



# **Creatinine-to-cystatin C ratio and bioelectrical impedance analysis for the assesement of low lean body mass in cancer patients: Comparison to L3-computed tomography scan**

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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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Abstract:

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

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

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

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

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

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

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

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

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  $LBM = 0.3 \times SMA + 6.06$

Indexing SMA to the squared height defines the skeletal muscle index (SMI). myopenia was 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 [12].

#### **Bio-impedance Analysis:**

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

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

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

### 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.



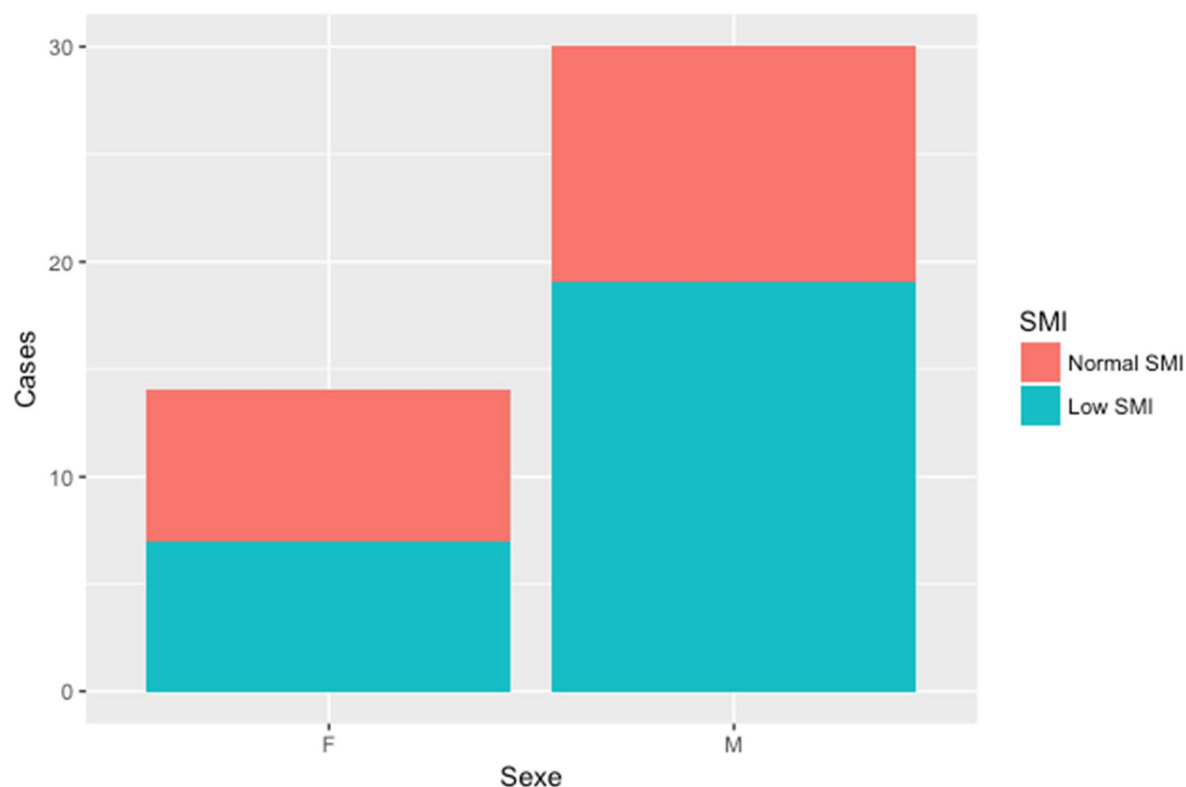
**Results:**

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

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

Table I: Main characteristics of the study population

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



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

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

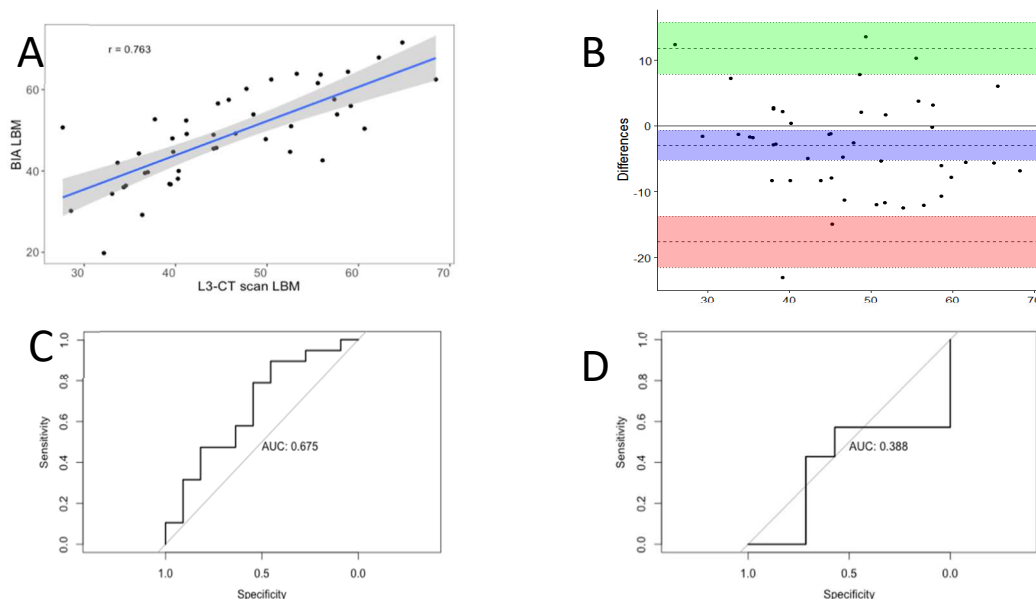
F: Female, M: Male, SMI: Skeletal Muscle Index

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

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.

Therefore, BIA tended to overestimate LBM compared to CT scan.

On ROC curve analysis to assess the ability of BIA to detect low muscle mass, AUC for men was 0.675 with, for a  $SMI_{BIA}$  threshold of 19.75 kg/m<sup>2</sup>, a sensitivity of 89% and a specificity of 45%; for women, AUC was 0.388 with two equivalent thresholds: 13.84 kg/m<sup>2</sup> (sensitivity 57% and specificity 57%) and 13.54 kg/m<sup>2</sup> (sensitivity 43% and specificity 71%). Although the proportions of patients with myopenia did not differ significantly between the two methods (Fisher exact test,  $p = 0.177$ ), the BIA resulted in misclassifying 14 patients [32%; 6 females (50%) and 8 males (27%)], resulting in 4 more male patients with myopenia and one less female patient.



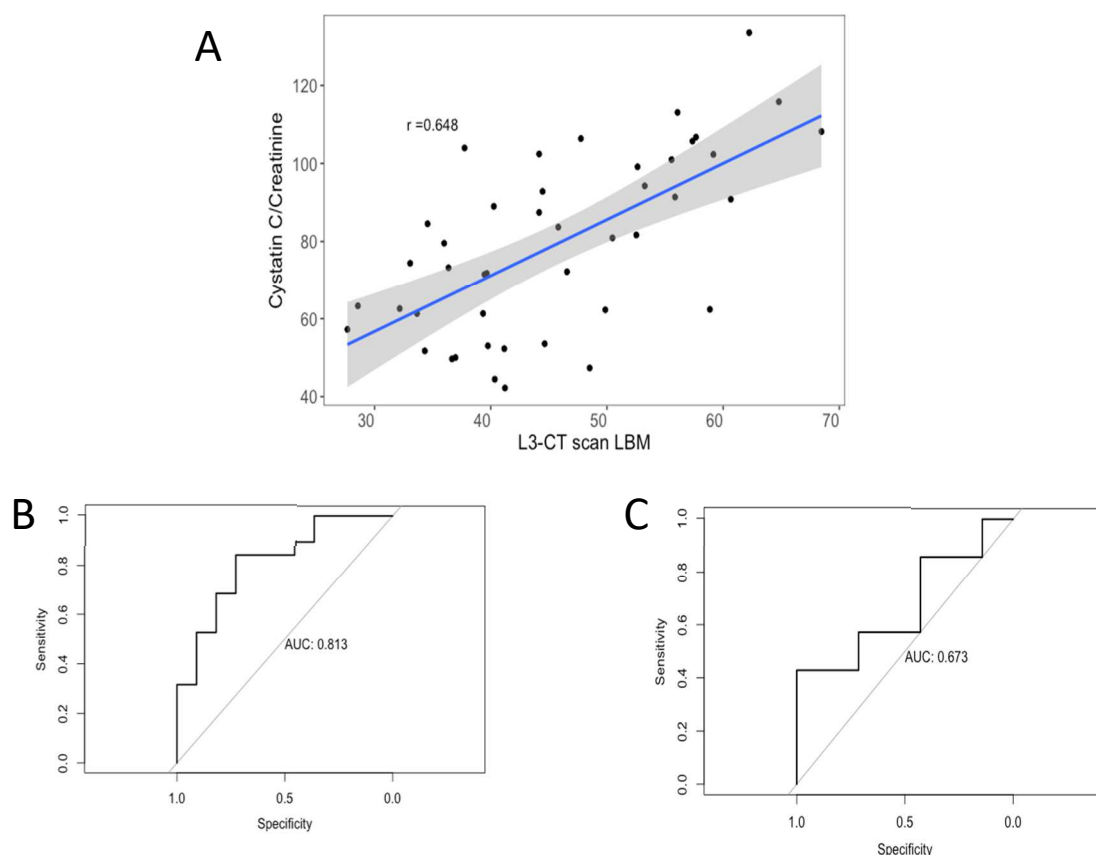
**Figure 2:** Comparison of LBM determined by CT-scan and BIA

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

analysis of the performance of BIA ( $LBM/height^2$ ) to detect low muscle mass in men (C: AUC= 0.675, best threshold: 19.75 kg/m<sup>2</sup>, sensitivity: 89%, sensibility: 45%) and in women (D: AUC= 0.388, best threshold: 13.84 or 13.54 kg/m<sup>2</sup> sensibility: 57 or 43% and specificity: 43 or 71% respectively).

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

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



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

*A: Correlation between LBM determined by L3-CT scan and the CC ratio ( $r = 0.648$ ,  $p < 10^{-6}$ ). 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: 96.7, sensitivity: 84%, sensibility: 72%) and for women (C: AUC= 0.673 , best threshold: 73.9, sensitivity: 43 %, specificity: 100%).*

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

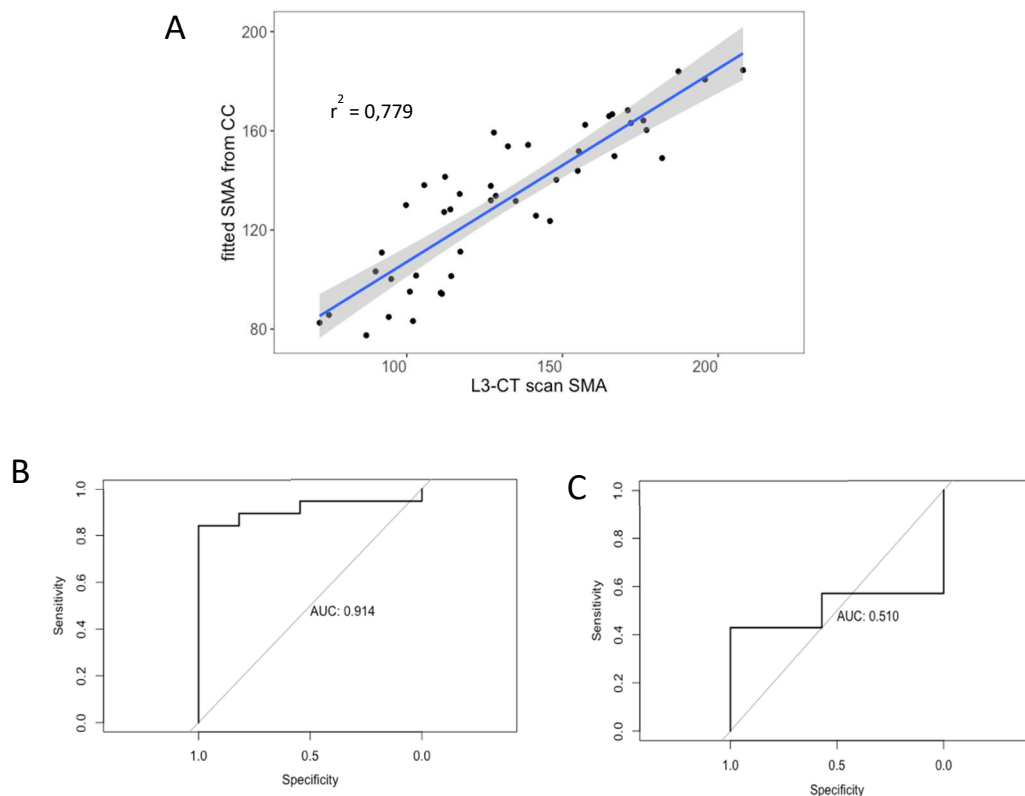
We derived an equation to calculate SMA from the CC ratio, weight, sex, age and height.

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

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

with sex = 1 for men and 0 for women.

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



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

*A: Plot of the CC-ratio, weight, age and sex –derived SMA to SMA by CT-scan ( $r = 0.779$ ). B, C: ROC curve analysis for the capacity of CC-derived SMI to determine low LBM in men (B: AUC= 0.914, best threshold: 49.7 kg/m<sup>2</sup>, sensitivity: 84%, sensibility: 100%) and in women (C: AUC= 0.510, best threshold: 40.3, sensitivity: 43%, specificity: 100%).*

*SMA: Skeletal muscle surface area; SMI: Skeletal muscle index (SMA/height<sup>2</sup>)*

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

## Discussion:

In this study aiming at evaluating BIA and CC ratio performances for evaluating muscle mass in cancer patients, our data show relatively good correlations between LBM

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

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

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



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

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

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

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

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

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

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

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

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

Last, concerning the CC ratio, besides the influence of thyroid function or inflammation on cystatin C, gender and fat mass appear as significant determinant of cystatin C plasma levels 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

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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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