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This is the peer reviewed version of the following article: Villani, Anthony Michael, Crotty, Maria, Cameron, Ian D., Kurrle, Susan E., Skuza, Pawel P., Cleland, Leslie G., . . . Miller, Michelle D. (2014). Appendicular skeletal muscle in hospitalised hip-fracture patients: Development and cross-validation of anthropometric prediction equations against dual-energy X-ray absorptiometry. Age and Ageing, 43(6), 857.

which has been published in final form at

DOI: https://doi.org/10.1093/ageing/afu106

Appendicular skeletal muscle in hospitalized hip-fracture patients: Development and cross-validation of anthropometric prediction equations against dual-energy X-ray absorptiometry

Running Title: Development and validation of appendicular skeletal muscle equations for hip fracture patients

Abstract

Background: Accurate and practical assessment methods for assessing appendicular skeletal muscle (ASM) is of clinical importance for diagnosis of geriatric syndromes associated with skeletal muscle wasting.

Objectives: The purpose of this study was to develop and cross-validate novel anthropometric prediction equations for the estimate of ASM in older adults post-surgical fixation for hip fracture, using dual energy X-ray absorptiometry (DEXA) as the criterion measure.

Subjects: Community-dwelling older adults (aged ≥65 years) recently hospitalised for hip fracture.

Setting: Participants were recruited from hospital in the acute phase of recovery.

Design: Validation measurement study.

Measurements: A total of 79 hip fracture patients were involved in the development of the regression models (MD group). A further 64 hip fracture patients also recruited in the early phase of recovery were used in the cross-validation of the regression models (CV group). Multiple linear regression analyses were undertaken in the MD group to identify the best performing prediction models. The linear coefficient of determination (R^2) in addition to the standard error of the estimate (SEE) were calculated to determine the best performing model. Agreement between estimated ASM and ASM_{DEXA} in the CV group was assessed using paired *t* tests with the 95% limits of agreement (LOA) assessed using Bland-Altman analyses.

Results: The mean age of all participants was 82.1 ± 7.3 years. The best two prediction models are presented as follows: $ASM_{PRED-EQUATION\_1}$: 22.28 - (0.069 * age) + (0.407 * weight) – (0.807 * BMI) – (0.222 * MAC) (adjusted R^2: 0.76; SEE: 1.80kg); ASM_{PRED-}

$_{\text{EQUATION\_2}}$: $16.77 - (0.036 * \text{age}) + (0.385 * \text{weight}) - (0.873 * \text{BMI})$ (adjusted R^2: 0.73;

SEE: 1.90kg). Mean bias from the CV group between ASM_{DEXA} and the predictive equations

are as follows: $\text{ASM}_{\text{DEXA}} - \text{ASM}_{\text{PRED-EQUATION\_1}}$: 0.29 ± 2.6kg (LOA: -4.80, 5.40kg);

$\text{ASM}_{\text{DEXA}} - \text{ASM}_{\text{PRED-EQUATION\_2}}$: 0.13 ± 2.5kg (LOA: -4.77, 5.0kg). No significant

difference was observed between measured ASM_{DEXA} and estimated ASM (ASM_{DEXA}: $16.4 \pm$

3.9kg; $\text{ASM}_{\text{PRED-EQUATION\_1}}$: 16.7 ± 3.2kg ($P = 0.379$); $\text{ASM}_{\text{PRED-EQUATION\_2}}$: 16.6 ± 3.2kg (P

$= 0.670$))

Conclusions: We have developed and cross-validated novel anthropometric prediction

equations against DEXA for the estimate of ASM designed for application in older

orthopaedic patients. Our equation may be of use as an alternative to DEXA in the diagnosis

of skeletal muscle wasting syndromes. Further validation studies are required to determine

the clinical utility of our equation across other settings, including hip fracture patients

admitted from residential care, and also with longer-term follow-up.

Introduction

Body composition assessment, particularly skeletal muscle mass (SMM), is a key component of assessing the health and functional status of older adults[1]. Assessing SMM, specifically appendicular skeletal muscle (ASM), is a key diagnostic feature for the assessment of geriatric syndromes associated with skeletal muscle wasting, such as sarcopenia[2] and geriatric cachexia[3]. Older adults with recent hip fractures are an important clinical group at increased risk of significant reductions in SMM and adverse health outcomes including frailty, progressive disability, institutionalization and subsequent mortality post-surgery [4, 5].

Dual energy X-ray absorptiometry (DEXA) is commonly referred to as a reference technique for assessing body composition [6]. However its high cost, routine availability within the clinical setting and the potential challenges for measurement of frail older adults recovering from surgery highlights the need for practical alternatives [7].

Upper-arm anthropometry offers a quick, portable and inexpensive method of assessing body composition. Previous prediction models using a set of appendicular circumferences and skinfolds have been developed and cross-validated [8-10]. However such validation studies are yet to be undertaken in nutritionally vulnerable hospitalized older adults with hip fracture. Visvanathan et al [11] recently developed and validated an anthropometric predication equation for application in older adults; however, the sample used to establish and validate this equation were not representative of a hip fracture sample, with few participants aged ≥80years, few having BMIs ≤22kgm-2 and were otherwise healthy community dwelling adults (mean age: 50.6 ± 15.7 years); moreover, it has been suggested that the application of general predictive equations in populations different to which they are derived should be

26   avoided[12]. Therefore, the objective of this study was to develop and cross-validate novel

27   anthropometric prediction models for the assessment of ASM in a sample of older adults

28   post-surgical fixation for hip fracture using DEXA as the criterion measure.

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Methods

Patients and Recruitment

These were cross-sectional analyses performed in older adults post-surgical fixation for hip fracture. Body composition data were collected at baseline in a sample of hip fracture patients recruited from two randomized controlled trials (RCT) conducted by our group: 1) INTERACTIVE trial (ACTRN 12607000017426) [13]; 2) ATLANTIC trial (ACTRN 12609000241235) [14].

Participants were eligible for each respective study if they were admitted to hospital with a diagnosis of hip fracture confirmed by radiology report, had a Mini Mental State Examination (MMSE) score of $\geq$18/30, had a body mass index (BMI) between 18.5kgm-2 and 35kgm-2 and were community-dwelling. This study was conducted according to the guidelines described in the Declaration of Helsinki with all procedures involving human subjects approved by the Human Research Ethics Committee at each recruitment site.

Body composition measurements and procedures

A detailed description of all outcome measures from both investigations are reported elsewhere [13, 14]. For the purpose of the present validation study, participants recruited from the INTERACTIVE trial were used as the model development (MD) group. Predictor variables including weight, BMI, mid-arm circumference (MAC), triceps skinfolds (TSF), age and gender were used in the development of the prediction model. Using the same predictor variables, participants recruited from the ATLANTIC trial acted as the cross-validation (CV) group.

Weight and height

Body weight was recorded to the nearest 0.1kg using calibrated digital scales with participants wearing light clothing and without footwear. Participants who were unable to mobilize were weighed using a calibrated weigh chair. Height was estimated from knee height using validated age and gender specific equations[15]. BMI was calculated as weight (kg) divided by the square of estimated height (m).

Dual-energy X-ray absorptiometry

Whole body and regional body composition were estimated using Lunar Prodigy DEXA and automated reporting GE EnCORE bone densitometry software (version 10.51.006). The system software also provides estimates of ASM, defined as the sum of lean soft tissue mass in both arms and legs [6].

Upper arm anthropometry

MAC was measured at the mid-point between the superior and lateral border of the acromion process and the proximal and lateral border of the radial head to the nearest 0.1cm using a flexible steel measuring tape. TSF thickness was measured at the marked posterior mid-acromiale-radiale to the nearest 0.2mm using a calibrated Harpenden skinfold calliper. All anthropometric measures were performed by trained staff. Unless affected by injury, all anthropometric measures were taken on the right-hand side of the body.

Statistical Analyses

Analyses were performed using SPSS for Windows 21.0. Significance was set at $P < 0.05$.
Differences between the MD and CV cohorts were examined by independent samples t-test.
Using ASM_{DEXA} as the criterion measure, multiple linear regression analysis was undertaken
in the MD group to identify the best performing predictive models. In the development of the
prediction model, we selected predictor variables based on the results of the correlation
analyses and their relationship with ASM_{DEXA}. Variables displaying no significant
relationship in the regression model were removed from the final prediction model. The
linear coefficient of determination (R^2) in addition to the standard error of the estimate (SEE)
were calculated. The equations developed in the MD group were used to calculate predicted
ASM in the CV group. Agreement between estimated ASM and ASM_{DEXA} was assessed
using paired t tests to identify fixed bias with the limits of agreement (LOA) between the two
measures assessed using Bland and Altman analyses [16, 17].

Results

79 participants in the MD group (Male, n = 23; Female, n = 56) and 64 participants (Male, n = 14; Female, n = 50) in the CV group contributed data. Mean (SD) weight, BMI, MAC, TSF thickness and ASM for both groups are presented in **Table 1**.

In relation to all other predictor variables in the model, TSF thickness and gender resulted in a weak, non-significant contribution to the regression model (TSF thickness: β = 0.093; P = 0.260; Gender: β = 0.142; P = 0.095).

The best two performing prediction models are presented as follows:

ASM$_{PRED-EQUATION\_1}$: 22.28 - (0.069 * age) + (0.407 * weight) – (0.807 * BMI) – (0.222 * MAC); Adjusted R^2: 0.76; SEE: 1.80kg

ASM$_{PRED-EQUATION\_2}$: 16.77 – (0.036 * age) + (0.385 * weight) – (0.873 * BMI); Adjusted R^2: 0.73; SEE: 1.90kg

[Age in years; weight in kg; BMI: weight (kg) divided by the square of height (m) (kgm-2); MAC in cm].

When assessing agreement in the CV group, no significant difference was observed between measured ASM$_{DEXA}$ and estimated ASM (ASM$_{DEXA}$: 16.4 ± 3.9kg; ASM$_{PRED-EQUATION\_1}$: 16.7 ± 3.2kg (P = 0.379); ASM$_{PRED-EQUATION\_2}$: 16.6 ± 3.2kg (P = 0.670)). Mean bias from the CV group between ASM$_{DEXA}$ and the predictive equations are as follows: ASM$_{DEXA}$ – ASM$_{PRED-EQUATION\_1}$: 0.29 ± 2.6kg (LOA: -4.80, 5.40kg); ASM$_{DEXA}$ – ASM$_{PRED-EQUATION\_2}$: 0.13 ± 2.5kg (LOA: -4.77, 5.0kg). Bland-Altman plots of the comparisons are highlighted in **Figure 1**.

Discussion

To the best of our knowledge, this is the first study to develop and validate anthropometric

predictive equations for the estimate of ASM in hip fracture patients. Our equations may be

of use for clinical application and useful as an alternative to DEXA for inclusion in the

assessment of geriatric syndromes.

 At present, there are several published predictive equations that use bioelectrical impedance

analysis as a reference method developed for application in older adults for the assessment of

SMM, ASM and/or FFM [18-22]; however, the development of body composition predictive

equations amongst hip fracture patients is scant. We have previously applied one these

equations [22] to our MD sample of hip fracture patients and reported clinically unacceptable

discordance from SMM_{DEXA}, thus supporting the argument for population specific algorithms

that demonstrate clinically acceptable agreement with DEXA [23, 24].

Results from the present study are consistent with those presented by Visvanathan et al (Adj

$R^2 = 0.87$; SEE = 1.95)[11]. Unlike our prediction models, the best performed model

established by Visvanathan et al [11] used BMI, weight, age and gender. Although the model

proposed by Visvanathan et al [11] explained a greater variance of ASM_{DEXA}, this is likely

attributable to the heterogeneity in the body composition status of our hip fracture sample,

differences in age and the acute phase of injury. Unexpectedly, in the present study, gender

demonstrated a weak and non-significant contribution to the regression model and was

subsequently removed from both final prediction models; it is possible that this could be

attributable to a gender discrepancy among both hip fracture cohorts with males

underrepresented relative to females.

177 A major strength of this study was the fact that we developed and cross-validated our

178 prediction models in the hip fracture population. Moreover, our prediction equation also

179 included simple upper arm limb circumference as a predictor variable, in addition to more

180 routine anthropometric measures such as weight and BMI. Although TSF thickness was

181 originally a selected independent variable of interest, it demonstrated a weak and non-

182 significant contribution to the regression model and accordingly was not included in the

183 predictive equations. The significant difference observed in TSF thickness between the two

184 hip fracture cohorts was likely associated with the sample recruited, with investigators from

185 the CV group specifically recruiting cachectic hip fracture patients [14]. Less likely, but

186 possible, is that protocol violations in measurement of TSF may have been responsible for the

187 significant difference observed in TSF thickness between the two hip fracture cohorts and the

188 lack of association between TSF thickness and ASM_{DEXA}. Measurement of TSF can be

189 challenging and despite best efforts to train and monitor staff performance, we cannot be

190 certain that measures were routinely undertaken according to protocol.

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192 A potential limitation of the present study was the exclusion of additional predictor variables

193 which may have strengthened our model, including additional appendicular limb

194 circumferences and isometric handgrip strength. Importantly, the potential for selection bias

195 at study entry (i.e. BMI between 18.5 and 35 kgm-2, community dwelling, medically stable

196 and ambulatory pre-fracture) resulted in potential sarcopenic and cachectic patients being

197 excluded from the study, which may indeed limit the generalisability of these equations; the

198 latter considerations are pertinent because validation studies for our prediction models are

199 required, particularly in a larger sample of hip fracture patients which specifically include

200 more vulnerable patients such as those living in residential aged care facilities.

201

202 In conclusion, we have developed and cross-validated novel anthropometric prediction

203 equations for the estimate of ASM designed for application in older adults post-surgery for

204 hip fracture. Our prediction equations have potential to contribute to the diagnosis of skeletal

205 muscle wasting syndromes in clinical care settings when DEXA scans are unavailable or

206 unsuitable.

207

234   **Table 1.** Post-surgical anthropometric characteristics in two hip fracture cohorts

235   (all such variables reported as mean ± SD)

	All		MD group [a] (INTERACTIVE) n = 79		CV group [b] (ATLANTIC) n = 64	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age (years)	82.1	7.3	82.7	5.9	81.1	8.9
Weight (kg)	64.3	13.8	65.4	14.0	62.6	13.3
BMI (kgm-2)	24.7	4.2	24.9	4.0	24.3	4.5
MAC (cm)	26.0	4.0	26.2	3.8	25.6	4.2
TSF thickness (mm)	14.6	5.9	15.2[c]	5.6	13.5[c]	6.2
ASM_{DEXA} (kg)	16.8	3.8	17.2	3.8	16.4	3.9

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237   *MD*, model development group; *CV*, cross-validation group; *BMI*, body mass index; *MAC*,

238   mid-arm circumference; *TSF*, triceps skinfold thickness; *ASM*, appendicular skeletal muscle;

239   *DEXA*, dual energy X-ray absorptiometry.

240   [a] INTERACTIVE participants used in the development of the prediction models; *n* = 79 hip

241   fracture patients with complete DEXA and anthropometric data.

242   [b] ATLANTIC participants used in the cross-validation of the prediction models; *n* = 64 hip

243   fracture patients with complete DEXA and anthropometric data.

244   [c] Significant differences in predictor variables between the MD and CV groups assessed by

245   independent samples *t*-test (*P* <0.05).

246   All data were collected at baseline within 14-days post-surgery for INTERACTIVE

247   participants or within 7-days post-surgery for ATLANTIC participants.

248

249 **Figure 1.** Bland-Altman Plots: mean bias and 95% limits of agreement (LOA) for the

250 assessment of predicted ASM and measured ASM_{DEXA}, the reference technique. In this

251 technique, the difference between measured ASM_{DEXA} and predicted ASM (i.e. mean bias)

252 was plotted along the vertical axis against the mean of the two measures on the horizontal

253 axis where the aim was to describe the variability in agreement between the two measures.

254 Assuming a normal distribution of differences, theoretically, 95% of the differences are

255 expected to be within $\pm$ 2SD; a) ASM_{DEXA} vs $ASM_{PRED-EQUATION\_1}$; b) ASM_{DEXA} vs ASM_{PRED-}

256 $_{EQUATION\_2}$. The solid bold line represents the mean difference between measured ASM_{DEXA}

257 and predicted ASM. The two dashed lines illustrate the 95% LOA ($\pm$ 2SD) between the two

258 measures.

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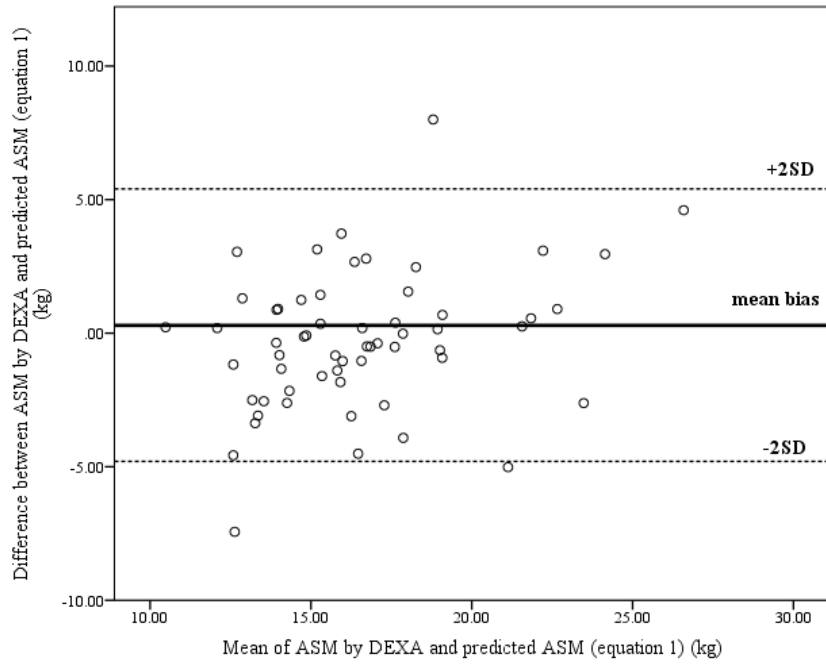274 **a)**

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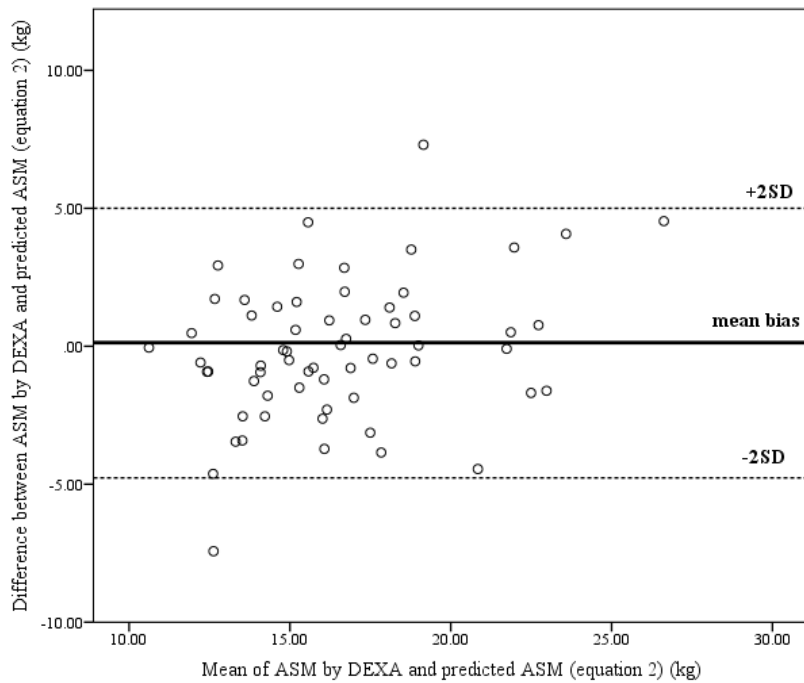
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