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Quantifying appendicular muscle mass in geriatric inpatients: Performance of different single frequency BIA equations in comparison to dual X-ray absorptiometry

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ABSTRACT

Background: Quantification of skeletal muscle mass is mandatory for diagnosing sarcopenia, a highly prevalent geriatric syndrome. While dual energy X-ray absorptiometry (DXA) is the reference method in a clinical context, bioimpedance analysis (BIA) is more readily applicable on a broad scale. Recently BIA equations for the prediction of appendicular skeletal muscle mass in higher age groups have been published, but data on their performance in geriatric inpatients are lacking.
Methods: In 144 geriatric inpatients (86 women and 58 men, mean age 80.7 ± 5.6 years) appendicular skeletal muscle mass was predicted by 4 different BIA equations and measured by DXA. Results were compared by linear regression analysis and Bland Altmann plots. The agreement with DXA in classifying subjects to have normal or reduced muscle mass was calculated for the BIA based approaches.
Results: The 4 BIA equations showed only minor differences in regression analysis, but major differences in mean error (range −0.98 kg to + 0.19 kg in women and −2.47 kg to −0.58 kg in men). Considering regression parameters and mean error, the equation of Scafoglieri et al. performed best, resulting in an agreement with DXA of more than 83%. Sensitivity to detect subjects with reduced muscle mass was < 70% in the whole group for all BIA equations.
Conclusion: The BIA equation of Scafoglieri et al. performs best in geriatric inpatients, with more than 83% of subjects classified correctly as having normal or reduced muscle mass compared to DXA. Low sensitivity to detect subjects with reduced muscle mass in geriatric inpatients remains a limitation of BIA.

1. Introduction

Quantification of skeletal muscle mass emerges as an increasingly important issue in geriatric medicine due to the upcoming clinical importance of sarcopenia, a highly prevalent, potentially treatable geriatric syndrome associated with negative health outcomes including falls, disability and death (Beaudart, Zaaria, Pasleau, Reginster, & Bruyere, 2017; Cruz-Jentoft et al., 2014). Sarcopenia has recently been ascribed an ICD code and there is consent about the necessity to implement sarcopenia concepts in clinical routine, but the optimal diagnostic algorithm is a matter of debate (Vellas et al., 2018). Broad agreement, however, exists that the diagnosis of sarcopenia requires both, reduced muscle function and reduced muscle mass (Cruz-Jentoft et al., 2010; Fielding, Vellas, & Evans, 2011). Dual-energy X-ray absorptiometry (DXA) is regarded as the reference method in clinical routine for quantification of muscle mass (Buckinx et al., 2018). By DXA

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the lean mass of all four extremities is measured and its sum is approximatively referred to as appendicular skeletal muscle mass (ASMM). Although regarded as reference method, the use of DXA is limited in clinical routine by its availability, limited portability, the need for specialized staff and high costs. As an alternative, bioimpedance analysis (BIA) holds a lot of promise from a practical point of view. BIA is easy to use, low-cost, portable, and well tolerated predisposing it for large-scale use. BIA equations were initially generated to predict total skeletal muscle mass (TSMM), preventing direct comparison with DXA measured (appendicular) muscle mass (Janssen, Heymsfield, Baumgartner, & Ross, 2000). Consecutively cut offs for reduced muscle mass could only be used in a method-specific way. Hereinafter equations for measurement of ASMM have been developed and meanwhile ASMM based BIA cut offs for reduced muscle mass in Caucasian subjects have been published (Kim et al., 2014; Kyle, Genton, Hans, & Pichard, 2003; Rangel Peniche, Giorguli, & Alema´n-Mateo, 2015; Scafoglieri et al., 2017; Sergi et al., 2015; Yoshida et al., 2014). Interestingly, in recent studies in Germany ASMM based BIA cut offs have been shown to be close to the most widely used DXA based cut offs of Baumgartner et al. pointing towards a better, direct comparability of the two techniques, at least in similar populations (Baumgartner et al., 1998; Kemmler, Stengel, Engelke, Sieber, & Freiberger, 2016; Kemmler et al., 2017). Since BIA is based on a spatial frame model of the human body and body morphology is subject to major changes within the aging process, several single frequency BIA (sfBIA) equations have been generated specifically for the prediction of ASMM in higher age groups (Rangel Peniche et al., 2015; Scafoglieri et al., 2017; Sergi et al., 2015). In these studies, however, mainly healthy subjects were included, while in clinical practice the age-dependent increase of sarcopenia parallels the rising prevalence of multimorbidity, thereby questioning the usefulness of sfBIA in geriatric inpatients (Barnett et al., 2012; Shaw, Dennison, & Cooper, 2017). On this background and in light of the scarce sfBIA data for prediction of ASMM in geriatric patients the aim of this study was first to compare the published sfBIA equations in predicting ASMM in geriatric inpatients and thereafter to evaluate their accuracy in classifying patients as having normal or reduced ASMM compared to DXA as part of the diagnostic algorithm for sarcopenia in clinical routine.

2. Methods

2.1. Study population

In 2013 and from 2015 to 2017 we recruited 144 geriatric inpatients at the department of geriatric medicine, Paracelsus Medical University Salzburg. Recruitment was done by staff physicians in the context of their daily work. Apart from being admitted to a geriatric ward, subjects had to be able to walk a few meters and to lie still for five minutes. The lower age limit was 70 years. Exclusion criteria were critical or terminal illness, advanced dementia or delirium, indwelling electrical devices such as pacemakers and complete or partial amputation of one or more limbs. Morbidity of subjects was determined by reviewing diagnoses of medical records and, in case of diabetes and chronic kidney disease, by reviewing available laboratory values. All patients gave written informed consent. The study was approved by the local ethics committee of the state of Salzburg and performed in accordance with the Declaration of Helsinki.

2.2. Assessment of muscle function

Gait speed was measured over a distance of 5 m. Hand grip strength was determined by using a dynamometer (JAMAR hydraulic hand dynamometer). In total 6 measurements were performed alternating left and right side and the maximum value selected. For sarcopenia according to the EWGSOP consensus low gait speed was defined by $\leq 0{,}8$ m/s and low hand-grip strength was defined by < 30 kg for men and < 20 kg for women (Cruz-Jentoft et al., 2010).

2.3. Measurement of muscle mass by DXA

The Hologic Discovery A (Hologic Inc., Marlborough, Mass.) was used for all DXA scans. The scan measurements and analyses were conducted following standard procedures. Participants were measured wearing only gowns to eliminate possible artifacts due to clothing and fasteners. Whole body scans were manually analyzed for the manufacturer defined regions of interest (ROI) following the standard analysis protocol in the Hologic User Manual. Customized ROI were also analyzed using the Hologic whole body and subregion analysis modes (software ver. 13.3.01). Appendicular skeletal muscle mass (ASMM) was directly derived from the appendicular soft lean tissue compartment in the DXA studies and denoted $ASMM_{DXA}$.

2.4. Measurement of muscle mass by BIA

Single frequency tetra-polar BIA (AKERN BIA 101, Florence, Italy) was performed using an 800 mA (50 kHz) alternating current. Patients adopted a supine position with arms spread apart from the body and legs separated. Signal input and output electrodes were placed on the dorsum of the right hand and foot. Recording electrodes were placed at standard positions at wrist and ankle. Total body resistance (R) and reactance (Xc) were measured in ohms. Appendicular skeletal muscle mass ($ASMM_{BIA}$) was calculated using the following equations based on single frequency (50 Hz) BIA:

BIA_{Kyle} (Kyle et al., 2003):

$$ASMM_{Kyle}\,(kg) = -4.211 + (Ht^2/R^*\ 0.267) + (0.095^*\ BW) + (1.909^*\ sex) + (-0.012^*\ age) + (0.058^*Xc),$$

BIA_{Sergi} (Sergi et al., 2015):

$$ASMM_{Sergi}\,(kg) = -3.964 + (Ht^2/R^*\ 0.227) + (0.095^*\ BW) + (1.384^*\ sex) + (0.064^*\ Xc),$$

$BIA_{Scafoglieri}$ (Scafoglieri et al., 2017):

$$ASMM_{Scafoglieri}\,(kg) = 4.957 + (Ht^2/R^*\ 0.196) + (0.060^*\ BW) - (2.554^*\ sex),$$

$BIA_{Rangel\ P.}$ (Rangel Peniche et al., 2015):

$$ASMM_{Rangel\ P.}\,(kg) = -0.05376 + (Ht^2/R^*\ 0.2394) + (2.708^*\ sex) + (0.065^*BW),$$

where Ht is height in centimeters; BW is body weight in kg; age is in years; R is resistance and Xc is reactance derived from BIA; for sex men = 1 and women = 0 for $BIA_{Kyle,}$ BIA_{Sergi} and $BIA_{Rangel\ P}$. Of note: For $BIA_{Scafoglieri}$ men = 0 and women = 1.

For the generation of all 4 equations Hologic devices were used as DXA reference. Kyle et al. performed their study in Switzerland (Geneva). The study population consisted of healthy Caucasians 22–94 years old (48.4% older than 55 years) with a mean BMI of 24.1/25.3 kg/m^2 and mean DXA measured ASMM of 17.3/25.8 kg for women/men, respectively. The generated BIA equation was also validated in patients involved in pre-transplant evaluation or post-transplant follow up with an age of 18–70 years. Patients with ascites or fluid abnormalities were excluded. The mean BMI in the patient group was 23.0/24.6 kg/m^2, the mean DXA measured ASMM was 15.2/22.1 kg for women/men, respectively. Following a standard procedure BIA was performed about 2 h after eating and within 30 min after voiding. Sergi et al. performed their study in Italy (Padova) with healthy Caucasians older than 60 years (mean age 71 years) engaged twice weekly in a fitness program. The mean BMI in the whole group was 27.0 kg/m^2 and mean DXA measured ASMM was 18.6 kg. BIA was performed after an overnight fasting and bladder voiding. In the study of Scafoglieri et al. (PROVIDE study) Caucasians older than 65 years were recruited from

18 study centers in six European countries. The mean age in the subgroup, relevant for the generation of the equation used in this study (Hologic group), was 79 years. Subjects had functional limitations and sarcopenia, but no chronic diseases or acute inflammation. The mean BMI was 25.6 kg/m^2 and mean DXA measured ASMM was 16.5 kg. Again BIA was performed after an overnight fasting and bladder voiding. The study sample of Rangel Peniche et al. consisted of healthy Mexicans older than 60 years (mean age 69 years). The mean height and body weight of study participants were reported to be 151.5/163.8 cm and 62.6/68.9 kg corresponding to a BMI of 27.3/25.7 kg/m^2 for women/men, respectively. Mean DXA measured ASMM was 13.4/19.8 kg in women/men, respectively.

2.5. Cut offs for reduced muscle mass

To evaluate the effect of the different BIA equations on the accuracy to classify subjects as having normal or reduced muscle mass compared to DXA, we applied two different appendicular muscle mass indices (ASMMI). Following the recommendations of the European Working Group on Sarcopenia in Older People (EWGSOP) (Cruz-Jentoft et al., 2010) we applied ASMM adjusted for height^2 using the DXA based thresholds communicated by Baumgartner et al.: ASMMI $<$ 5.5 kg/m^2 for women and $<$ 7.26 kg/m^2 for men. The cut offs refer to 2 standard deviations below the mean of a young reference population (non-Hispanic white men and women aged 18–40 years) participating in the Rosetta Study (Baumgartner et al., 1998). Meanwhile BIA based ASMMI cut offs in Bavarian subjects have been published which are close to the DXA based cut-offs of Baumgartner et al. ($\leq$5.66 kg/m^2 for women and $\leq$7.18 kg/m^2 for men, respectively (Kemmler et al., 2016, 2017). The second ASMMI applied is recommended by the Foundation for the National Institutes of Health Sarcopenia Project (FNIH) and based on ASMM adjusted for BMI. The cut offs were generated by sensitivity analysis for muscle weakness. The cut offs are ASMMI $<$ 0.512 for women and $<$ 0.789 for men (Studenski et al., 2014).

2.6. Statistics

Statistical analysis was performed with IBM SPSS 24. Descriptive variables are presented as mean ± standard deviation (± SD). Significance of differences between women and men was determined by unpaired *t*-test and chi-square test. DXA-derived and BIA-derived muscle mass were compared by linear regression, mean error, 95% limits of agreement and Bland-Altman-Plots. Significance of mean error from DXA (= 0) was tested by one sample *t*-test, between BIA equations by paired *t*-test. Outcomes of the DXA- and BIA-based approaches for classifying subjects as having normal or reduced muscle mass were compared by raw agreement with 95% confidential intervalls (CI). Differences in agreement between subgroups were determined by chi-square test or Fisher exact test where appropriate. A p-value $<$ 0.05 was considered significant.

3. Results

3.1. Study population

148 subjects have been recruited. DXA data were missing in 4 subjects (2 patients discontinued the study, 1 patient each couldn't be postioned or scanned for technical reasons) resulting in 144 subjects for analyses. The basic characteristics of the study population are shown in Table 1. 60% of the subjects were women, 40% men. Age was not significantly different between women and men (mean age 80.9 years vs. 80.4 years). Men had significantly more often a history of cerebrovascular disease. They also had a higher comorbidity burden and were more often sarcopenic according to the definition of the EWGSOP. As expected, women were more often osteoporotic and showed lower hand grip strength and gait speed.

3.2. Comparison of the different sfBIA equations for predicting appendicular muscle mass

The Pearson correlation coefficients between DXA derived appendicular skeletal muscle mass ($ASMM_{DXA}$) and BIA predicted appendicular skeletal muscle mass were only slightly different between equations and ranged from 0.827 (BIA_{Sergi}) to 0.838 (BIA_{Kyle}) in women and 0.864 ($BIA_{Rangel\ P.}$) to 0.892 (BIA_{Sergi}) in men (Table 2). In both, women and men, $BIA_{Scafoglieri}$ had the lowest standard error of the estimate (SEE; 1.17 and 1.31, respectively). The equations differed substantially in the mean error ranging from −0.98 kg (BIA_{Kyle}) to + 0.19 kg ($BIA_{Rangel\ P.}$) in women and from −2.47 kg (BIA_{Kyle}) to -0.58 kg ($BIA_{Scafoglieri}$) in men. Only the mean errors of $BIA_{Scafoglieri}$ and $BIA_{Rangel\ P.}$ in women were not significantly different from DXA. The mean error of $BIA_{Scafoglieri}$ was the lowest in the whole group, in women and men and differed significantly from the other 3 equations. 95% limits of agreement were smallest for $BIA_{Scafoglieri}$ in women (range 5.80 kg) and for BIA_{Sergi} in men (range 6.04 kg). Exemplarily, the Bland Altman plots for $BIA_{Scafoglieri}$ are shown in Fig. 1.

3.3. Agreement between sfBIA and DXA in classifying subjects as having normal or reduced muscle mass

Using the EWGSOP recommended ASMMI cut offs, the raw agreement between the BIA- and DXA- based approaches differed only slightly between the four equations. In the whole sample, agreement was highest using $BIA_{Scafoglieri}$ (83.3%), followed by BIA_{Sergi} (82.6%), $BIA_{Rangel\ P.}$ (79.9%) and BIA_{Kyle} (77.1%) (Table 3). Strikingly, all BIA equations had a low sensitivity to detect subjects with reduced muscle mass. Within all 3 groups, the whole sample, women and men, sensitivity correlated most times with the extent of the mean error (Table 4). Sensitivity was 37%, 55%, 63% and 61% in the whole group for BIA_{Kyle}, BIA_{Sergi}, $BIA_{Scafoglieri}$ and $BIA_{Rangel\ P.}$. In gender segregated analysis all equations resulted in a sensitivity $<$ 70% in women. In men sensitivity was highest for $BIA_{Scafoglieri}$ and BIA_{Sergi} with 74% for both equations. Using the FNIH recommended ASMMI cut offs agreement results were in general similar with the highest agreement and sensitivity for $BIA_{Scafoglieri}$ in the whole sample (84% and 55%, respectively; Tables 3 and 4). Subanalysis in the whole group using $BIA_{Scafoglieri}$ showed no significant differences in agreement between groups with/without diabetes, heart failure, chronic kidney disease ≥ stage 3, orthopedic implants, obesity and functional dependence defined by a Barthel Index cut-off of ≤70 points (data not shown).

4. Discussion

The availability of new BIA equations allowing for direct comparison with DXA in older subjects on the one hand and the co-occurance of sarcopenia and multimorbidity on the other hand, prompted us to evaluate the accuracy of sfBIA in geriatric inpatients. Our study population shows reduced functionality, multimorbidity, polypharmacy and a mean age > 80 years as typically encountered on geriatric wards. Although we are not aware of a study comparing the 4 different BIA equations in a similar population, Steihaug et al. reported for the equation of Kyle et al. and Sergi et al. the mean errors of −1.1 kg/−2.3 kg and −0.80 kg/−0.70 kg in women/men, respectively, in a sample of hip fracture patients with a mean age of 79 years (Steihaug, Gjesdal, Bogen, & Ranhoff, 2016). Our analysis gave essentially the same results with mean errors of −0,98 kg/−2,47 kg and −0,69 kg/−0,80 kg (women/men, respectively) underscoring the validity of our data. When comparing the 4 different sfBIA equations, gender segregated analysis shows that the Pearson correlation coefficients vary only marginally between the tested equations, but they are consistently lower as reported in the original and complementary studies (Bosaeus, Wilcox, Rothenberg, & Strauss, 2014; Kyle et al., 2003; Rangel Peniche et al., 2015; Scafoglieri et al., 2017; Sergi et al., 2015). Additionally, in

Table 1
Clinical characteristics of study participants.

	total n (%)	women n (%)	men n (%)	p value$^{\Omega}$
Number of participants	144 (100)	86 (60)	58 (40)	
Age (y, mean ± SD)	80,7 ± 5,6	80,9 ± 5,5	80,4 ± 5,8	*n. s.*
Community dwelling	133 (92)	77 (90)	56 (97)	*n. s.*
Malnutrition (MNA < 17)	79 (55)	51 (59)	28 (48)	*n. s.*
BMI (kg/m^2)	26.5 ± 4.6	26.4 ± 4.8	26.8 ± 4.3	*n. s.*
Obesity (BMI > 30 kg/m^2)	32 (22)	17 (20)	15 (26)	*n. s.*
Morbidity:				
Coronary heart disease	39 (27)	19 (22)	20 (35)	*n. s.*
Chronic heart failure	26 (18)	14 (16)	12 (21)	*n. s.*
Cerebrovascular disease*	49 (34)	23 (27)	26 (45)	0,025
Art. Hypertension	116 (81)	71 (83)	45 (78)	*n. s.*
COPD	16 (11)	6 (7)	10 (17)	*n. s.*
Diabetes	46 (32)	24 (28)	22 (38)	*n. s.*
CKD (≥stage 3)	56 (39)	31 (36)	25 (43)	*n. s.*
Cancer #	25 (17)	11 (13)	14 (24)	*n. s.*
Mild or moderate dementia	21 (15)	9 (11)	12 (21)	*n. s.*
Comorbidity (≥2 of listed diseases)	112 (78)	60 (70)	52 (90)	0,005
Comorbidity (≥3 of listed diseases)	82 (57)	43 (50)	39 (67)	0,040
Osteoporosis	43 (30)	35 (41)	8 (14)	0,001
Orthopedic implants	55 (38)	36 (42)	19 (33)	*n. s.*
Sarcopenia (DXA, EWGSOP)	41 (28)	19 (22)	22 (38)	0,039
Polypharmacy (≥5 drugs taken)	121 (84)	72 (84)	49 (84)	*n. s.*
Dependency in ADL (Barthel < 70)	68 (47)	40 (47)	28 (48)	*n. s.*
Gait speed [m/s] (mean ± SD)	0,80 ± 0,33	0,72 ± 0,31	0,91 ± 0,33	0,001
Grip strength [kg] (mean ± SD)	24,0 ± 9,4	19,1 ± 6,2	31,2 ± 8,7	< 0,001

SD, standard deviation; MNA, Mini Nutritional Assessment; BMI, Body Mass Index; CKD, chronic kidney disease (stage 3 referring to a GFR < 60 ml/min/1.73 m^2; ADL, Activities of Daily Living; * : includes also patients with a history of transient ischaemic attacks; # : includes patients with a history of malignancy independent of current evidence of active disease. Ω for significance of differences between women and men, *n.s.*: not significant (significance level: $p < 0.05$).

Table 2
Performance of the different BIA equations to predict ASMM in comparison to DXA.

	Pearsons R	R^2	SEE	ASMM mean (± SD), kg	mean error (95%CI), kg	p $^{\alpha}$	p$^{\beta}$	95% limits of agreement (range), kg
total n = 144								
DXA				18,1 (± 4,5)				
BIA_{Kyle}	0,941	0,885	1,71	19,6 (± 5,0)	−1,58 (−1,87; −1,30)	< 0,001	< 0,001	−4,97; 1,81 (6,78)
BIA_{Sergi}	0,940	0,884	1,46	18,8 (± 4,3)	−0,73 (−0,98; −0,48)	< 0,001	< 0,001	−3,71; 2,25 (5,96)
$BIA_{Scafoglieri}$	0,933	0,871	1,55	18,3 (± 4,3)	−0,21 (−0,48; 0,05)	0,119	–	−3,36; 2,94 (6,30)
$BIA_{Rangel\ P.}$	0,933	0,871	1,80	18,6 (± 5,0)	−0,51 (−0,81; −0,21)	0,001	< 0,001	−4,04; 3,02 (7,06)
women n = 86								
DXA				15,4 (± 2,7)				
BIA_{Kyle}	0,838	0,702	1,48	16,3 (± 2,7)	−0,98 (−1,31; −0,65)	< 0,001	< 0,001	−3,98; 2,02 (6,00)
BIA_{Sergi}	0,827	0,684	1,34	16,0 (± 2,4)	−0,69 (−1,01; −0,36)	< 0,001	< 0,001	−3,66; 2,28 (5,94)
$BIA_{Scafoglieri}$	0,836	0,698	1,17	15,3 (± 2,1)	0,04 (−0,28; 0,36)	0,792	–	−2,86; 2,94 (5,80)
$BIA_{Rangel\ P.}$	0,835	0,698	1,38	15,2 (± 2,5)	0,19 (−0,14; 0,51)	0,253	0,001	−2,74; 3,12 (5,86)
men n = 58								
DXA				22,1 (± 3,4)				
BIA_{Kyle}	0,887	0,787	1,60	24,5 (± 3,4)	−2,47 (−2,90; −2,05)	< 0,001	< 0,001	−5,66; 0,72 (6,38)
BIA_{Sergi}	0,892	0,796	1,37	22,9 (± 3,0)	−0,80 (−1,21; −0,39)	< 0,001	0,031	−3,82; 2,22 (6,04)
$BIA_{Scafoglieri}$	0,869	0,755	1,31	22,7 (± 2,6)	−0,58 (−1,04; −0,13)	0,013	–	−3,97; 2,80 (6,77)
$BIA_{Rangel\ P.}$	0,864	0,746	1,58	23,6 (± 3,1)	−1,54 (−1,99; −1,08)	< 0,001	< 0,001	−4,93; 1,85 (6,78)

$^{\alpha}$: significance for difference of mean error from DXA (= 0); $^{\beta}$: significance for difference of mean error from $BIA_{Scafoglieri}$.

our study, standard errors of the estimate (SEE) tend to be higher and, with a few exceptions, equations show a significant mean error. Beside differences in sample size, removal of outliers and differences in ethnicity as causative factors, two other issues have to be mentioned. First of all, the subjects in our study were substantially older compared to the studies, in which the BIA equations were generated. In the study of Kyle et al. subjects were within a wide age range (22–94 years) with more than 50% being younger than 55 years. In the studies of Sergi et al. and Rangel P. et al. subjects were on average about 10 years younger. Only in the study of Scafoglieri et al., the mean age was close to that in our study, with a difference of about 2 years. Secondly, in our study population multimorbidity and consecutively polypharmacy was frequent, while in the studies of Kyle et al., Sergi et al. and Rangel P. et al. only healthy subjects were included for the generation of the BIA equations. In the study of Scafoglieri et al., subjects had no chronic diseases or inflammation either, but showed functional limitations and sarcopenia. In view of the fact that nearly half of our study population showed clinical relevant, reduced functionality (Barthel Index < 70 points) and 28% were sarcopenic according to the definition of the EWGSOP, it is tempting to speculate that this, in combination with the similar mean age of study populations, might explain the somewhat better results of $BIA_{Scafoglieri}$ compared to the other equations. Nevertheless, for all four equations the variance around the regression line is substantial (SEE ranging in the whole group from 1.42 to 1.80 kg), which is in line with a

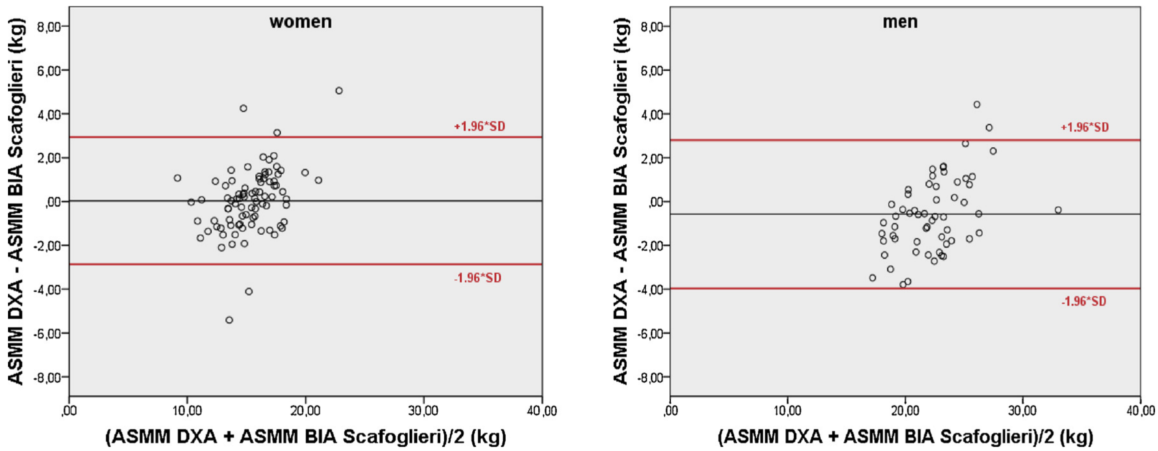

Fig. 1. Bland Altmann plots for $BIA_{Scafoglieri}$ for women and men, respectively.

sub-analysis in the patient group of the study by Kyle et al. with a SEE of 1.50 kg (Kyle et al., 2003). In principle, this might not be a major limitation in epidemiologic studies since the variance on both sides of the regression line will counterbalance from a cohort perspective, at least, if there is no substantial mean error. From the clinical, individual-centered perspective, however, this may increase misclassification and potentially cause inappropriate or missed therapeutic interventions. In our study sample, additionally, most often equations showed a significant mean error that also was variable between women and men. Finally, classification for muscle mass status by the four different sfBIA equations agreed with DXA in a range of 77%–83% and 79%–84% using the EWGSOP and FNIH recommended ASMMI cut offs, respectively. Sensitivity for detecting subjects with reduced muscle was less than 70% in the whole group. We previously found in a pragmatic pilot study, comparing classification by DXA with BIA based on total muscle mass and corresponding cut offs somewhat lower values for agreement (73%–80%) (Reiss et al., 2016). Beside the lower agreement, a major disadvantage in that study was the use of method-specific muscle mass cut offs. Therefore the interaction of both, inaccuracy in muscle mass measurement and mismatch of muscle cut offs, could have been responsible for agreement results. As recently BIA based ASMMI cut-offs showed to be close to the DXA based cut offs of Baumgartner et al. in a comparable population to ours, we believe that the incomplete agreement with DXA is now above all accounted for by the variability and mean error of muscle mass measurement by sfBIA. Therefore, improvement of BIA equations, specifically adapted for geriatric inpatients remains an important future research question. Unexpectedly, we were not able to identify a single clinical factor that distorts agreement results in our sample using $BIA_{Scafoglieri}$. In this context, one limitation of our study is that this sub-analysis for single disease states, like heart failure, was only guided by established clinical diagnosis without information on the actual severity of the disease. For example, patients with heart failure, who are at the time of BIA measurement fully recompensated, might not negatively influence the overall accuracy of sfBIA, while fluid retention might do so. We therefore cannot draw any definite conclusions about the impact of single clinical factors on overall accuracy of sfBIA, which needs further investigations. Another limitation of our study is that muscle measurement by sfBIA was not strictly standardized. Subjects, for example, had not routinely to be in the fasting state or void before the examination, what might, again, compromise the accuracy of BIA. Moreover, we focused on single frequency BIA only in our study and therefore cannot draw any conclusions about the accuracy of other devices, like multifrequency or segmental BIA.

In summary, the generation of sfBIA equations to predict appendicular muscle mass has led to a better comparability with DXA, enabling the use of common, method unspecific cut offs for reduced muscle mass in our setting. For classification of geriatric inpatients as having normal or reduced muscle mass the sfBIA equation of Scafoglieri et al. seems to perform best, mainly independent of the type of ASMMI cut offs used, although the differences to the other sfBIA equations are quite small. $BIA_{Scafoglier}$ correctly classifies more than 83% of the geriatric

Table 3
Agreement between the BIA and DXA based approaches for classification of subjects to have normal or reduced muscle mass using the EWGSOP (a) and FNIH (b) recommended ASMMI cut-offs, respectively.

a) EWGSOP (ASMM/height^2)

	total % (95%CI)	women % (95%CI)	men % (95%CI)
BIA_{Kyle}	77,1 (70,2–84,0)	82,6 (74,5–90,6)	69,0 (57,1–80,9)
BIA_{Sergi}	82,6 (76,5–88,8)	81,4 (73,2–89,6)	84,5 (75,2–93,8)
$BIA_{Scafoglieri}$	83,3 (77,2–89,4)	82,6 (74,5–90,6)	84,5 (75,2–93,8)
$BIA_{Rangel\ P.}$	79,9 (73,3–86,4)	81,4 (73,2–89,6)	77,6 (66,9–88,3)

b) FNIH (ASMM/BMI)

	total % (95%CI)	women % (95%CI)	men % (95%CI)
BIA_{Kyle}	78,5 (71,8–85,2)	81,4 (73,2–89,6)	74,1 (62,9–85,4)
BIA_{Sergi}	81,3 (74,9–87,6)	81,4 (73,2–89,6)	81,0 (70,9–91,1)
$BIA_{Scafoglieri}$	84,0 (78,0–90,0)	87,2 (80,2–94,3)	79,3 (68,9–89,7)
$BIA_{Rangel\ P.}$	83,3 (77,2–89,4)	87,2 (80,2–94,3)	77,6 (66,9–88,3)

Table 4
Positive predictive value, negative predictive value, sensitivity and specificity of the different BIA equations to detect subjects with reduced appendicular muscle mass in reference to DXA using the EWGSOP (a) and FNIH (b) recommended ASMMI cut-offs, respectively.

a) EWGSOP (ASMM/height^2)

	total				women				men			
	PPV (%)	NPV (%)	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)	Sens .(%)	Spec. (%)	PPV (%)	NPV (%)	Sens. (%)	Spec. (%)
BIA_{Kyle}	90,0	75,0	36,7	97,9	88,9	81,8	36,4	98,4	90,9	63,8	37,0	96,8
BIA_{Sergi}	90,0	80,7	55,1	96,8	87,5	80,8	31,8	98,4	90,9	80,6	74,1	93,5
$BIA_{Scafoglieri}$	83,8	83,2	63,3	93,7	73,3	84,5	50,0	93,8	90,9	80,6	74,1	93,5
$BIA_{Rangel\ P.}$	75,0	81,7	61,2	89,5	62,5	88,7	68,1	85,9	93,8	71,4	55,6	96,8

b) FNIH (ASMM/BMI)

	total				women				men			
	PPV (%)	NPV (%)	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)	Sens .(%)	Spec. (%)	PPV (%)	NPV (%)	Sens. (%)	Spec. (%)
BIA_{Kyle}	84,6	77,9	27,5	98,1	66,7	82,5	22,2	97,1	100	70,6	31,8	100
BIA_{Sergi}	88,2	80,3	37,5	98,1	75,0	81,7	16,7	98,5	92,3	77,8	54,5	97,2
$BIA_{Scafoglieri}$	81,5	84,6	55,0	95,2	81,8	88,0	50,0	97,1	81,3	78,6	59,1	91,7
$BIA_{Rangel\ P.}$	80,8	83,9	52,5	95,2	70,6	91,3	66,7	92,6	100	73,5	40,9	100

PPV: positive predictive value; NPV: negative predictive value; Sens.: sensitivity; Spec.: specificity.

inpatients, but sensitivity to detect reduced muscle mass is low. Nethertheless sfBIA still might have a role in the diagnostic algorithm for sarcopenia, since clinical diagnosis requires above all accuracy around a certain cut-off. The role of sfBIA as a screening instrument with validation by DXA in case of results close to the cut offs for reduced muscle mass might diminish the number of required DXA scans and should be clarified in future studies.

Authors' contributions

JR, BI, RR: study design. JR, BI, RR, RA, BMP, PD: patient recruitement. MK: data collection. HK, CP: muscle mass measurement by DXA. JR, RR, WT data analysis. JR, RR manuscript preparation. JR, BI, MK, RA, BMP, WT, HK, CP, PD, RR: interpretation of data analyses, critical reviews and final approval of the manuscript.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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