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1 Creatinine to Cystatin C Ratio and BIA for the Assessment of Low Lean Body Mass in Cancer

2 Patient: Comparaison to L3 CT-scan

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16

17

18 Abstract:

19 **Background:** Lean body mass (LBM) is an important prognosis factor in cancer patients.

20 Although the L3 CT-scan is considered as a reference method for its assessment, a
21 convenient and easily available method for longitudinal follow-up is required. While
22 bioelectrical impedance analysis (BIA) is widely used its accuracy is discussed; plasma
23 creatinine-to-cystatin C (CC) ratio could be an attractive alternative. The aim of this study
24 was to evaluate CC ratio and BIA ability to detect myopenia in cancer patients compared to
25 the CT-scan use as a standard.

26 **Methods:** Patients with any kind of cancer had body composition evaluation by CT-scan, BIA
27 and CC. Statistical analysis included correlation test, Bland & Altman and ROC curve analysis.

28 **Results:** Forty-four patients (14 women) were included, 59% of whom had myopenia on CT-
29 scan. Both BIA LBM and CC ratio were well correlated with CT-scan LBM ($r = 0.763$ and 0.648
30 respectively) but concordance analysis revealed a 3 kg constant bias towards BIA compared
31 to CT-scan. In terms of ability to detect myopenia, AUC for BIA were 0.675 and 0.388 for men
32 and women respectively. For CC ratio, AUC were 0.813 and 0.673 .

33 **Conclusion:** This study shows that LBM assessed by the CC ratio or BIA is well correlated with
34 that determined by L3 CT-scan. The CC ratio capacity to detect myopenia is better to that of
35 BIA. We show that CC ratio can be conveniently used in cancer patient as a reliable
36 biomarker of muscularity.

37

38 **Introduction:**

39 Cachexia is a frequent complication of cancer and is characterized by a massive loss of lean
40 mass and, frequently, fat body mass [1]. It affects as much as 80% of patients with advanced
41 cancer and is of poor prognosis in terms of response and tolerance to treatment as well as
42 mortality. Therefore, an adequate evaluation of body composition in cancer patients is
43 mandatory as low lean body mass (LBM) has also proven to be an independent risk factor for
44 increased treatment toxicity, postoperative complications, decreased treatment
45 effectiveness and increased mortality [2].

46 While dual X-ray absorptiometry (DXA) remains the most reliable method for assessing body
47 composition, it is not available everywhere and its inclusion in the patient's care plan is often
48 difficult [3]. This has led to the development of alternative approaches. Mourtzakis et al.
49 showed that the muscle surface area at the third lumbar vertebra on computed tomography
50 (CT) scanner image was a strong predictor of LBM [4]. CT-scan is widely available and most
51 cancer patients have CT images taken for diagnosis and disease extension assessment.
52 However, surface area determination on CT-scan is time-consuming and operator-
53 dependent. In addition, since CT scans are based on X-rays, the assessment of body
54 composition by these means cannot be repeated frequently. An alternative could be
55 bioelectrical impedance analysis (BIA). BIA is based on the measurement of the body's
56 resistance to the passage of alternating currents of low intensity and variable frequencies to
57 determine the body's water compartments, intracellular water enabling to determine LBM.
58 This method is non-invasive, available at the bedside and suitable for longitudinal follow-up
59 [5,6]; however, since calculations use equations derived from healthy populations, its
60 accuracy in oncology remains controversial [7]. Recently plasma creatinine-to-serum cystatin

61 (CC) ratio, sometimes called sarcopenia index, has been proposed for the estimation of
62 muscle mass [9,21,22]. Creatinine and cystatin C are two compounds freely filtered by the
63 kidney and their plasma concentration is used in several equations to evaluate glomerular
64 filtration rate and renal function [8]. Cystatin C being produced at a constant rate by every
65 nucleated cells and creatinine only by muscle, the CC ratio should therefore vary with muscle
66 mass independently of kidney function [9–11].

67 Considering that the L3 CT-scan is the best compromise between availability and reliability,
68 the aim of this study was to evaluate the level of agreement between LBM assessed from L3
69 CT-scan and that evaluated either by BIA or by the CC ratio and their ability to detect
70 insufficient muscle mass (myopenia) based on Prado et al. criteria for skeletal muscle index
71 [12]. From the CC ratio we also derived an equation for skeletal muscle area, also
72 incorporating age, weight, height and sex.

73

74 **Patients and methods:**

75 **Patients – study design:**

76 This prospective pilot study was conducted in the outpatient unit of the oncology
77 department of Cochin hospital between October 2017 and April 2018.

78 Patients were recruited during their one-day pre-therapeutic multidisciplinary risk
79 assessment visit. All patients with active cancer, regardless of the stage and localization,
80 were included, provided they were fasted for BIA and had an abdominal CT-scan no later
81 than 6 weeks before BIA and blood test.

82 Written informed consent was obtained for all patients. The study was approved by the
83 Cochin Institutional Review Board according to the declaration of Helsinki.

84 Exclusion criteria were age under 18, absence or withdrawal of consent, severe obesity (BMI
85 > 40) and severe or terminal kidney failure (calculated creatinine clearance < 30 ml/min).

86

87 **L3-CT scan:**

88 Skeletal muscle surface areas (SMA) were measured on CT scans on two consecutive images
89 at the middle of the third lumbar vertebra with ImageJ® software. Delimitation of the muscle
90 surface was done manually, and the quantification was done for attenuation between -29
91 and + 150 Houndfield units. LBM was computed using the equation of Mourtzakis et al. [4] :

92 $LBM = 0.3 \times SMA + 6.06$

93 Indexing SMA to the squared height defines the skeletal muscle index (SMI). myopenia was
94 defined as $SMI < 52.4 \text{ cm}^2/\text{m}^2$ in men and $SMI < 38.5 \text{ cm}^2/\text{m}^2$ following Prado's et al criteria
95 [12].

96

97 **Bio-impedance Analysis:**

98 BIA was done with a multifrequency BodyStat Quadscan 4000® (Euromedix, Leuven,
99 Belgium) according to the manufacturer's recommendations. It was measured in patients in
100 the fasted state, after emptying their bladder, and after a rest of at least 15 min. Two
101 electrodes were placed on the back of the right hand and right foot at the base of the third
102 finger and two others, parallel to the first, on the wrist and the ankle. The non-disclosed in-
103 device equations were used to calculate LBM from impedance values. This BIA apparatus
104 does not give access to the resistance and reactance parameters. SMI_{BIA} was calculated by
105 dividing the lean body mass obtained from BIA by the squared height.

106

107 **Cystatin C-to-Creatinine C ratio:**

108 Plasma creatinine (mg/dL) was assayed on a Roche Cobas 8000® analyzer (Roche diagnostic,
109 Meylan, France) by the compensated Jaffé's method and plasma cystatin C (mg/L) by
110 immunonephelometry on a Siemens BNII® analyzer (Siemens Healthcare SAS, Saint-Denis,
111 France). CC ratio was defined as $[\text{creatinine (mg/dL)}/\text{cystatin C (mg/L)}] \times 100$.

112

113 **Statistical analysis**

114 Statistical analysis was done with RStudio software (v. 1.1.463). Normality of data
115 distribution was checked by Shapiro test. Proportions were compared with homogeneity chi
116 squared test or Fisher exact test. Correlations were assessed by Pearson or Spearman
117 correlation test depending on the normality of the data. Concordance between BIA and CT
118 was assessed by the Bland Altman method. Linear regression with stepwise selection and 5-
119 fold cross validation was done to calculate SMA from the CC ratio. We did ROC curve analysis
120 to assess the ability of BIA and of the CC ratio to predict low muscle mass according to
121 Prado's scan criteria.

122 **Results:**

123 Among 53 consecutive patients initially recruited, 9 had to be excluded from the study, their
 124 CT-scan being older than 1.5 months at the time of inclusion. One of them also had morbid
 125 obesity. Thirty men and 14 women completed the study. Patients mainly had non-small cell
 126 lung cancer (27%), prostate cancer (16%) or bladder cancer (11%). Eighty-two percent of the
 127 patients had metastatic disease. 26% had major thoracic or abdominal surgery and 37% had
 128 a previous line of chemotherapy in the year preceding inclusion. Patients' main
 129 characteristics are given in Table I. Mean age was 65 years (SD = 12.7 years) and mean BMI
 130 was 24.4 (SD = 3.4).

131

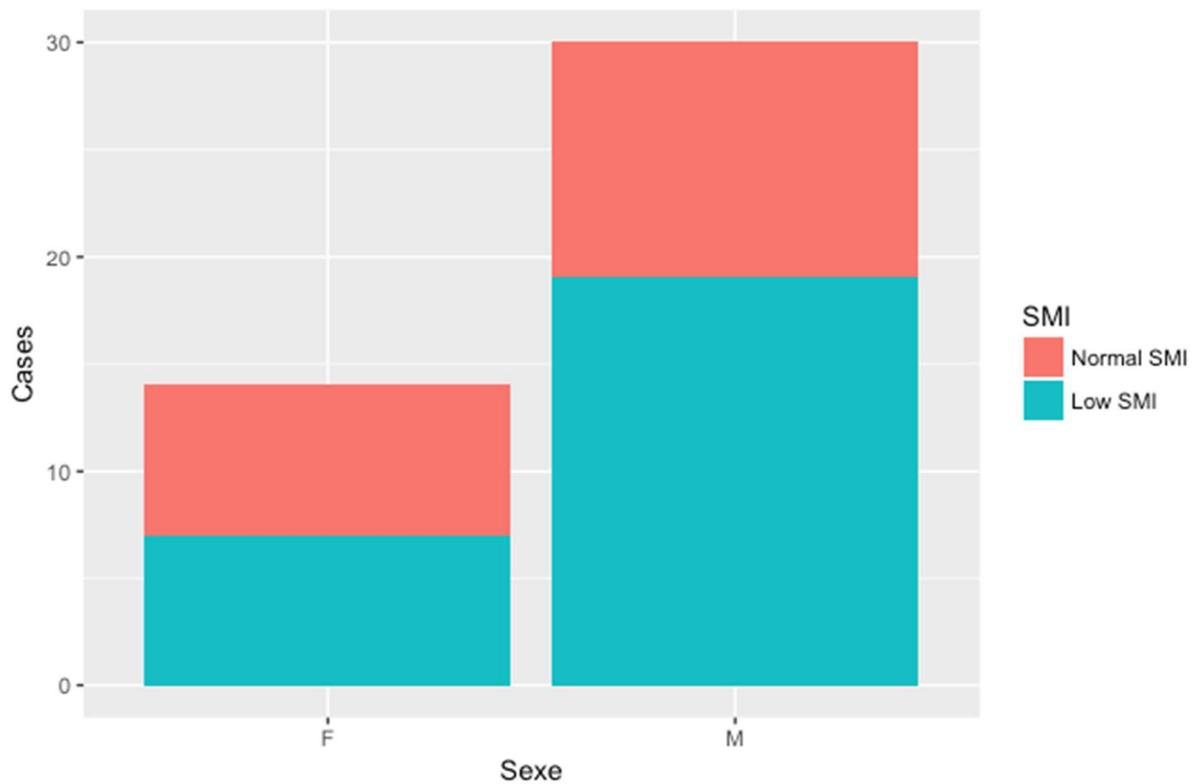
	Mean	SD
Age (y)	65.0	12.7
Weight (kg)	70.2	12.2
Height (m)	1.7	0.1
BMI (kg/m ²)	24.4	3.4
LBM (CT scan, kg)	45.7	10.3
LBM (BIA, kg)	48.6	11.3
SMI (kg/m ²)	45.5	9.2
Cystatin C/ Creatinine	79.4	22.9

132

133 Table I: Main characteristics of the study population

134

135 According to Prado et al. criteria [12], 59% of patients had low lean body mass (Figure 1) and
136 this was slightly more frequent in men (63%) than in women (50%, chi squared test, $p =$
137 0.611).



138

139 **Figure 1:** Prevalence of low muscle mass according to sex

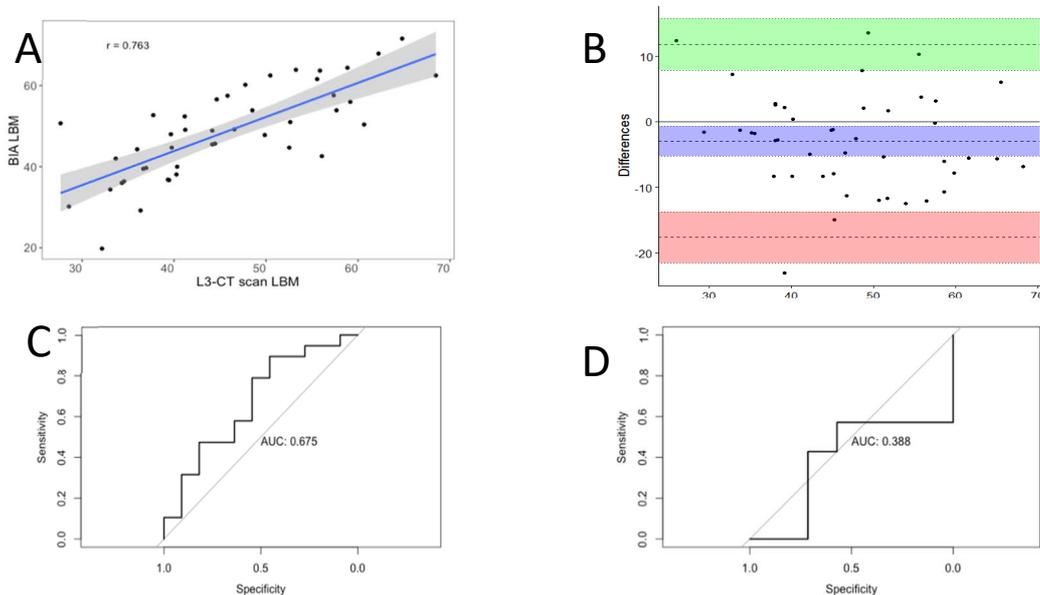
140 *Low muscle mass was defined according to Prado et al. criteria [12] based on skeletal muscle index derived*
141 *from L3 CT-scan.*

142 *F: Female, M: Male, SMI: Skeletal Muscle Index*

143

144 Figure 2 shows method agreement for LBM evaluation between L3 CT-scan and the in-device
145 BIA equation. Pearson correlation coefficient was 0.763 ($p < 10^{-8}$, Figure 2A). The Bland
146 Altman analysis (Figure 2B) revealed that 3 patients (7%) had values outside the agreement

147 limits (−17.6 kg; +11.7 kg) and that there was a constant bias of 3 kg (CI: 0.7 to 5.2) for BIA.
 148 Therefore, BIA tended to overestimate LBM compared to CT scan.
 149 On ROC curve analysis to assess the ability of BIA to detect low muscle mass, AUC for men
 150 was 0.675 with, for a SMI_{BIA} threshold of 19.75 kg/m^2 , a sensitivity of 89% and a specificity of
 151 45%; for women, AUC was 0.388 with two equivalent thresholds: 13.84 kg/m^2 (sensitivity
 152 57% and specificity 57%) and 13.54 kg/m^2 (sensitivity 43% and specificity 71%). Although the
 153 proportions of patients with myopenia did not differ significantly between the two methods
 154 (Fisher exact test, $p = 0.177$), the BIA resulted in misclassifying 14 patients [32%; 6 females
 155 (50%) and 8 males (27%)], resulting in 4 more male patients with myopenia and one less
 156 female patient.



157

158 **Figure 2:** Comparison of LBM determined by CT-scan and BIA

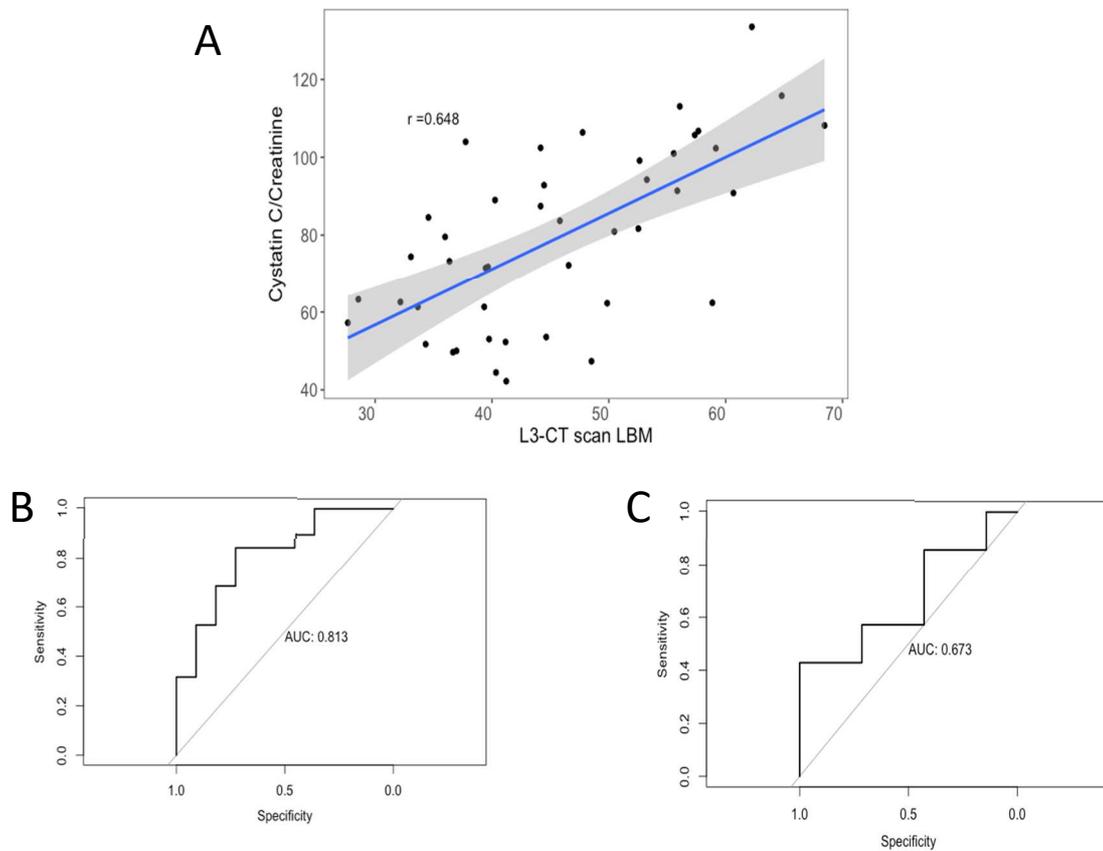
159 *A: Pearson correlation between LBM measured by L3 CT-scan and BIA ($r = 0.763$, $p\text{-value} < 10^{-8}$). B: Bland-*
 160 *Altman analysis of the concordance between L3 CT-scan and BIA (constant bias: 3kg). Colored boxes*
 161 *represent 95% confidence intervals for lower and upper limits of agreement and bias. C, D: ROC curve*

162 *analysis of the performance of BIA (LBM/ height²) to detect low muscle mass in men (C: AUC= 0.675, best*
163 *threshold: 19.75 kg/m², sensitivity: 89%, sensibility: 45%) and in women (D: AUC= 0.388, best threshold:*
164 *13.84 or 13.54 kg/m² sensibility: 57 or 43% and specificity: 43 or 71% respectively).*

165 *AUC: area under curve, BIA: bioelectric impedance analysis, LBM: lean body mass, ROC: receiver operating*
166 *characteristics*

167

168 The CC ratio presented a good correlation with LBM measured by CT scan (Figure 3A, $r =$
169 0.648 , $p = 2.0 \times 10^{-6}$, CC correlation with SMI: $r = 0.500$, $p = 0.0001$). We also assessed the
170 ability of the ratio to classify the patient in term of muscle mass according to Prado's scan
171 criteria by ROC curve analysis. AUC were 0.813 for male patients, with a sensitivity of 84%
172 and a specificity of 73% for a CC threshold of 96.7 (Figure 3B), and 0.673 for women (Figure
173 3C), with a sensitivity of 43%, and a specificity of 100% for a CC threshold of 73.9. This
174 method misclassifies 16 patients (36%; Fisher exact test $p = 0.002$): 10 females (71%, notably
175 every female with myopenia as determined by L3-CT scan) and 6 males (20%, 3 with
176 myopenia and 3 without).



177

178

Figure 3: Comparison of LBM determined by CT-scan and CC ratio

179

A: Correlation between LBM determined by L3-CT scan and the CC ratio ($r = 0.648$, $p < 10^{-6}$).

180

B, C: ROC curve analysis for the capacity of the CC ratio to detect low muscle mass for men (B : AUC= 0.813, best threshold:

181

96.7, sensitivity: 84%, sensibility: 72%) and for women (C: AUC= 0.673 , best threshold: 73.9, sensitivity: 43

182

%, specificity: 100%).

183

AUC: area under curve, CC: Creatinine to Cystatin C ratio, LBM: lean body mass, ROC: receiver operating

184

characteristics

185

186

We derived an equation to calculate SMA from the CC ratio, weight, sex, age and height.

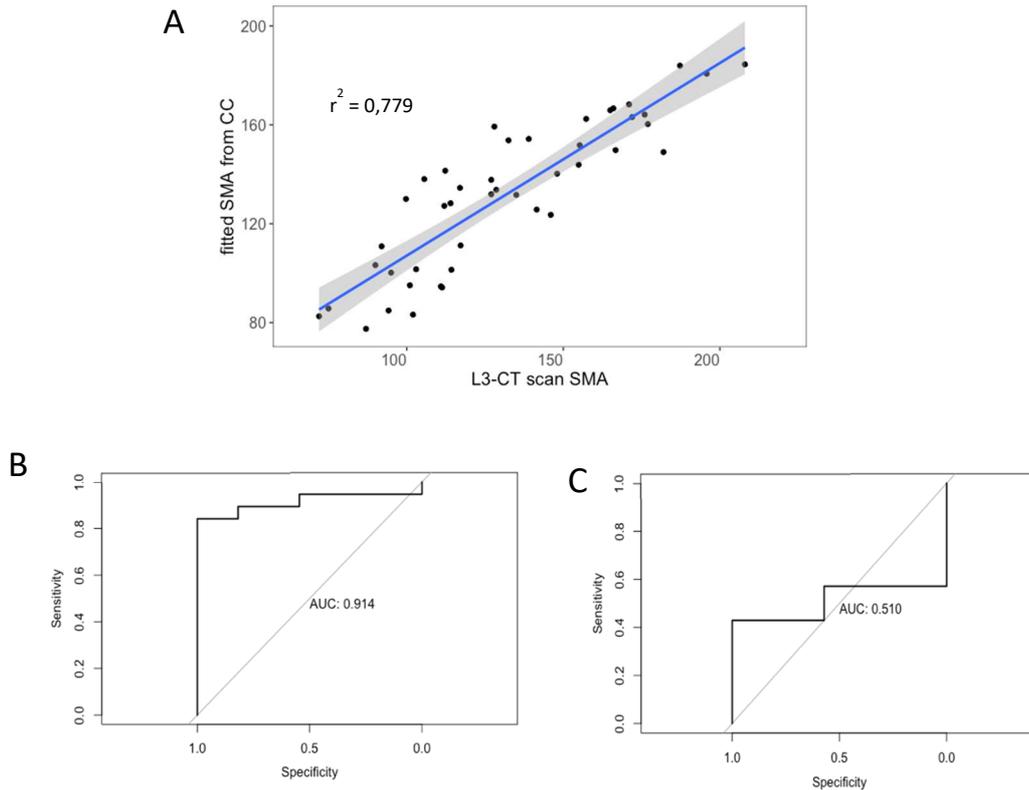
187

After linear modeling and stepwise selection, we proposed the following equation:

188
$$SMA = 74.3 + 0.52 \times CC + 29.5 \times Sex + 0.69 \times Weight - 0.79 \times age$$

189 with sex = 1 for men and 0 for women.

190 R^2 was 0.779 and the root mean square error (RMSE) 16.9 cm² (Figure 4A) and, after 5-fold
191 cross validation, R^2 was 0.739 and the RMSE 19.1 cm². Using these fitted values divided by
192 squared height enables to establish a CC-derived SMI. On ROC curve analysis of the ability of
193 this SMI_{CC} to detect low muscle mass, AUC was 0.914 for men (Figure 4B) with a threshold
194 value for low SMI of 49.7 cm²/m² for a sensitivity of 84 % and a specificity of 100%; for
195 women, AUC was 0.510 (Figure 4C) with a threshold value for low SMI of 40.3 cm²/m² for a
196 sensitivity of 43% and a specificity of 100%. Using these values, 13 patients [30%; 10 females
197 including all who had myopenia (71%) and 2 males with myopenia (6.6%)] were misclassified
198 (Fisher exact test, $p < 10^{-4}$).



199

200

Figure 4: Comparison of SMA determined by CT-scan or derived from CC ratio

201

A: Plot of the CC-ratio, weight, age and sex –derived SMA to SMA by CT-scan ($r = 0.779$). B, C: ROC curve

202

analysis for the capacity of CC-derived SMI to determine low LBM in men (B: AUC= 0.914, best threshold:

203

49.7 kg/m², sensitivity: 84%, sensibility: 100%) and in women (C: AUC= 0.510, best threshold: 40.3,

204

sensitivity: 43%, specificity: 100%).

205

SMA: Skeletal muscle surface area; SMI: Skeletal muscle index (SMA/height²)

206

AUC = area under curve, BIA = bioelectric impedance analysis, LBM = lean body mass, ROC = receiver

207

operating characteristics

208

Discussion:

209

In this study aiming at evaluating BIA and CC ratio performances for evaluating

210

muscle mass in cancer patients, our data show relatively good correlations between LBM

211 measured by these two methods and that evaluated from L3 CT-scan. However, the ability of
212 these two methods to detect myopenia, based on Prado's criteria, is moderate for BIA and
213 better for the CC ratio with, for the two methods, better performance for men than for
214 women.

215 In our study, we considered the L3 CT-scan as the reference method for LBM
216 determination in cancer patients. The use of single slice CT-scans has indeed been validated
217 against DXA, despite some studies reporting a strong correlation but weak agreement with
218 DXA [13]. This might be due to the fact that muscle surface at the L3 level does not always
219 reflect whole body composition, especially in patients with rapid weight loss. Still, L3 CT-scan
220 remains the most widely used technic for LBM determination in oncology probably due to its
221 high availability. However, its use for body composition monitoring remains limited as the
222 high radiation exposure prohibits its use outside the frame of disease progression
223 monitoring. In our patient population, the prevalence of low LBM, determined by this
224 method, is 59%, slightly higher in men (63%) than in women (50%). A recent systematic
225 review [2] including nearly 6 900 patients (mainly with digestive cancer) from 35 studies, 29
226 of which evaluated body composition by L3 CT-scan, revealed that about 39% of patients
227 had a low muscle mass before cancer treatment. Interestingly 65% of the studies for which
228 prevalence of sarcopenia was available by sex found a difference in prevalence of more than
229 20% between men and women. This systematic review also showed that patients with low
230 muscle mass had a poorer response to treatment. This highlights the importance of having
231 an accurate means of measuring LBM in order to be able to monitor its evolution throughout
232 the course of the disease and its treatment.

233 Discrepancies between BIA and CT-scan are a consistent issue in the assessment of
234 body composition. Bland-Altman concordance analysis of our data reveals poor agreement

235 between BIA and L3 CT-scan. The limits of agreement between BIA and CT-scan are wide
 236 representing approximately as much as 35% of the mean LBM of the population and BIA
 237 shows a mean overestimation of LBM of approximately 3 kg. Such result has been repeatedly
 238 described for example in patients with gastrointestinal cancer [14], in patients with or
 239 without esophageal cancer and a large range of BMI [15] or in critically ill patients [16].
 240 These results, confirmed on various populations, are not surprising as BIA already showed
 241 poor agreement with DXA in the original work by Mourtzakis et al. that initiated the use of
 242 L3-CT scan in cancer [4]. In fact, the accuracy of BIA's assessment of body composition is
 243 very dependent on the equations used to calculate the body compartments. The use of BIA
 244 in cancer patients is indeed sometimes discussed given the lack of available population-
 245 specific equations [7]. The common impedancemeter we used does not allow the full
 246 exploitation of the measured parameters and the non-disclosed equations of our device
 247 were used to calculate LBM from impedance values. These in-device equations are derived
 248 not only from subjects in apparent good health but also from a population aged less than 70
 249 years while 17 patients of our population (39%) are aged 70 y or older.

250 Discrepancies between BIA and CT-scan are further illustrated by ROC curve analysis
 251 revealing moderate performance of BIA to identify low muscularity in men (AUC = 0.675)
 252 and poor performance in women (AUC = 0.388). Despite these biases, it has been suggested
 253 that, used in the most standardized manner, BIA should be of use for the longitudinal follow
 254 up of the patient's body composition; however, this deserves to be evaluated.

255 How does the CC ratio work on its side? There is a statistically significant correlation
 256 between the CC ratio and the LBM determined from L3-CT scan ($r = 0.648$, $p = 2.0 \cdot 10^{-6}$) and
 257 according to ROC curve analysis CC ratio achieves better performance than BIA in classifying
 258 patients according to their muscularity (AUC = 0.813 and 0.673 in men and women

259 respectively). After linear regression with sex, weight and age in order to derive a CC ratio-
260 based SMI, the AUC even reached 0.914 in men but dropped to 0.510 in women. CC ratio has
261 been used as a proxy of muscle mass or sarcopenia in critically ill patients [9,17], in patients
262 with diabetes [18] and in apparently healthy subjects [19]. A correlation between the CC ratio
263 and different muscle mass evaluation parameters has been found in renal or lung transplant
264 patients [20,21] in critically ill [9,17], in colorectal cancer [22] or in elderly [23]. CC ratio has
265 been shown to be associated with disease severity in amyotrophic lateral sclerosis [10] or in
266 COPD [24]. One report showed the prognostic value of the CC ratio in cancer patients in
267 terms of treatment tolerance but body composition was not evaluated [25]. Of note, the
268 study by Kashani et al. clearly shows that lowered CC ratio is associated with a negative
269 outcome and increased hospital and 90-day mortality among critically ill patients. Our data
270 further extends the interest of the CC ratio to cancer patients in the assessment of muscle
271 mass. Two studies, respectively in elderly [23] and in type 2 diabetes [18] have evaluated the
272 performances of the CC ratio at detecting low appendicular muscle mass and obtained AUC
273 ranging from 0.505 to 0.683. Our results indicate even better performance in our patients'
274 population. Our results clearly show that the use of simple blood markers in the CC ratio
275 could have a better ability to evaluate the risk linked to LBM insufficiency than BIA.

276 Surprisingly, besides differences in performance between BIA and CC ratio,
277 performance of both methods markedly differs between males and females. These
278 differences are probably largely inherent to the techniques used and the choice of CT-scan
279 as the reference technique.

280 The use of the CT-scan is based on a linear relationship between the L3 muscle surface and
281 the appendicular muscle mass after normalization to the square of the height. Mourtzakis et

282 al [4] did not conduct separate regression analysis between DXA and single-slice CT scan for
283 males and females considering that sex does not impact the relationship. However, in their
284 study, they showed underestimation of LBM in patients with high LBM and overestimation in
285 others while their female patients had also lower LBM than males; we can wonder whether
286 the bias is proportional or sex-linked. Shen et al [26], in their study linking single cross-
287 sectional abdominal CT-scan areas and total skeletal muscle volume on magnetic resonance
288 imaging observed that sex was a statistically significant covariate of their regression model.
289 Another aspect linked to CT-scan is the choice of the thresholds for low muscle mass: we
290 have preferred to use the threshold values determined by Prado et al. [12] that correspond
291 to sex-specific cut-offs associated with mortality rather than those of Moutzarkis obtained
292 by extrapolation from literature data [4].

293 The most challenging issue with BIA is the need of population-specific equations. Our BIA
294 device did not give us access to the resistance and reactance parameters and we could not
295 derive our own equation. We also probably would have been statistically underpowered to
296 derive sex-specific equations.

297 Another limitation of our study is the relatively low number of patients included. The main
298 reason is the delay between scan and inclusion. Re-sampling the male population to limit the
299 number of inclusions to 14 still showed better correlation and diagnostic performance for
300 both BIA and CC in men than in women (data not shown). Nonetheless, a larger study is
301 required in order to validate our new equation in a control population.

302 Last, concerning the CC ratio, besides the influence of thyroid function or inflammation on
303 cystatin C, gender and fat mass appear as significant determinant of cystatin C plasma levels
304 with increased in cystatin C production by adipose tissues in obese patients [27,28].

305 However, the influence of the physiological gender-associated differences in adiposity is
306 unknown.

307 As a conclusion, CC ratio is a good surrogate for LBM in men and can predict low
308 muscle mass in patients with cancer. The lower accuracy of BIA and CC ratio in women needs
309 further investigation but could be linked to a difference of fat-mass repartition. Further
310 studies comparing CC ratio to DXA are needed. CC ratio seems a promising biomarker for
311 muscle mass. Its prognostic value for sarcopenia and survival deserves to be further
312 investigated.

313

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318 Conflict of interest

319 The authors have no conflict of interest to disclose relevant to this study

320 Funding

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322 Authors' contributions

323 GU is responsible for designing the study. GU and JK gathered data and performed
324 statistical analysis. GU and JPDB wrote the manuscript. All authors contributed to the
325 interpretation of the data and proof-reading the manuscript.

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327

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