Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Clinical Nutrition ESPEN 49 (2022) 474–482

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Original article

Protein requirements and provision in hospitalised COVID-19 ward and ICU patients: Agreement between calculations based on body weight and height, and measured bioimpedance lean body mass

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ARTICLE INFO

Article history:
Received 28 February 2022
Accepted 2 March 2022

Keywords:
Lean body mass
Fat-free mass
Dietary protein
COVID-19
Bioelectric impedance
Bioimpedance
Nutrition support
Critical care
Nutritional protein requirements

SUMMARY

Background: A large proportion of hospitalised COVID-19 patients are overweight. There is no consensus in the literature on how lean body mass (LBM) can best be estimated to adequately guide nutritional protein recommendations in hospitalised patients who are not at an ideal weight. We aim to explore which method best agrees with lean body mass as measured by bioelectric impedance (LBM_{BIA}) in this population.

Methods: LBM was calculated by five commonly used methods for 150 hospitalised COVID-19 patients previously included in the BIAC-19 study; total body weight, regression to a BMI of 22.5, regression to BMI 27.5 when BMI>30, and the equations described by Gallagher and the ESPEN ICU guideline. Error −standard plots were used to assess agreement and bias compared to LBM_{BIA}. The actual protein provided to ICU patients during their stay was compared to targets set using LBM_{BIA} and LBM calculated by other methods.

Results: All methods to calculate LBM suffered from overestimation, underestimation, fixed- and proportional bias and wide limits of agreement compared to LBM_{BIA}. Bias was inconsistent across sex and BMI subgroups. Twenty-eight ICU patients received a mean of 51.19 (95%-BCa CI 37.1;64.1) grams of protein daily, accumulating to a mean of 61.6% (95%-BCa CI 43.2;80.8) of $Target_{BIA}$ during their ICU stay. The percentage received of the target as calculated by the $LBM_{Gallagher}$ method for males was the only one to not differ significantly from the percentage received of $Target_{BIA}$ (mean difference 1.4% (95%-BCa CI -1.3;4.6) $p = 1.0$).

Conclusions: We could not identify a mathematical method for calculating LBM that had an acceptable agreement with LBM as derived from BIA for males and females across all BMI subgroups in our hospitalised COVID-19 population. Consequently, discrepancies when assessing the adequacy of protein provision in ICU patients were found. We strongly advise using baseline LBM_{BIA} to guide protein dosing if possible. In the absence of BIA, using a method that overestimates LBM in all categories may be the only way to minimise underdosing of nutritional protein.

Trial registration: The protocol of the BIAC-19 study, of which this is a post-hoc sub-analysis, is registered in the Netherlands Trial Register (number NL8562).

Abbreviations: ABW, adjusted body weight; 95% BCa CI, 95% bias-corrected accelerated bootstrapped confidence interval; BIA, bioelectric impedance analysis; BMI, body mass index; COVID-19, coronavirus disease 2019; DXA, dual-energy X-ray absorptiometry; ESPEN, European Society for Clinical Nutrition and Metabolism; ICU, intensive care unit; IQR, interquartile range; LBM, lean body mass; LL, lower limit of agreement; LOS, length of stay; TBW, total body weight (measured); UL, upper limit of agreement.

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https://doi.org/10.1016/j.clnesp.2022.03.001

1. Background

Obesity is a significant independent risk factor for hospitalisation in Coronavirus Disease 2019 (COVID-19) patients [1,2]. A large proportion of hospitalised COVID-19 patients, and by extend, ICU patients, are thus overweight. The prevalence of sarcopenic obesity has increased infection rates and morbidity related to COVID-19 [3]. A positive correlation between high nutritional risk and adverse clinical outcomes of COVID-19 has been observed [4].

It is suggested that a high protein diet is beneficial during COVID-19 [3], as protein provision may prevent further breakdown of muscle protein for the purpose of gluconeogenesis, and thereby prevent the patient from going into a further catabolic state. Nutrition guidelines advise increasing the protein quantity that is provided as the illness becomes more severe, but vary between prescribing 1.2–2.5 g/kg of protein a day in the intensive care unit (ICU) [5–7]. One study showed that although targets of >1.2 g/kg/day of protein were hard to achieve in COVID-19 ICU patients, a supply of at least 0.8 g/ideal body weight (IBW)/day was already related to lower mortality rates [8].

However, setting protein targets is challenging when patients are not at IBW. Because the overweight (Body mass index (BMI) $\geq$ 25 kg/m^2), or obese body (BMI$\geq$ 30 kg/m^2) usually contains less protein per kilogram of body weight, the use of total body weight (TBW) likely results in an overestimation of protein needs in overweight and obese persons. Currently, numerous mathematical formulas try to account for variations in body composition (such as between biological sexes) by estimating fat-free or lean body mass (LBM), which is assumed to be the true determinant of protein requirement [9]. It is still unclear which method is superior, which is reflected by discrepancies, or vagueness in recommendations between, and sometimes within, nutritional guidelines, that either suggest multiple methods, or fail to state whether TBM, LBM, or IBW should be used [7,9–11]. Slight variations in the definitions of fat-free mass (FFM) and LBM between sources further confuse the discussion.

Bioelectric impedance analysis (BIA) is a technique that calculates the volume of body water compartments through the use of measured electric reactance and resistance. The incorporated software then derives LBM through validated regression analyses based on a healthy reference population. BIA derived LBM (LBM_{BIA}) for calculating protein needs has substantial theoretical advantages over mathematical methods regarding body composition [12]. In addition, BIA measurements can be performed at the bedside, in contrast to other direct methods such as dual-energy X-ray absorptiometry. However, BIA is not ubiquitously available and can pose challenges related to disinfection when used on a high volume of patients with a transmittable disease such as COVID-19. Therefore, it is worth exploring the agreement between BIA and commonly used mathematical formulas.

We previously conducted a prospective observational study in which all hospitalised patients for COVID-19 underwent BIA measurements within 24 h of hospital admission [13]. The current post-hoc study compares the agreement between LBM_{BIA} and five mathematical methods in estimating LBM in this COVID-19 population. In addition, we retrospectively compare protein provision adequacy in our COVID-19 ICU population based on $LBM_{BIA,}$ to that based on LBM predicted by other methods.

2. Methods

For this post-hoc sub-study, baseline data previously collected for the prospective BIAC-19 study were used. The Bioelectric impedance body composition and phase angle concerning 90-day adverse outcome in hospitalised COVID-19 ward and ICU patients: the prospective BIAC-19 study aimed to associate baseline (<24 h of hospital admission) BIA body composition parameters with 90-day adverse outcome of COVID-19 [13]. The BIAC-19 study protocol has been registered in the Netherlands Trial Register (number NL8562).

2.1. Study setting

The study was performed between April 10th and 17th, 2020, and again between October 10th 2020 and February 11th 2021, at Gelderse Vallei Hospital, a teaching hospital in Ede, The Netherlands. The hospital has two ICU units, with a combined capacity of 18 beds. Thirty-eight general ward COVID-19 beds were available during the study period.

2.1.1. Protein provision ward

Protein targets in the wards are set according to actual (BMI 20–30 kg/m^2) or corrected body weight (BMI <20 kg/m^2 adjusted to 20 kg/m^2; BMI >30 kg/m^2 adjusted to 27 kg/m^2). In addition, the Gallagher method is described in the local protocol. Gallagher et al. developed an equation to calculate percentage body fat through sex, age, BMI, ethnicity and regression models based on the measured (by 4-compartment model (4C) or dual-energy X-ray absorptiometry (DXA)) body fat of 1626 healthy adults with a BMI $\leq$35 kg/m^2 [14]. The Dutch dietary guidelines use a transformation of the original Gallagher formula, to approximate LBM at which protein provision is targeted [15]. This method is currently not routinely used in our hospital but is mentioned in the protocols as a potentially superior method [9,16].

2.1.2. Protein provision ICU

Protein targets in the ICU are calculated by our computerized nutrition protocol, and are set according to actual (BMI <27 kg/m^2), corrected (BMI 27–30 kg/m^2; regression to BMI of 27 kg/m^2), or ideal body weight (BMI >30 kg/m^2; regression to BMI 21 kg/m^2 in women and BMI 22.5 kg/m^2 in men), and amount to 1.5 g/kg/day in BMI <30 kg/m^2, 2.0 g/kg/day in BMI 30–40 kg/m^2 or 2.5 g/kg/day in BMI $\geq$40 kg/m^2. A progressive feeding strategy towards 100% of targets at admission day four is used [10]. Actual (par)enteral nutritional and non-nutritional energy and protein provision is automatically calculated hourly. Oral nutrition is currently not incorporated, as it cannot be done automatically and oral nutrition is not usually a substantial contribution to the total nutritional intake in ICU patients.

2.2. Study participants

The BIAC-19 study included patients aged 18 years or above admitted to the hospital with COVID-19 symptoms and proved SARS-CoV-2 positive through polymerase chain reaction-test in whom BIA measurements were performed within 24 hours after hospital admission. Exclusion criteria were pregnancy, electrical implants, wounds or skin damage at the designated electrode sites, or inability to maintain posture for 5 minutes.

Patient subgroups for the current study were defined by biological sex (female/male) and BMI category. Normal weight was defined as a BMI <25 kg/m^2, overweight as BMI 25–30 kg/m^2 and obese as BMI>30 kg/m^2.

For the secondary research question addressing protein provision adequacy in the ICU, patients who were admitted to the ICU after transfer to another hospital were excluded, as no ICU nutrition records were available in those cases. In addition, patients who only received oral nutrition were excluded, as protein contents of oral nutrition are not registered.

2.3. BIA measurements

Trained researchers conducted BIA measurements with the InBody S10® (InBody Co., Ltd., Seoul, Korea). This multi-frequency, segmental impedance analyser requires height, weight, and sex as input parameters. Height and weight as measured upon hospital admission were used. When circumstances did not allow measurements, height as provided by the patient or their representative was entered. BIA measurements were performed in a supine position with reusable electrodes attached to the left and right thumb and middle finger, and both ankles.

2.3.1. Definition of lean body mass

Inbody regards FFM and LBM as synonyms, defined as TBW minus non-essential storage fat mass (FM), corrected for hydration status through extracellular/total body water ratio [12]. In this definition, FFM/LBM includes essential fats, such as those stored in organs, the central nervous system and bone marrow. In other sources TBW minus FM is usually regarded as the LBM, whereas FFM is defined as LBM minus essential body fat. To avoid confusion, we choose to use only the term LBM for TBW minus FM.

2.4. Data collection

Demographic and clinical data previously collected for the BIAC-19 study from local electronic medical record systems MetaVision® (iMDsoft, Tel Aviv, Israel) and NeoZIS® (MI Consultancy, Katwijk, The Netherlands) and NeoZIS® (MI Consultancy, Katwijk, The Netherlands) were reused for the current study, i.e., age, sex, ethnicity, height, weight, and protein provision, specifics of the length of stay (LOS) and ventilation in ICU patients.

2.5. Lean body mass methods

In addition to measured TBW (kg), four equations for LBM were chosen for comparisons with LBM_{BIA} (kg). The methods aim to approximate IBW [1], adjusted body weight (2/3) or LBM [4], which in all methods is regarded as a proxy for the true determinant of protein requirement: LBM [9]. To improve readability, 'LBM' is the term that is used in all equations from hereon.

(1) Adjustment towards a BMI of 22.5, commonly regarded as IBW;
   - $LBM_{22.5}$ (kg) = 22.5 * height^2
(2) Adjustment towards a BMI of 27.5 in case of obesity (Dutch perioperative guidelines) [17];
   - $LBM_{27.5}$ (kg) = 27.5 * height^2 *if* BMI>30 kg/m^2
(3) Calculation of LBM as stipulated by the ESPEN guidelines on ICU nutrition [10];
   - LBM_{ESPEN} (kg), with
     Male IBW_{ESPEN} (kg) = 0.9 × height^2 − 100
     Female IBW_{ESPEN} (kg) = 0.9 × height^2 - 106
(4) The adjusted Gallagher formula for non-Asians [14];
   - $LBM_{Gallagher}$ (kg), with
     Male $LBM_{Gallagher}$ = (0.466 × weight) − (0.00087 × weight x age) + (9.438 × height^2)
     Female $LBM_{Gallagher}$ (kg) = (0.24 × weight) − (0.00053 × weight x age) + (10.978 × height^2)

2.6. Statistical analysis

Descriptive statistics were calculated for demographics and protein provision in ICU patients. The quantile−quantile plots were visually assessed for the normality of the distribution of continuous data. Continuous values are reported as mean (95% bias-corrected accelerated bootstrap confidence intervals (95%-BCa CI) based on 1000 samples) or median (interquartile range), discrete data are presented as numbers (%). Biological males were compared to female patients. Differences were assessed using independent samples t-tests for continuous data or chi-squared tests for categorical data. When test assumptions were not met, Mann−Whitney U tests or Fisher's exact tests were used.

2.6.1. Agreements between lean body mass methods

We visually checked that the scatter plots showed a monotonic relation between LBM_{BIA} and each method, for all subgroups. Subsequently, a correlation analysis was conducted using Spearman's rank correlation coefficient, as the distribution of the variables was not normal. For this and all subsequent agreement analyses, the normal weight and overweight groups were disregarded when considering the $LBM_{27.5}$ method, as it uses TBW in BMI <30 kg/m^2. As Spearman's correlation only reveals the strength and mean direction of the association but does not reveal information on the presence of a systematic bias, we continued to construct error−standard plots. In this method, the difference or error between two measurements is plotted against the reference or standard method, in this case, BIA-LBM. This method was chosen over the Bland−Altman plot, where the difference is plotted against the mean of the two methods, as this can lead to underestimation of proportional bias, and in this case, the BIA-LBM method was considered the reference/standard method (Concept illustrated in Additional File 1). The 95-% Limits of agreements (average difference ± 1.96 standard deviations) with their 95% confidence intervals were calculated and plotted for each comparison. A significant result on a one-sample t-test comparing the mean of the differences to 0 was used to confirm fixed bias whenever visual inspection of the plots was suggestive of one (males and females separately). Where relevant, a sensitivity analysis of the t-test excluding visual outliers was conducted. The presence of proportional bias (i.e. a relationship between the size of the error and size of the reference value) was assessed visually and formally by regressing the difference on the reference value (i.e. LBM_{BIA}) (males and females separately). The assumption for homogeneity of variance for linear regression was confirmed by non-significance of a Levene's test. Proportional bias was considered proven when a relationship was identified (i.e., a significant slope of the regression line).

2.6.2. Protein provision ICU

Protein targets were calculated as 1.3 g/day/LBM and incorporated progressive feeding during the first three days of ICU admission (i.e (1.3 * LBM * duration of admission − first three calendar days) + (0.25 (1.3/24 * duration of the first admission day in hours * LBM) + (0.5 (1.3 * LBM)) + (0.75 (1.3 * LBM)) (note: 1.3 g/kg was chosen as a working example and is not a recommendation. We comment on varying amounts per kilogram between methods in the Discussion section). A Wilcoxon signed-rank test was used to calculate the median difference between the percentages of protein provided to the ICU patients according to target between $Target_{BIA}$ and the other methods. A logarithmic transformation was used to meet the assumption for symmetrical distribution of the differences.

IBM SPSS statistics 27 (I.B.M. Corp, Armonk, NY, USA) was used for all analyses. Only two-sided analyses were used. P-values ≤0.05 were considered statistically significant. P-values are reported to a single significant figure unless 0.2 ≥ P ≥ 0.01, in which case two significant figures are shown.

3. Results

One-hundred-and-fifty patients were included in the BIAC-19 prospective study and subsequent post-hoc analyses. All the

included patients were of white of Western-European descent. Table 1 summarises baseline characteristics and measurements and compares those of biological males and females.

3.1. Agreements between lean body mass methods

All mathematical methods for calculating LBM correlated significantly with LBM_{BIA} at the level of p-value <0.001 (Additional File 2, Table 1). $LBM_{Gallagher}$ showed the highest correlation coefficient for all subgroups except overweight females, where $LBM_{27.5}$ reached the same coefficient as $LBM_{Gallagher}$.

Fig 1 and 2 show the error–standard plots for all methods compared to LBM_{BIA} Visual inspection of the plots suggested a fixed bias for all methods when regarding males and females separately. A one-sample t-test confirmed that the mean value of the difference differed significantly from 0 in all methods, except for the LBM_{ESPEN} for males (−1.7 (95%-BCa CI -3.7; 0.3, p = .096) (Additional File 2, Table 2). The visual outlier on all plots except LBM_{TBW} discerned herself from the cohort with an LBM% of 80% compared to a mean of 62% (95%-BCa CI 59.5–64.9) for females. A sensitivity analysis excluding this outlier did not change the significance of these findings.

Proportional bias was suspected from visual inspection of all plots except for TBW and confirmed by regressing the difference between the methods and LBM_{BIA}, separately for males and females. A relationship between the error size and the reference value size was confirmed in all methods except TBW (males p = .8; females p = .087) (Additional File 2, Table 3).

3.2. Protein provision ICU

Forty-one (27%) patients eventually had to be admitted to the ICU. Two ICU patients (5%) were admitted to the ICU after transfer from another hospital, and eleven (27%) only received oral nutrition, which meant that no ICU nutrition records were available in those cases. Consequently, 28 (68%) of the ICU patients could be included in the protein provision ICU sub-analyses (Table 2). ICU patients had a median ICU-LOS of 16 days (IQR 17), during which 21 (75%) patients were ventilated for 14 days (IQR 40), of whom 13 (46%) were in the prone position, for four days (IQR 8).

Patients received 51.19 g (95%-BCa CI 37.1; 64.1) of protein daily during their ICU stay (38.7% (95%-BCa CI 28.5; 48.1) of the target as set by the local protocol. When the protein target was calculated by LBM_{BIA} (including a three-day progression strategy), ICU patients received a mean of 61.6% (95%-BCa CI 43.2; 80.8) of $Target_{BIA}$ during ICU admission. Comparisons with the percentage of target delivered as calculated by the other methods are shown in Table 3. The percentage of protein received of the target as calculated by the $LBM_{Gallagher}$ for males was the only one that did not significantly differ from the percentage received of $Target_{BIA}$ (mean difference 1.4% (95%-BCa CI -1.3; 4.6) p = 1.0).

4. Discussion

We aimed to assess which method approximates lean body mass best compared with bioelectric impedance in the hospitalised COVID-19 population. Total body weight and four other common methods were used; regression to a BMI of 22.5 kg/m^2, regression to BMI 27.5 kg/m^2 when BMI>30 kg/m^2, and the equations described by Gallagher and the ESPEN ICU guideline [10,14]. Although all methods were correlated with the reference method LBM_{BIA}, we could not identify a mathematical method for calculating LBM that had an acceptable agreement with LBM_{BIA} for males and females across the BMI subgroups.

Although the $LBM_{Gallagher}$ had the smallest overall 95%-CI, this still meant over-and underestimation of the LBM of 16.4 kg. Furthermore, all methods were subject to fixed bias (mean difference deviates from 0) when assessing males and females separately, except the LBM_{ESPEN} for males. All methods except TBW also had proportional bias (association between the difference between measurements and the size of the value measured). The confidence intervals were wide for all methods studied, and visual inspection of the plots suggested that the regression slopes for proportional bias were different per sex/BMI subgroup. We are confident that there is no easy workaround to correct both fixed and proportional bias and make one of the methods agree on an acceptable level with LBM_{BIA} across the whole cohort.

4.1. Breaking down the bias

The overestimation of LBM based on TBW (Figs. 1 and 2 panels D) could be expected, as the fat% is never zero, especially in the current population. Our results show that the size of the overestimation varied widely, although it understandably increased with BMI. The same can be said for $LBM_{27.5}$, as this method essentially presumes a weight equivalent of BMI 27.5 kg/m^2 to be the LBM. For example, a person of 170 cm in height with a BMI of 31 kg/m^2, is presumed to have a LBM of (27.5 * 1.7^2 =) 79.5 kg on a weight of 89,6 kg, giving him a LBM% of (78.5/89.6 * 100 =) 89%. In reality, excluding the very athletic, most of our patients with a BMI of 31 kg/m^2 will not have a fat% of (100–89 =) 11%. Thus, the $LBM_{27.5}$ method becomes more realistic as actual BMI increases (up to a certain point), explaining the proportional bias that can be seen in Fig. 1 panel C. Indeed a previous study compared protein targets considering LBM_{BIA}, TBW and adjusted body weight (ABW) (BMI <20 kg/m^2 adjusted to BMI = 20 kg/m^2 and BMI> 27.5 kg/m^2

Table 1
Patient characteristics upon hospital admission[a].

	All Patients (N = 150)	Males (n = 100)	Females (n = 50)	P-value
Age, years	68 (66–70)	68 (66–71)	66 (62–71)	0.500
Physical characteristics				
Height, cm	174 (173–176)	178 (177–180)	167 (165–168)	**0.001**
Weight (TBW), kg	88 (85–91)	91 (87–94)	84 (79–89)	**0.031**
Body Mass Index, kg/m^2	29 (28–30)	28 (28–30)	30 (28–32)	0.110
Normal weight (BMI <24.9)	33 (22%)	21 (21%)	12 (24%)	0.400
Overweight (BMI 25–29.9)	65 (43%)	51 (51%)	14 (28%)	0.090
Obese (BMI ≥30)	52 (35%)	28 (28%)	24 (48%)	**0.019**
LBM_{BIA}, kg	58.5 (56.3–60.7)	62.1 (59.9–64.2)	51.1 (48.3–54.1)	**0.001**
LBM_{BIA} percentage of TBW, %	66.9 (65.2–68.7)	69.3 (67.0–71.4)	62.0 (59.5–64.9)	**0.001**

[a] Data are presented as number (percentage, %) or mean (95% bias-corrected accelerated bootstrapped confidence interval).[b] Differences between males and females with a p-value <0.05 are regarded as statistically significantly different and are displayed in bold. Abbreviations: TBW, total body weight; BMI, body mass index; BIA, bioelectric impedance analysis; LBM_{BIA}, lean body mass as measured by BIA.

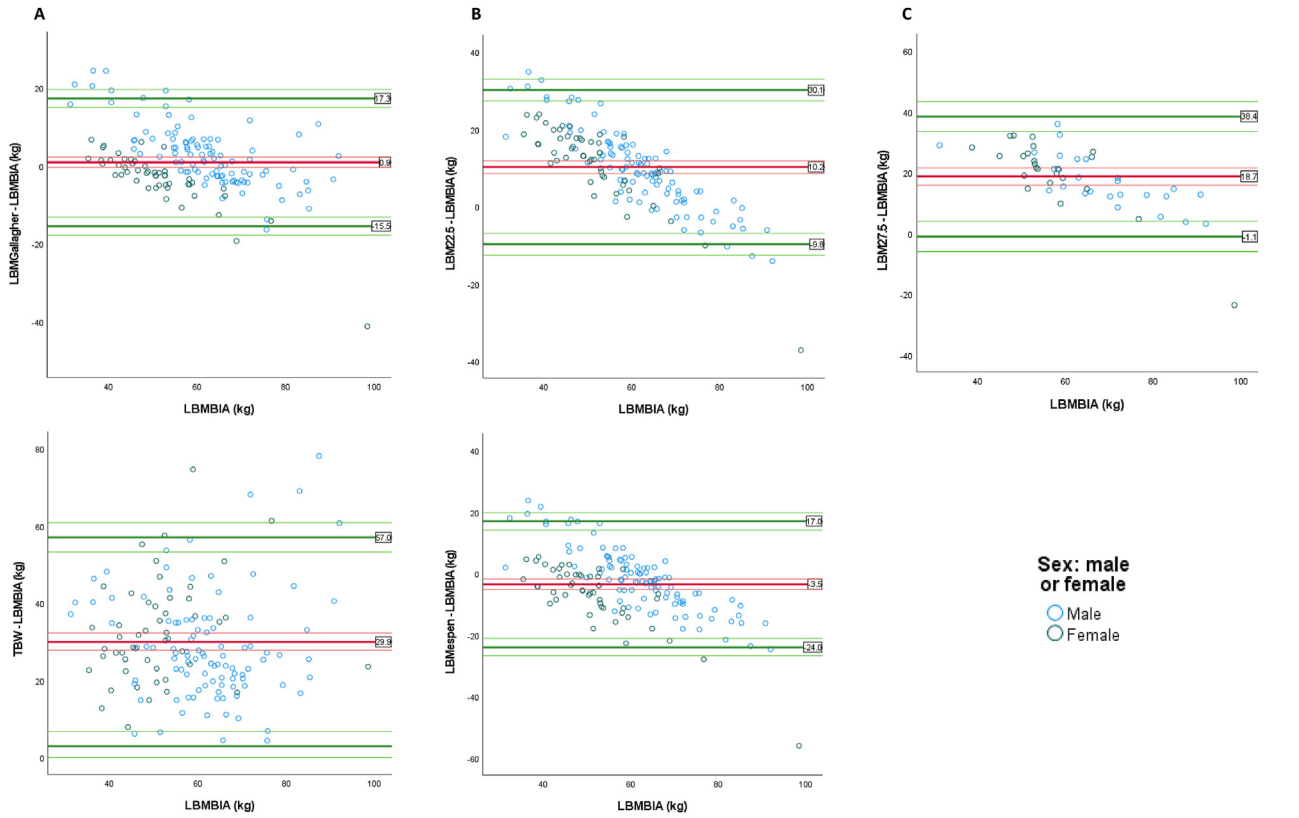

Fig. 1. Error–Standard plots comparing the difference (error) in kilograms between LBM_{BIA} and LBM as calculated by the four formulas and LBM_{TBW} (A. $LBM_{Gallagher}$; B. $LBM_{22.5}$; C. $LBM_{27.5}$ (patients with a BMI> 25 kg/m2); D. LBM_{TBW}; E. LBM_{ESPEN}) to LBM_{BIA} (standard) in kilograms, showing colour grouping for males and females, n = 150 (except LBM27.5 where n = 52).

adjusted to BMI = 27.5) in 115 hemodialysis patients and concluded that mean protein needs estimated by (adjusted) TBW were higher than those based on LBM_{BIA}, across all BMI categories ($P < .01$), and most explicitly in obese patients [18]. This overestimation occurred eventhough a correction factor in grams/kg was used (LBM_{BIA} * 1.5, whereas (adjusted) TBW * 1.2). A Dutch study comparing protein targets (1.2 g * LBM) set by LBM_{BIA}, ABW (BMI <20 kg/m^2 adjusted to BMI = 20 kg/m^2 and BMI> 30 kg/m^2 adjusted to BMI = 27.5) or TBW in 661 outpatients, showed that ABW estimated LBM_{BIA} correctly (<5% over- or underestimation) in only 33% of their obese patients, whilst LBM_{TBW} estimated between 1% (obese persons) and 33% (underweight persons) correctly [16]. These reports are in line with our findings that TBW and regression to a BMI of 27.5 severely overestimated LBM and thereby protein requirements.

The same explanation can be offered for the proportional bias seen in $LBM_{22.5}$. Similar to the $LBM_{27.5}$ method, this method led to more overestimation in females than males (Fig. 1 Panel B). Underestimation occurred in more males than females, which is likely the result of the difference in the relationship between TBW and LBM in males and females. Forbes described a semilogarithmic relation between LBM and TBW, with slightly different coefficients for men and women [19]. Indeed when we plot TBW and LBM in our cohort (excluding outliers of the mean±2SD), quadratic regression lines for men and women are different, and a common one for both does neither justice (Fig. 3). Thus, the same is likely the case for LBM equations.

The Gallagher formula and the ESPEN method were the only two LBM equations used that acknowledge the difference in body composition between males and females. Although ESPEN offers no reference for their method, the Gallagher formula uses regression models based on DXA studies [14]. As BIA is also validated against DXA, a strong agreement was expected and found (Additional file 2, Table 1). In addition, $LBM_{Gallagher}$ had the smallest overall 95%-CI. Nevertheless, LBM was often underestimated in women. The previously mentioned Dutch study by Velzeboer et al. [16] found that although $LBM_{Gallagher}$ was an improvement over LBM_{TBW} and $LBM_{27.5}$, protein targets set by $LBM_{Gallagher}$ * 1.5 g agreed (<5% over- or underestimation) with LBMBIA * 1.2 g in only 9% (underweight persons) to 54% (obese persons) of the cases. A possible explanation could be differences in body composition between Gallagher's cohort of (white) British and Northern American volunteers and the Dutch cohorts. Indeed white women had a BMI of 24.5 ± 4.5 kg/m^2 in the Gallagher cohort, compared to a mean BMI of 30 (95%-BCa CI 28–32) kg/m^2 in ours. The LBM_{ESPEN} method was not subject to fixed bias in males, although gross over- and underestimation were still common and only appeared to cancel each other out around a mean of 0 (Figs. 1 and 2).

Notably, for the female outlier with an LBM% of 80%, underestimation of LBM occurred in all methods except LBM_{TBW}, alluding to the fact that the studied equations may be even less appropriate for non-sarcopenic obese persons.

4.2. Protein provision ICU

As a real-world exploration of the subject, a secondary aim of this study was to retrospectively compare actual protein provision adequacy in our COVID-19 ICU population based on LBM_{BIA} to that based on LBM predicted by other methods. There, we found that ICU patients received a mean of 38.7% protein of the local target, or 61.6% (95%-BCa CI 43.2; 80.8) of $Target_{BIA}$ during ICU admission. This discrepancy shows that our local targets overestimated protein requirements by a third. However, proteins were generally underdelivered by either target. Our findings align with findings

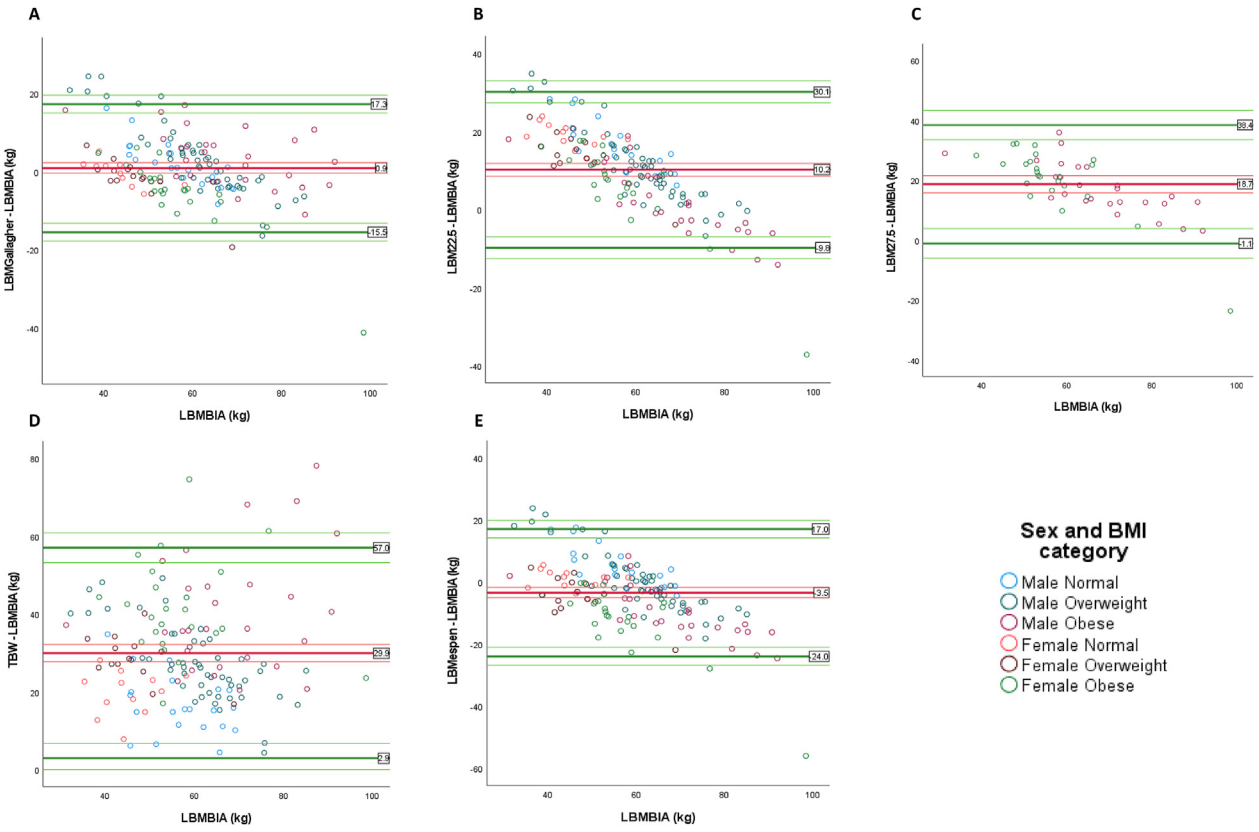

Fig. 2. Error–Standard plots comparing the difference (error) in kilograms between LBM_{BIA} and LBM as calculated by the four formulas and LBM_{TBW} (A. $LBM_{Gallagher}$; B. $LBM_{22.5}$; C. $LBM_{27.5}$ (patients with a BMI> 25 kg/m2); D. LBM_{TBW}; E. LBM_{ESPEN}) to LBM_{BIA} (standard) in kilograms, showing colour grouping for different sex and BMI subgroups, n = 150 (except LBM27.5 where n = 52).

Table 2
ICU Patient characteristics upon hospital admission[a].

	All ICU Patients (N = 28)	Males (n = 20)	Females (n = 8)	
Age, years	70 (67–73)	71 (67–73)	68 (62–74)	0.500
Physical characteristics				
Height, cm	173 (170–177)	177 (173–179)	165 (161–170)	**0.001**
Weight (TBW), kg	88 (84–93)	91 (86–95)	83 (73–92)	0.100
Body Mass Index, kg/m^2	29 (28–31)	29 (27–31)	30 (27–33)	0.600
Normal weight (BMI <24.9)	5 (18%)	3 (15%)	2 (25%)	0.600
Overweight (BMI 25–29.9)	11 (40%)	10 (50%)	1 (12.5%)	0.100
Obese (BMI ≥30)	12 (43%)	7 (35%)	5 (62.5%)	0.200
LBM_{BIA}, kg	60.8 (57.5–63.9)	64.4 (61.5–67.7)	52.0 (47.1–57.8)	**<0.001**
LBM_{BIA} percentage of TBW, %	69.3 (65.9–72.6)	71.8 (67.1–76.8)	63.1 (59.7–66.3)	**0.025**

[a] Data are presented as number (percentage, %) or mean (95% bias-corrected accelerated bootstrapped confidence interval).[b] Differences between males and females with a p-value <0.05 are regarded as statistically significantly different and are displayed in bold. Abbreviations: TBW, total body weight; BMI, body mass index; BIA, bioelectric impedance analysis; LBM_{BIA}, lean body mass as measured by BIA.

from other studies proving that adequate protein provision is difficult to achieve in the ICU population, including COVID-19 patients [8,20,21]. When comparing the percentage of target delivered as calculated by the other methods to $Target_{BIA}$, all methods except $Target_{Gallagher}$ for males differed significantly. Therefore, using targets set to LBM based on mathematical methods or TBW is likely to lead to significant over-or under-dosing of protein in all other groups. This is in line with findings in other patient categories [16,18].

4.3. Clinical implications

In practice, it has proven difficult to achieve even low-end protein targets in hospitalised COVID-19 patients [8]. This is an urgent issue, as there is reason to assume that a high protein diet is beneficial during COVID-19 [3,4]. Therefore, we strongly recommend measuring LBM_{BIA} upon hospital admission (as quickly as possible, to prevent bias through hydration shifts) to guide protein provision.

However, if admission LMB_{BIA} measurements are not feasible, we argue that it is probably safer to accept a certain degree of overestmation rather than underestimation of LBM by formulas, as protein overdoses based on any target have proven less likely to happen than underdosing. Consequently, our results may argue a preference towards the use of $Target_{22.5}$, as it had the lowest overestimation with its entire confidence interval above 0 for both sexes in the ICU cohort (Table 3). Nevertheless, regarding the entire cohort (Fig. 1), the use of $LBM_{22.5}$ still led to underestimating LBM in

Table 3
Comparing the percentage of protein received between the different targeting methods and the $Target_{BIA}$ (n = 28).

Method	Males (n = 20)[a]							Females (n = 8)[a]						
	Percentage of target received			Compared to percentage of $Target_{BIA}$ 61% (95%-BCa CI 39–85)				Percentage of target received			Compared to percentage of $Target_{BIA}$ 61% (95%-BCa CI 24–100)			
	Mean	95%-BCa CI		Mean difference	95%-BCa CI		P-value[b]	Mean	95%-BCa CI		Mean difference	95%-BCa CI		P-value[b]
		UL	LL		UL	LL			UL	UL		UL	LL	
$Target_{TBW}$	43	27	59	18.7	11.9	26.0	**<0.001**	39	15	65	21.9	7.1	36.3	**0.012**
$Target_{Gallagher}$	61	38	83	1.4	−1.3	4.6	1.000	67	26	110	−6.5	−14.3	−0.8	**0.012**
$Target_{22.5}$	56	35	77	6.3	3.6	9.0	**0.001**	51	20	81	10.3	1.5	21.1	**0.012**
Target $_{27.5}$ (n = 7/5)	56.4	20.4	86.4	19.5	7.7	31.2	**0.018**	31.5	2.9	65.2	9.3	1.1	17.8	**0.043**
$Target_{ESPEN}$	67	42	93	−5.0	−8.9	−1.9	**0.001**	75	29	122	−14.0	−26.2	−2.6	**0.012**

[a] Unless stated otherwise.[b] Differences with p-values <0.05 are regarded as statistically significantly different and are displayed in bold. Abbreviations: BIA, bioelectric impedance analysis; 95%-BCa CI, 95% bias-corrected accelerated bootstrapped confidence interval; UL; upper limit of agreement; LL lower limit of agreement; TBW, total body weight; ESPEN, European Society for Clinical Nutrition and Metabolism.

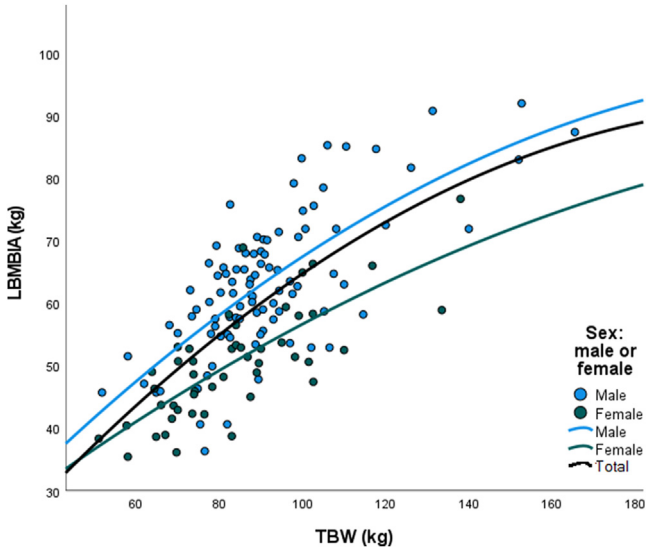

Fig. 3. Scatterplot of the relationship between LBM_{BIA} and TBW with fitted quadratic regression lines for men, women and the total cohort, excluding outliers (LBM% men max. 69.3 ± 2 *11.4 kg, LBM% women max. 62.0 ± 2 * 9.2 kg), n = 142.

quite a few cases, mostly overweight and obese males. On the other hand, $target_{27.5}$ and $Target_{TBW}$ have a confidence interval above 0 for both sexes on the LBM plots of the entire cohort (Fig. 1) and regarding targets in the ICU (Table 3). However, this would mean excepting a mean overestimation of LBM of 23.4 kg or 29.9 kg (Fig. 1), respectively. It is up to the dietician and clinical to decide whether this is acceptable for their patient.

Although a practical exploration of the subject goes beyond the scope of the current paper, future research could explore the possibility of stratifying methods for estimating LBM according to which works best for which sex/BMI group, if not devising a new universal method based on LBM_{BIA}. Alternatively, the difference between LBM and TBW is sometimes acknowledged through a correction of the amount of protein per kilogram of either (i.e. 1.9 g/kg LBM or 1.5 g/kg TBW) [15,16]. However, this correction is based on the assumption of a fixed LBM/TBW ratio, which is an oversimplification that leads to a large error in many individuals (Fig. 1). Based on our findings we think it is highly unlikely that a static correction such as the one in the example will improve accuracy of protein targets, and we do not recommend its use without further scientific exploration of the subject.

4.4. Limitations

This research is subject to several limitations. No sample size calculation was performed as the data were dependent on the sample size of the mother study, and not all ICU patients could be included in the protein adequacy analyses. The subsequent relatively small cohort size prevented subdividing into BMI categories for these analyses. Segmenting data could be a point of attention for future studies focusing more specifically on protein provision in the ICU.

The formulas used by the Inbody S10 software to calculate the derived BIA parameters (such as LBM) are not publicly available and therefore cannot be provided here. However, Inbody S10 (LBM) calculations are based on regression formulas derived from reference groups, and have independently been validated against other methods such as Dual-Energy X-ray Absorptiometry in peer-reviewed studies in various populations [22–24]. Nevertheless, caution is warranted when applying the results of this study in other populations or BIA devices.

We did not regard underweight persons as a separate category for this study. When regarding BMI 18.5 kg/m^2 as the lower limit of normal weight, the current cohort included three underweight persons (two males with BMI 16 kg/m^2 and 17.3 kg/m^2, one female with BMI 18 kg/m^2), who were grouped in with 30 others in the normal weight category. None of these patients was in the ICU cohort. We do not expect this to have impacted the main findings of this study.

Although we incorporated progressive feeding during the first three days of ICU admission into our targets, accounting for a possibly incomplete first day of admission, we did not account for a possibly incomplete last day. This may lead to an overestimation of the target in the case of ICU discharge early in the day, thereby underestimating the percentage of target provided. As the median ICU-LOS was 16 days, we do regard this possible overestimation as significant. In addition, this bias would be in all methods, therefore not affecting comparisons between methods (and thereby the aim of this study). This study was performed in white, Dutch COVID-19 patients, and results should be interpreted with caution before its results have been confirmed in other populations.

5. Conclusion

We could not identify a mathematical method for calculating lean body mass that had an acceptable agreement with LBM as derived from bioelectric impedance analysis for males and females across all BMI subgroups in our hospitalised COVID-19 population. Consequently, discrepancies were observed when assessing the adequacy of protein provision in ICU patients, who on average only

received two-thirds of their protein target as set by BIA. We strongly advise using baseline LBM_{BIA} to guide protein dosing if possible. In the absence of BIA and awaiting a universally applicable method, using a method that overestimates LBM in all categories may be the only way to minimise underdosing of nutritional protein. We emphasise the importance of more research and discussion on this topic.

Funding

This research was funded by the Research Foundation of the Intensive Care of Gelderse Vallei Hospital, Ede, The Netherlands.

Author contributions

HM contributed to the conception, data collection, data analysis and interpretation, and writing and revising of the manuscript. AH performed BIA measurements and contributed to data collection, writing a preliminary version of the manuscript and revising the final manuscript. IJ contributed to the conception, data interpretation and revision of the manuscript. AvZ contributed to the conception, data interpretation and revision of the manuscript.

Ethics

This study was performed in line with the principles of the Declaration of Helsinki. The study was approved by the Ethics Committee of the Gelderse Vallei Hospital (no. 2008–063). Written informed consent was obtained from all patients or their legal representatives in the context of the mother study (NTR NL8562).

Consent for publication

Not applicable.

Availability of data and materials

The dataset supporting the conclusions of this article is available upon reasonable request from the corresponding author.

Declaration of competing interest

Prof. Dr Van Zanten reported receiving honoraria for advisory board meetings, lectures, research, and travel expenses from AOP Pharma, Baxter, Cardinal Health, Danone-Nutricia, DIM3, Fresenius Kabi, GE Healthcare, Mermaid, Rousselot, and Lyric. The other authors have nothing to declare.

Acknowledgements

We thank dr. MJ Caldas Paulo of the Wageningen University & Research for her advice regarding the statistical methodology of this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2022.03.001.

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