutritional risk [17]. These raw BIA measurements are independent of body weight.

BIA also measures muscle mass by using equations that combine electrical and anthropometric data. However, the confounding effect of an unreliable body weight and altered hydration status has led to cautious use of these equations in critically ill patients. Nonetheless, a recent study in Asian critically ill patients showed agreement and a high correlation between BIA and CT-derived muscle mass [18]. Therefore, BIA may be a potential tool to assess low muscle mass, one of the hallmarks of sarcopenia [19], in critically ill patients. However, further validation of the raw and calculated markers in the Caucasian population is needed.

The aims of the present study were to compare BIA- and CT-derived muscle mass in critically ill patients, to determine whether BIA and CT identify the same patients with low SMA using previously determined ICU-specific mortality-related cut-off points for low SMA [1], and to determine the relation between raw BIA and CT measurements.

2. Methods

This prospective observational study included patients admitted to the mixed medical-surgical ICU of a university hospital (Amsterdam University Medical Centers, location VU Medical Center) during a one-year period. Inclusion criteria were age ≥18 years, an abdominal CT-scan made for diagnostic or interventional reasons during ICU admission, and presence of a researcher to perform the BIA measurement. Exclusion criteria were inability to perform BIA measurement (e.g. agitation or shivering, the presence of internal- or external metal devices (as advised by the manufacturer for safety reasons), or if the CT-scan was not suitable for muscle analysis (e.g. L3 level not fully present on the scan, presence of artefacts, or insufficient scan quality due to low resolution or scattering).

The study was approved by the VU Medical Center institutional review board (IRB00002991, decision 2014/357). The need for informed consent was waived because of the use of coded data obtained from routine care. The study has been registered at ClinicalTrials.gov (NCT02555670).

2.1. Bioelectrical impedance analysis

BIA was performed within 72 h of the CT-scan using an AKERN BIA 101 Anniversary (GLNP Life Sciences, Breda, the Netherlands), a single frequency phase sensitive bioelectrical impedance device, which generates a 400 μA alternating electrical current with a 50 kHz frequency. One pair of adhesive gel electrodes (AKERN BIATRODES, Akern SRL, Pontassieve, Italy) was placed on the dorsum of the right hand and one pair on the dorsum of the ipsilateral foot, 5 cm apart. Measurements were performed in patients in supine position with a pillow supporting the head and the extremities slightly abducted to prevent contact between the legs. A small elevation (<20°) of the bed head was allowed.

Raw BIA measurements (resistance, reactance, and phase angle) were imported into BIA software (BodyGram Pro, Akern SRL, Pontassieve, Italy), which uses an equation developed by the manufacturer (Tony Talluri) to calculate muscle mass ($MM_{Talluri}$). For comparison, muscle mass equations developed by Janssen ($MM_{Janssen}$) and Kyle (MM_{Kyle}) [20,21] were used. The equations are presented in Table 1.

2.2. CT-scan analysis

CT-scans were analysed using Slice-O-matic versions 4.3 and 5.0 (TomoVision, Montreal, QC, Canada) by two certified investigators (WGPML and IMD, trained by the Cross Cancer Institute, Canada). CT-scans were analysed at the level of the third lumbar vertebra (L3), all muscles present on this level were included. The precision of single L3 slice CT scan analysis is high (inter- and intra-observer variability <2%) [22] and L3 SMA is strongly related to whole-body skeletal muscle volume ($r = 0.83–0.99$, $p < 0.01$) in healthy adults [23,24].

Muscle tissue was identified using boundaries in Hounsfield Units set to −29 to +150 [25]. Low SMA was defined using previously determined ICU-specific mortality-related cut-off points: males <170 cm^2 and females <110 cm^2 [1].

MM_{CT} was calculated by converting SMA to whole-body muscle volume using the Shen equation (Table 1) [23]. Subsequently, the volume was converted to muscle mass in kg using a density of

Table 1
Muscle mass equations.

BIA	
Talluri	**Total muscle compartment (kg)**
	$\frac{0.3 * fat\ free\ mass * \log(PA)}{0.88} + 0.15 * \left(\frac{total\ body\ water}{0.8} * \log(PA)\right)$
Janssen	**Skeletal muscle mass (kg)**
	$5.102 + \left(0.401 * \frac{height^2}{R}\right) + (3.825 * sex) + (-0.071 * age)$
Kyle	**Appendicular skeletal muscle mass (kg)**
	$-4.211 + \left(0.267 * \frac{height^2}{R}\right) + (0.095 * weight) + (1.909 * sex) + (-0.012 * age) + (0.058 * Xc)$
CT-Scans	
Shen	**Skeletal muscle volume (L)**
	$0.166 * L3\ area + 2.142$

BIA: bioelectrical impedance analysis, CT: computed tomography, L3 area: CT-derived muscle cross sectional area at 3rd lumbar vertebra (cm^2), PA: BIA-derived phase angle (°), R: BIA-derived resistance (Ω), Xc: BIA-derived reactance (Ω).
Height in cm; weight in kg; sex male = 1, female = 0.

$1.06\ g/cm^3$ [26]. SMD in Hounsfield Units was automatically calculated by the software from the mean radiological attenuation of all L3 muscle.

2.3. Other data

Baseline demographic data and variables in the Acute Physiology And Chronic Health Evaluation (APACHE) III score and its derived predicted mortality (APACHE IV) were collected from the ICU patient data management system (Metavision, IMDSoft, Tel Aviv, Israel). Patients were weighed using either an automatic bed scale or a lift-based weighing system. If neither was available or feasible, patients' weight was obtained from the patient or a family member; or estimated by a clinician. Height was measured in supine position using a flexible measuring tape.

Primary outcome was the correlation and agreement between BIA- and CT-derived muscle mass. Secondary post-hoc outcomes were the ability of BIA-derived muscle mass to identify patients with low SMA on CT-scan, and the relation between raw BIA measurements (resistance, reactance, and phase angle) and raw CT measurements (skeletal muscle area and -density).

2.4. Statistical analysis

Values are reported as number (%), mean ± standard deviation (SD), or median (25–75% interquartile range, IQR). Data are presented for all patients, and for male and female patients separately because the CT-derived cut-off points for low SMA are sex-specific [1].

Independent samples T-tests, Mann–Whitney U-tests, Chi-squared-tests, and Fisher's exact tests were used to compare male and female patients, as applicable. Paired samples T-tests were used to assess the difference between CT- and BIA-derived muscle mass. To determine the relation between CT- and BIA-derived muscle mass the Pearson correlation coefficient was calculated between MM_{CT} and $MM_{Talluri}$, $MM_{Janssen}$, and MM_{Kyle}. Additionally, to assess agreement Bland-Altman plots were constructed for MM_{CT} and $MM_{Talluri}$, $MM_{Janssen}$, and MM_{Kyle} respectively. The 95% confidence intervals (95% CI's) of the limits of agreement were calculated using Bland and Altman's approximate method with bootstrapping [27]. One-sample T-tests were used to test whether the bias (the mean difference of the CT- and BIA-derived MM) was significantly different from zero to determine whether significant bias was present. The SD's of the bias were compared using Levene's test for equality of variances to determine which equation has the lowest variance. Linear regression analysis with difference as dependent- and average as independent variable was used to determine whether the bias was proportional. To determine the ability of $MM_{Talluri}$, $MM_{Janssen}$, and MM_{Kyle} to identify patients with low SMA on CT-scan, receiver operating characteristic (ROC) curves were made. Finally, the relation between BIA-derived raw measurements (resistance, reactance, and phase angle) and CT-derived raw measurements (SMA and SMD) was determined using the Pearson correlation coefficient, and previously determined phase-angle cut-off points for nutritional risk in hospitalized patients by Kyle et al. (5.0 for men, 4.6 for women) [17] and for mortality in critically ill patients by Stapel et al. (4.8 for both men and women) [16] were used to determine whether CT-derived raw measurements were significantly different in patients with a low versus normal phase angle. A sensitivity analysis was performed including only patients with <24 h between the CT scan and BIA measurement to limit the possible effects of altered hydration status. A second sensitivity analysis was performed including only patients with a reliable weight (i.e. not estimated). IBM SPSS Statistics 22 (IBM Corp, Armonk, NY, USA), GraphPad Prism 7 (GraphPad Software, La Jolla, CA, USA), and an online tool for Bland–Altman analysis [28] were used for statistical analysis. All statistical tests were conducted two-sided. A $p < 0.05$ was considered statistically significant.

3. Results

During the study period, 1654 patients were admitted to the ICU with a mean age of 63 ± 16 years, and a mean APACHE IV predicted mortality of 24.5 ± 30.1%. One hundred eighty-five patients fulfilled the inclusion criteria. In nine patients, the BIA measurement could not be performed within 72 h of the CT scan. Forty-five patients were excluded because their CT-scan was unsuitable for analysis due to artefacts, scattering, muscles cut-off due to windowing, or insufficient scan quality; 12 patients because BIA could not be performed due to the presence of internal or external metal devices; and 9 patients due to erroneous BIA values because of shivering, dyspnea, or the inability to obtain correct positioning. A total of 110 patients were included in final analyses (Fig. 1).

Patient characteristics are presented in Table 2 for the entire population, and for male and female patients separately. Mean age was 59 ± 17 years, and 75/110 (68%) were male. Male patients had a significantly higher height (179 ± 7 vs. 169 ± 6 cm, $p < 0.001$) and weight (84.9 ± 15.2 vs. 76.8 ± 16.0 kg, $p = 0.012$) than females. Other characteristics were not significantly different between males and females. The CT-scan was performed on the day of admission in 75 patients (68%). The BIA measurement was performed a median of 1 day after CT (0–1), and in 97 patients within one day of the CT scan (88%).

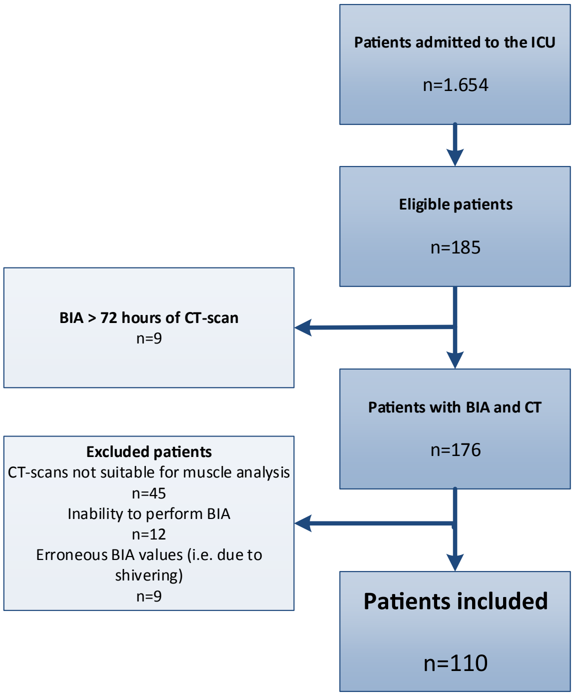

Fig. 1. Consort diagram showing the inclusion process. BIA: Bioelectrical impedance analysis, CT: Computed Tomography.

3.1. Correlation and agreement muscle mass

Mean MM_{CT} was 29.2 ± 6.7 kg (Table 3). $MM_{Talluri}$ and $MM_{Janssen}$ were significantly higher (36.0 ± 9.9 kg and 31.5 ± 7.8 kg, respectively) and MM_{Kyle} significantly lower (25.2 ± 5.6 kg) than MM_{CT} (all $p < 0.001$). Muscle mass (both CT- and BIA-derived) and phase angle and were significantly higher in male patients, while resistance was higher in female patients and reactance was not significantly different between sexes.

Of all BIA-derived muscle mass equations, $MM_{Talluri}$ had the strongest correlation with CT-derived muscle mass ($r = 0.834$, $p < 0.001$; Fig. 2).

On Bland–Altman analysis a significant bias of 6.87 kg (95%CI 5.79–7.95, $p < 0.001$) between $MM_{Talluri}$ and MM_{CT} was apparent, with limits of agreement −4.31 kg (95%CI -6.37 to −2.66) to 18.06 kg (95%CI 16.41–20.12; Fig. 2). Regression analysis showed that the bias was proportional (B 0.428, $p < 0.001$), with an increasing disagreement between $MM_{Talluri}$ and MM_{CT} at higher muscle mass values, whereby $MM_{Talluri}$ was higher than MM_{CT} at higher muscle mass.

Bias between $MM_{Janssen}$ and MM_{CT} was 2.38 kg (95%CI 1.19–3.57, $p < 0.001$) with limits of agreement −9.93 (95%CI -12.19 to −8.11) to 14.68 kg (95%CI 12.87–16.95). Again, proportional bias was found with an increasing disagreement at higher muscle mass (B 0.198, $p = 0.03$). Finally, the bias between MM_{Kyle} and MM_{CT} was −3.98 kg (95%CI -4.88 to −3.08, $p < 0.001$) with limits of agreement −13.29 (95%CI -15.00 to −11.91) to 5.33 kg (95%CI 3.95–7.04). Regression analysis showed an inverse proportional bias, disagreement was

Table 2
Patient characteristics.

	All patients (n = 110)	Male patients (n = 75)	Female patients (n = 35)	*P*-value Male vs. Female
Age, y	59 ± 17	59 ± 18	59 ± 14	0.947
Height, cm	176 ± 8	179 ± 7	169 ± 6	**<0.001**
Weight, kg	82.4 ± 15.8	84.9 ± 15.2	76.8 ± 16.0	**0.012**
Bmi, kg/m^2	25.3 (23.1–29.4)	25.4 (22.9–29.7)	25.1 (23.5–28.8)	0.827
Underweight	0 (0%)	0 (0%)	0 (0%)	
Normal weight, no (%)	52 (47%)	35 (47%)	17 (49%)	
Overweight, no (%)	33 (30%)	22 (29%)	11 (31%)	
Obese, no (%)	17 (16%)	15 (20%)	2 (6%)	
Morbidly obese, no (%)	8 (7%)	3 (4%)	5 (14%)	
Admission type				0.536
Medical, no (%)	45 (41%)	28 (37%)	17 (49%)	
Surgical, no (%)	25 (23%)	18 (24%)	7 (20%)	
Trauma, no (%)	40 (36%)	29 (39%)	11 (31%)	
Diagnosis type				0.578
Cardiovascular, no (%)	9 (8%)	7 (9%)	2 (6%)	
Metabolic/renal, no (%)	3 (3%)	3 (4%)	0 (0%)	
Neurologic, no (%)	7 (6%)	5 (7%)	2 (6%)	
Post resuscitation, no (%)	5 (5%)	2 (3%)	3 (9%)	
Post surgery, no (%)	25 (23%)	18 (24%)	7 (20%)	
Respiratory insufficiency, no (%)	11 (10%)	6 (8%)	5 (14%)	
Sepsis, no (%)	8 (7%)	4 (5%)	4 (11%)	
Trauma, no (%)	40 (36%)	29 (39%)	11 (31%)	
Other, no (%)	2 (2%)	1 (1%)	1 (3%)	
APACHE II score[a]	17 [11–25]	18 [11–25]	17 [12–24]	0.799
APACHE IV predicted mortality[b], %	16 (6–46)	16 (5–48)	20 (7–46)	0.585
Mechanically ventilated, no (%)	72 (66%)	49 (65%)	23 (66%)	1.000
Time between icu admission and ct scan, d	0 (0–0)	0 (0–0)	0 (0–0)	0.419
Time between icu admission and bia, d	1 (0–1)	1 (0–1)	1 (0–1)	0.646
Time between ct scan and bia, d	1 (0–1)	1 (0–1)	1 (0–1)	0.100

APACHE: acute physiology and chronic health evaluation, BIA: bioelectrical impedance analysis, BMI: body mass index, CT: computed tomography, ICU: intensive care unit, d: days.
P-values in bold indicate a significant difference.
[a] n = 106, four missing values due to missing data.
[b] n = 109, one missing value due to missing data.

Table 3
CT- and BIA-derived muscle mass and raw measurements.

BIA	All patients (n = 110)	Male patients (n = 75)	Female patients (n = 35)	*P*-value Male vs. Female
Muscle mass				
Talluri equation[a], kg	36.0 ± 9.9	39.4 ± 9.7	28.7 ± 5.7	**<0.001**
% Of body weight	44 ± 10	47 ± 10	38 ± 7	**<0.001**
Janssen equation[b], kg	31.5 ± 7.8	34.6 ± 6.8	25.0 ± 5.7	**<0.001**
% Of body weight	39 ± 9	41 ± 8	33 ± 8	**<0.001**
Kyle equation[c], kg	25.2 ± 5.6	27.3 ± 5.0	20.6 ± 4.0	**<0.001**
% Of body weight	31 ± 5	32 ± 4	27 ± 5	**<0.001**
Raw measurements				
Resistance, Ω	465 ± 101	450 ± 91	498 ± 115	**0.019**
Resistance/m, Ω/m	265 ± 60	252 ± 52	295 ± 65	**<0.001**
Reactance, Ω	40 ± 15	40 ± 15	38 ± 15	0.550
Reactance/m, Ω/m	23 ± 9	23 ± 9	23 ± 9	0.903
Phase angle, °	4.8 ± 1.4	5.0 ± 1.5	4.3 ± 1.1	**0.013**
CT-scans				
Muscle mass				
Shen equation[b], kg	29.2 ± 6.7	31.6 ± 6.3	23.9 ± 3.5	**<0.001**
% Of body weight	36 ± 7	38 ± 7	32 ± 6	**<0.001**
Raw measurements				
Skeletal muscle area, cm^2	152 ± 38	166.6 ± 36.0	122.7 ± 20.2	**<0.001**
Low skeletal muscle area[d], no. (%)	52 (47%)	43 (57%)	9 (26%)	**0.002**
Skeletal muscle index, cm^2/m^2	49.2 ± 10.6	51.9 ± 10.7	43.3 ± 7.8	**<0.001**
Skeletal muscle density, hu	38.1 ± 12.7	40.0 ± 13.4	33.9 ± 10.0	**0.009**
Low skeletal muscle density[e], no. (%)	14 (13%)	4 (5%)	10 (29%)	**0.001**

BIA: bioelectrical impedance analysis, CT: computed tomography, HU: Hounsfield units.
For full equations see Table 1.
P-values in bold indicate a significant difference.
[a] Talluri equation calculates total muscle compartment.
[b] Janssen and Shen equations calculate skeletal muscle mass [19,22].
[c] Kyle equation calculates appendicular skeletal muscle mass [20].
[d] Skeletal muscle area cut-offs: 170 cm^2 for males and 110 cm^2 for females [1].
[e] Skeletal muscle density cut-offs based on BMI and age [32].

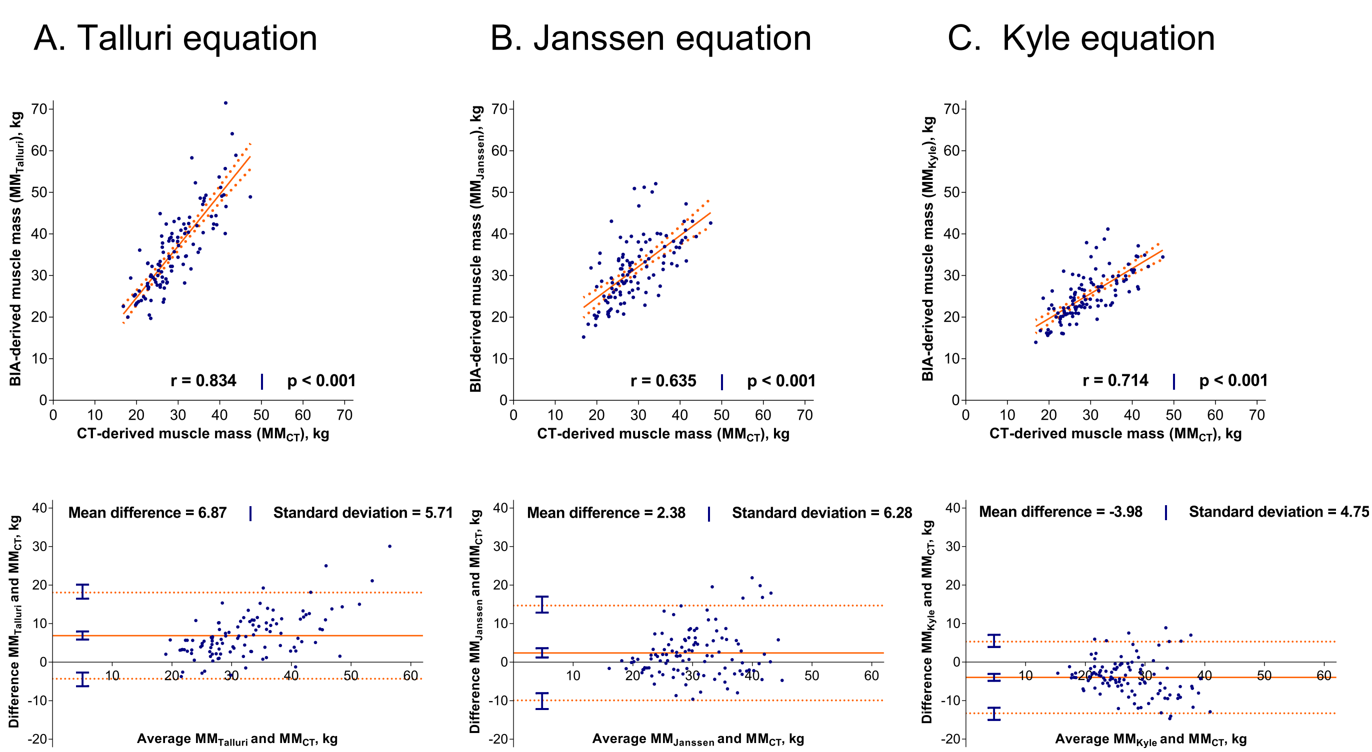

Fig. 2. Regression plots (upper panel) and Bland-Altman plots (lower panel) showing the correlation and agreement between CT-derived muscle mass (MM_{CT}) and the BIA-derived muscle mass equations. A. Talluri equation ($MM_{Talluri}$), B. Janssen equation ($MM_{Janssen}$), and C. Kyle equation (MM_{Kyle}). BIA: bioelectrical impedance analysis; MM: muscle mass.

higher at higher muscle mass, whereby MM_{Kyle} was lower than MM_{CT} at higher muscle mass (B −0.197, p = 0.013).

The bias of $MM_{Janssen}$ was significantly lower than that of $MM_{Talluri}$ and MM_{Kyle} ($p < 0.001$). The variance (SD of the bias) of MM_{Kyle} was significantly lower than of $MM_{Janssen}$ (F 5.86, p = 0.016). The variances of $MM_{Talluri}$ and MM_{Kyle} and of $MM_{Talluri}$ and $MM_{Janssen}$ were not significantly different.

3.2. Identification of low skeletal muscle area

For male patients, the area under the ROC curve (AUC) for $MM_{Talluri}$ to identify patients with low SMA on CT was 0.919 (95%CI 0.858−0.979, Fig. 3). For $MM_{Janssen}$ and MM_{Kyle} the AUC was 0.743 (95%CI 0.630−0.856) and 0.800 (95%CI 0.700−0.900), respectively. For female patients, the AUC for $MM_{Talluri}$ was 0.912 (95%CI 0.820−1.000), for $MM_{Janssen}$ 0.821 (95%CI 0.629−1.000), and for MM_{Kyle} 0.821 (95%CI 0.646−1.000).

3.3. Correlation raw measurements

Correlations between BIA-derived raw measurements (resistance, reactance, and phase angle) and CT-derived raw measurements (skeletal muscle area and -density) are shown in Table 4. BIA-derived phase angle and resistance were correlated with CT-derived SMA ($r = 0.542$, $p < 0.001$ and $r = -0.409$, $p < 0.001$, respectively). BIA-derived phase angle and reactance were correlated with CT-derived SMD ($r = 0.701$, $p < 0.001$ and $r = 0.539$, $p < 0.001$, respectively) (Fig. 4). Finally, both SMA and SMD were lower in patients with low phase angle when compared to those with normal phase angle using nutritional-risk based cut-off points [17]. SMA in females was 117 vs 130 cm^2 (p = 0,066) and in males 151 vs 183 cm^2 (p < 0,001), SMD in females was 28,2 vs 40,7 HU (p < 0,001) and in males 31,9 vs 48,3 HU (p < 0,001). Using the mortality-based cut-offs from Stapel et al. [16] similar differences were seen: SMA in females 119 vs 131 cm^2 (p = 0,088) and in males 145 vs 184 cm^2 (p < 0,001), SMD in females 30,2 vs 41,2 HU (p = 0,001) and in males 31,0 vs 47,1 HU (p < 0,001).

3.4. Sensitivity analyses

Sensitivity analyses were performed in patients in whom the BIA measurement was performed within one day of the CT scan (n = 97) and in those with a reliable weight (n = 85). Characteristics of patients with <24 h between BIA measurement and CT scan were not significantly different from those with a longer time interval (24−72 h) between CT scan and BIA measurement (Supplemental Tables 1 and 2), nor were those of patients with a reliable weight different from those with an estimated weight, except that more ventilated patients had an estimated weight (Supplemental Tables 3 and 4). Correlation and agreement between $MM_{Talluri}$, $MM_{Janssen}$, and MM_{Kyle} and MM_{CT} (Supplemental Figs. 1 and 3), ROC curves of $MM_{Talluri}$, $MM_{Janssen}$, and MM_{Kyle} identifying low SMA (Supplemental Figs. 2 and 4), and correlations between raw measurements (Supplemental Tables 3 and 6) from both sensitivity analyses were comparable to those found in all patients.

4. Discussion

This prospective observational study in 110 critically ill patients with an abdominal CT-scan shows that the agreement between BIA- and CT-derived muscle mass was poor, but the two are significantly correlated. Importantly, BIA identified critically ill patients with low skeletal muscle area on CT-scan, as defined by previously found cut-offs, and BIA-derived low phase angle corresponded to low CT-derived skeletal muscle area and -density.

In the present study, we used muscle mass equations, which rely on assumptions and primary measured variables. The poor agreement between muscle mass equations can primarily be explained by the fact that the different equations assess different muscle compartments and also by the fact that neither the Shen equation nor the BIA-derived MM-equations have been validated in intensive care patients, and both make assumptions that may not be accurate in this patient population.

Our findings are in agreement with a recent retrospective study in an Asian surgical critically ill population by Kim et al. in which skeletal muscle mass evaluation by BIA and CT was also compared [18]. The study showed good correlation and agreement between BIA and CT-derived skeletal muscle mass, also in subgroups of patients with low skeletal muscle mass and even in case of severe edema. Accuracy was determined by correlation and by agreement based on Bland−Altman analysis. . Unfortunately, the study does not describe the applied muscle mass equation, nor in which population this equation was validated. Since body composition is ethnicity specific [29], the results may not be applicable to the Caucasian population. Our prospective observational study further validates BIA as a potential tool in identifying Caucasian critically ill patients with low muscle mass on CT-scan.

We also found that the raw BIA measurements phase angle, resistance, and reactance correlated with the raw CT measurements skeletal muscle area and -density, and that low phase angle corresponded to low CT-derived muscle area and -density. This is important because the raw BIA and CT measurements are, in contrast to the muscle mass equations, independent of body weight, directly measured, and not dependent on assumptions which may not be valid in the critically ill population. Specifically, phase angle and reactance correlated with skeletal muscle density (as marker of muscle quality) and phase angle and resistance with muscle area (muscle mass).

Previous studies demonstrated that low phase angle and impedance ratio were associated with low muscularity on CT-scan, but only in a multivariable logistic regression model [30]. We found the strongest relation between phase angle and skeletal muscle density. Phase angle has previously been demonstrated to have prognostic significance in critically ill patient [15,16]. Phase angle therefore seems a simple and useful biomarker of cellular health. The presently found correlation with muscle density on CT scan, confirms the notion that phase angle not only reflects cellular mass but also the integrity of cell membranes and thus cellular quality [31]. Both phase angle and CT-derived muscle density at ICU admission were found to be associated with mortality [11,15,16]. The present study is the first study that assesses the relation between phase angle and CT-derived skeletal muscle area and -density.

Agreement between BIA- and CT derived muscle mass was poor. Of note, the three BIA-derived muscle mass equations use different raw BIA measurements in their calculations and assess different muscle compartments. $MM_{Talluri}$ assesses the total muscle compartment, $MM_{Janssen}$ assesses skeletal muscle mass, and MM_{Kyle} assesses appendicular skeletal muscle mass. This may partially explain the high bias between $MM_{Talluri}$ and MM_{CT}. The three extreme outliers in the Bland-Altman plot constructed for $MM_{Talluri}$ and MM_{CT} were all relatively young, male patients (median age 41) who were in good condition prior to their acute ICU admission. These patients might have relatively more skeletal muscle in arms and legs. Their muscle distribution may therefore deviate from the population in which the Shen equation for CT-derived muscle mass was developed, and cause single slice measurements at the L3 level to be inaccurate. Additionally, resistance, the most important determinant of muscle mass, depends on the cross-sectional area of the tissue the electrical current is passing through, and BIA

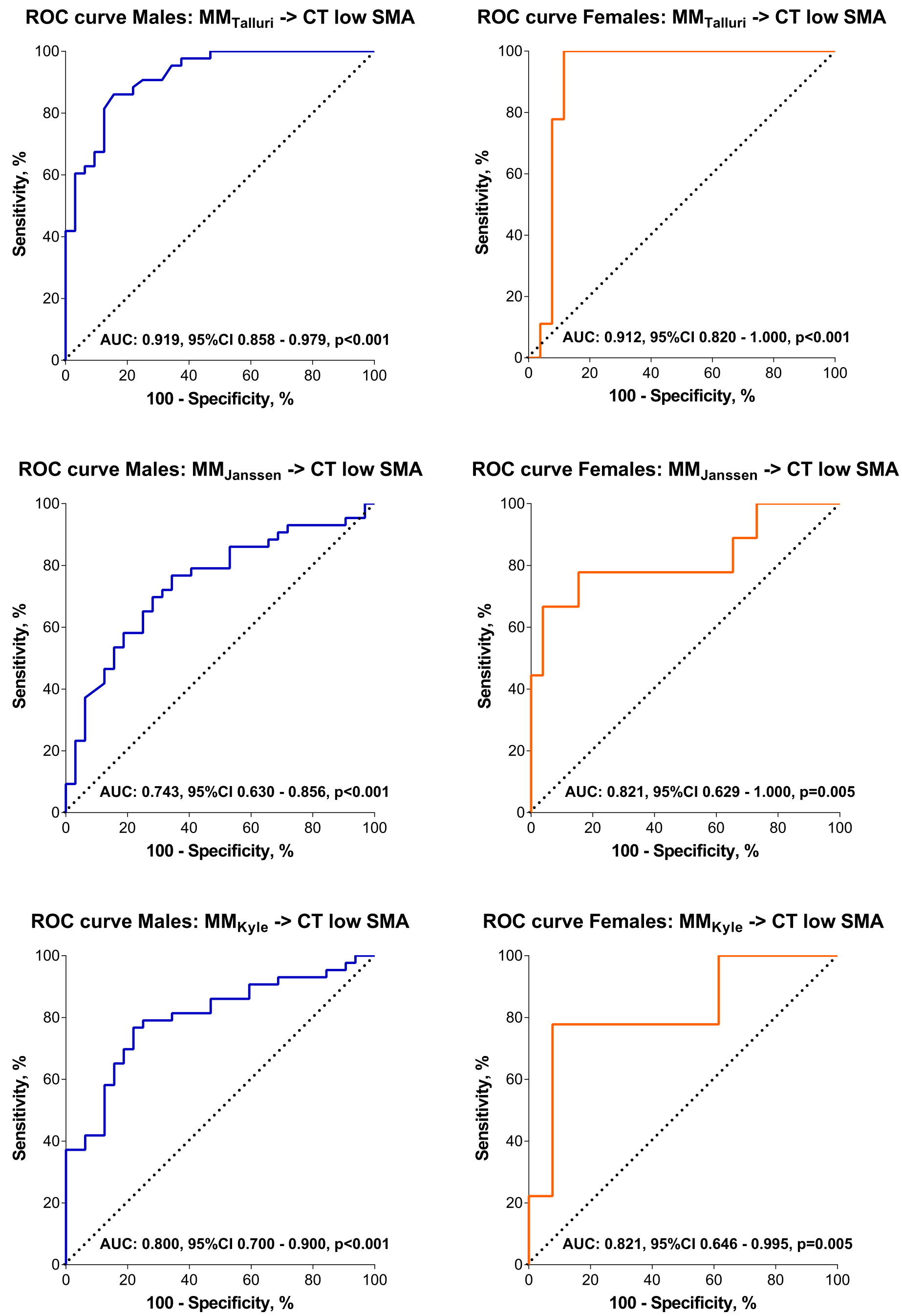

Fig. 3. Receiver operating characteristics (ROC) curves and area under the curves (AUC) showing the ability of the BIA-derived muscle mass equations ($MM_{Talluri}$, $MM_{Janssen}$, MM_{Kyle}) to identify patients with low muscle mass on CT-scan (CT low SMA). Curves for males (left panel) and females (right panel) are shown separately. BIA: bioelectrical impedance analysis; MM: muscle mass; SMA: CT-derived skeletal muscle area at lumbar level 3.

Table 4
Pearson correlation coefficients between CT- and BIA-derived raw measurements.

	Bia-derived raw measurements					
	Resistance		Reactance		Phase angle	
	R	*P*-value	*R*	*P*-value	*R*	*P*-value
Ct-derived raw measurements						
Skeletal muscle area	−0.409	**<0.001**	0.197	**0.039**	0.542	**<0.001**
Skeletal muscle density	−0.010	0.920	0.539	**<0.001**	0.701	**<0.001**

BIA: bioelectrical impedance analysis, CT: computed tomography. P-values in bold indicate a significant test result.

measurements may therefore be disproportionally influenced by arms and legs due to the smaller cross sectional area of extremities relative to the trunk.

All BIA-derived MM-equations showed proportional bias with increasing disagreement at higher muscle mass. However, in the lower muscle mass range, agreement was better. This explains why BIA-derived $MM_{Talluri}$ had a good discriminative capacity to identify patients with low SMA on CT-scan. Since this is the population at risk for adverse outcome, BIA might be a clinically useful tool to identify at-risk patients, not only by using phase angle but also by measuring muscle mass. However, further validation is needed.

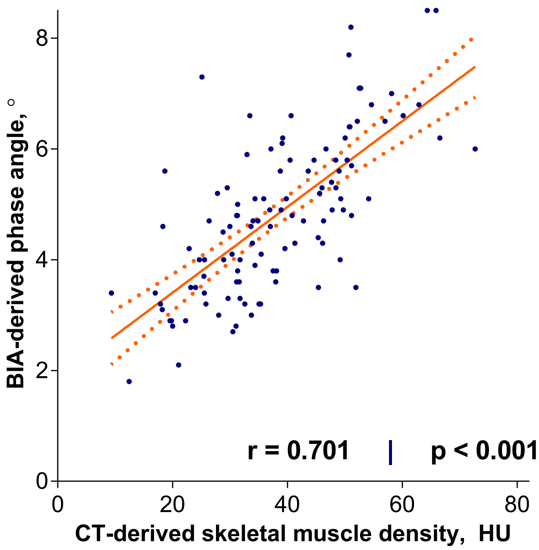

Fig. 4. Regression plot showing the correlation between the BIA- and CT-derived markers of muscle quality: phase angle and skeletal muscle density. BIA: bioelectrical impedance analysis; HU Hounsfield Units.

4.1. *Strengths and limitations*

Main limitations are that BIA and CT-scan are not reference methods for measuring muscle mass. Both assess muscle mass indirectly by using equations based on algorithms that are not validated in the critically ill population with altered hydration, altered membrane capacitance and an unreliable body weight. CT measures muscle area at a single L3 level and extrapolates this to total skeletal muscle mass, via the Shen equation and tissue density. CT-derived muscle area has been validated for the assessment of total skeletal muscle mass in healthy volunteers [23,24], however, a disproportionate muscle distribution cannot be assessed by CT analysis at a single L3 level.

BIA assesses muscle mass using algorithms that combine the raw BIA measurements with sex, age, height, and weight. The main limitation of all BIA equations in the critically ill is that they are influenced by hydration status. Resistance is highly sensitive to changes in fluid status, thus affecting the reliability of the muscle mass calculations. Furthermore, capillary leak may decrease the capacitance of cell membranes and leads to underestimation of muscle mass. CT-scans are also influenced by hydration status as muscles can become edematous. However, extrafacial edema present in the subcutaneous fat tissue can be identified, due to the difference in HU of water (HU 0) and muscle (mean HU 38.1). Other limitations are that in 12 patients the time between the CT-scan and the BIA measurement was longer than 24 h and that body weight was not measured in all patients. Hydration status changes rapidly in the critically ill and may have influenced either measurement in these patients. Nevertheless, a sensitivity analysis including only patients with less than 24 h between the CT scan and BIA measurement and including only patients with reliable body weight showed similar results.

Our study has several strengths. This is the first prospective study comparing BIA and CT measurements of the muscle compartment, and the first in the Caucasian population. Although showing disagreement, it demonstrates that BIA can identify the same population with low SMA. The cut-off points used for low SMA on CT-scan are previously determined ICU-specific cut-off points related to mortality [1]. Furthermore, the correlation between phase angle and skeletal muscle density, and the finding that low phase angle, as defined by nutritional risk- and mortality-related cut-off points [16,17], corresponded to low CT-derived muscle area and -density are new and provide future perspectives. Compared to the recent Korean study, the interval between BIA and CT measurements was smaller. Future research should focus on validating BIA-derived muscle mass in critically ill patients, for example by comparing regional BIA with three-dimensional measurements of the muscle compartment to CT scan or ultrasound and independent measures of body water, and to determine whether and how equations can correct for fluid imbalance. In addition, the relation between phase angle and skeletal muscle density as markers of cellular quality and health could be explored further.

5. Conclusion

The present study in critically ill patients demonstrates that absolute values of BIA- and CT-derived muscle mass are not comparable, but they are significantly correlated. Importantly, BIA and CT identified the same critically ill population with low muscle mass. The present study also shows a correlation between phase angle (BIA) and skeletal muscle density (CT), and that low phase angle corresponds to low muscle area and -density.

Funding

An unrestricted grand from Nutricia was used to buy the bioelectrical impedance device.

Availability of data

The data are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by the VU Medical Center institutional review board (IRB00002991, decision 2014/357). The need for informed consent was waived because of the use of coded data obtained from routine care.

Consent for publication

Not applicable.

Authors' contribution

HO, PW, WL, SS and AG designed the study. WL, SS, ID, SR and HR obtained the data and were responsible for the data management. WL and SS analysed the data. HO had primary responsibility for the collection, analysis and interpretation of the data and the final content. All authors contributed to drafting and writing the manuscript. All authors read and approved the final manuscript.

Conflict of interest

WL has received research support and speaking honoraria from Fresenius and congress support from Baxter. SS has received research support from Nestle and congress support from Baxter. PW has received financial support from Baxter, Fresenius, Nutricia and Nestlé. HO is a section editor for Critical Care and has received research support from Fresenius and speaking honoraria from Fresenius, Nutricia and Nestlé. The BIA-device has been bought with a grant from Nutricia. The other authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2019.07.020.

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