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Correction of Intensity of Bone Involvement (IBI) Index by Lean Body Mass and Body Surface Area

Correção do Índice Intensity of Bone Involvement (IBI) pela Massa Magra Corporal e Área da Superfície Corporal

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Abstract

The Intensity of Bone Involvement (IBI) parameter is utilized to quantitatively assess bone involvement in PET/CT images of multiple myeloma (MM) patients, providing an objective and reproducible analytical approach. This study proposes the mathematical correction of IBI for lean body mass (LBM) and body surface area (BSA) in ^{18}F-FDG PET/CT images of MM patients. Beyond the corrections, our aim is to evaluate the correlation of corrected IBIs and visual image analysis, along with their relationship with overall patient survival.

Methods: This retrospective study analyzed ^{18}F-FDG PET/CT images and clinical data from 73 MM patients. LBM was calculated using the James and Janma models, while BSA was calculated using the DuBois model. The conventionally calculated IBI parameter was then corrected for LBM and BSA. Three experienced nuclear medicine physicians visually classified the intensity of bone involvement as: negative, mild, moderate, marked, and very marked. We compared standard IBI and corrected indices with visual classification using Kruskal-Wallis test and Dunn's post-hoc test. Cox proportional hazards regression analysis was employed to test the association with overall patient survival. Statistical significance was established for p-values <0.05. Results: A positive relationship was observed between both standard IBI and its corrected values with visual image classification. No statistically significant association was found between IBI values and overall patient survival. Conclusions: IBI corrected for both LBM or BSA exhibited similar performance to standard IBI compared to visual image classification. However, IBI values (both standard and its corrections) were not associated with overall survival (OS) in our study.

Keywords: multiple myeloma; ^{18}F-FDG PET/CT; IBI; lean body mass; body surface area.

Resumo

O parâmetro Intensity of Bone Involvement (IBI) é empregado para quantificar o envolvimento ósseo em imagens PET/CT de pacientes com mieloma múltiplo (MM), proporcionando uma abordagem analítica objetiva e reprodutível. Este estudo propõe a correção matemática do IBI para massa corporal magra (MCM) e área de superfície corporal (ASC) em imagens PET/CT ^{18}F-FDG de pacientes com MM. Além das correções, objetivamos avaliar a correlação dos IBIs corrigidos com a análise visual da imagem e sua relação com a sobrevida global dos pacientes.

Métodos: Este estudo retrospectivo utilizou imagens PET/CT ^{18}F-FDG e dados clínicos de 73 pacientes com MM. Os modelos de James e Janma foram usados para calcular a MCM, enquanto o modelo de DuBois foi usado para calcular a ASC. O parâmetro IBI calculado de modo convencional foi então corrigido por MCM e ASC. Três médicos nucleares experientes classificaram visualmente a intensidade de comprometimento ósseo em: negativo, leve, moderado, acentuado e muito acentuado. Comparamos IBI padrão e os índices corrigidos com a classificação visual usando o teste de Kruskal-Wallis e teste post-hoc de Dunn. A análise de regressão de riscos proporcionais de Cox testou a associação com a sobrevida global dos pacientes. A significância estatística foi considerada para valores de p <0,05. Resultados: Houve relação positiva entre o IBI padrão e seus valores corrigidos com a análise visual das imagens. Não houve associação estatisticamente significativa entre os valores do IBI e a sobrevida global dos pacientes. Conclusões: O IBI corrigido por MCM e ASC teve desempenho semelhante ao do IBI padrão na relação com a classificação visual das imagens. No entanto, os valores do IBI (tanto o padrão quanto suas correções) não se mostraram associados à sobrevida global (SG) em nosso estudo.

Palavras-chave: *mieloma múltiplo; ^{18}F-FDG PET/CT; IBI; massa corporal magra; área de superfície corporal.*

1. Introduction

Multiple myeloma (MM) is a hematologic neoplasm characterized by the proliferation of clonal malignant plasma cells in the bone marrow microenvironment, the presence of monoclonal protein in the blood and/or urine, and association with organ dysfunctions, recognized by the acronym CRAB: hypercalcemia, renal failure, anemia, and bone lesions (1,2). Bone disease constitutes the primary cause of morbidity and mortality, significantly impacting the patient's quality of life. It is observed in approximately 80% of newly diagnosed MM cases and is linked to lytic lesions or osteopenia, resulting in severe pain,

pathological fractures, spinal cord compression, and vertebral collapse (1,3,4).

Given that early detection prevents the progression of osteopenia and defines the most appropriate treatment management, diagnostic imaging methods with high sensitivity and specificity in identifying osteolytic lesions are crucial for determining an efficient clinical treatment (4). In this regard, anatomical images provided by nuclear magnetic resonance (MRI) and hybrid imaging through positron emission tomography/computed tomography (PET/CT) with [18F] fluorodeoxyglucose (^{18}F-FDG) are the most recommended (3,5).

Due to its ability to distinguish metabolically active and inactive sites of disease and provide information indicating bone damage earlier than an MRI scan, ^{18}F-FDG PET/CT is considered a gold standard technique for assessing and monitoring the response to antimyeloma treatment (2,5). However, challenges persist in standardizing and ensuring interobserver reproducibility of imaging criteria in result interpretation (5). In this context, the Intensity of Bone Involvement (IBI) metabolic index was created to offer a numerical parameter for quantifying bone and bone marrow involvement. This aims to enhance the objectivity and reproducibility of the analysis (6). IBI is calculated by multiplying the percentage of bone involvement (PBI) by the average standardized uptake value (SUV) of the volume of interest (6). PBI is calculated as the volume of the skeleton with 18F-FDG uptake above hepatic uptake, divided by the total volume of the segmented skeleton (6).

The SUV calculation (7), in turn, is determined by the ratio of radiopharmaceutical activity concentration in the region of interest (ROI) to the fraction corresponding to the administered dose. Subsequently, it is divided by the patient's total body weight.

Although SUV normalized for gross body weight is the most popular method in daily clinical practice, this metric presents inconsistencies due to its high dependence on the patient's body size, specifically on weight and body fat content. Since white adipose tissue is metabolically less active, its ^{18}F-FDG uptake is minimal, potentially leading to an overestimated SUV result for obese patients (7,8). As IBI is dependent on SUV, it is also subject to limitations associated with the use of total body weight. Therefore, two correction factors, lean body mass (LBM) and body surface area (BSA), can be employed to mitigate SUV's dependence on the patient's total body weight (7,9)

This study presents a proposal for the application of mathematical corrections to IBI based on lean body mass and body surface area. Following the proposed corrections, we assessed the correlation of the corrected IBIs with visual image analysis and also their relationship with overall patient survival.

2. Materials and Methods

This retrospective analysis utilized clinical and imaging data previously collected in research carried out by our group (6, 10-12). We used data from 73 patients diagnosed with MM who underwent whole-body ^{18}F-FDG PET/CT examinations at the onset of their treatment at the Clinical Hospital of the University of Campinas between June 2013 and September 2018.

The patients were instructed to fast for a minimum of 6 hours. All scans covered the entire body, following the standard protocol for multiple myeloma at our center. Image acquisition commenced 60 minutes after injecting 0.12 mCi/kg of ^{18}F-FDG, using a Biography mCT40 PET/CT scanner from Siemens Medical, USA. The CT portion of the study utilized parameters of 120–140 kV, 120 mA, transaxial FOV 700 mm, rotation time of 0.8 s, and a slice thickness of 2.1 mm. Emission scans were conducted in a 3D mode, with 1.5 minutes per bed position. PET images were reconstructed using a standard iterative algorithm (3D-OSEM + PSF + TOF with 2 iterations and 21 subsets), with CT data employed for attenuation correction and image fusion. Corrections for dead-time, decay, and randoms were also performed.

These patients had previously undergone IBI and PBI calculations. PBI was determined using liver SUV as a threshold, and at that time, SUV was calculated based on patient body weight.

The characteristics of the patients included in the study are presented in Table 1.

Table 1. The characteristics of the patients included in the study.

Number of patients	73
Male Female	42 (57.5%) 31 (42.5%)
Height [cm] *mean±SD* *(mIn-max)*	 162.6±9.1 (141.0-183.0)
Weight [kg] *mean±SD* *(min-max)*	 67.1±15.4 (40.0-116.0)
Body Mass Index (BMI) *mean±SD* *(min-max)*	 25.3±5.3 (14.7-45.3)
Obesity (BMI>30)	12 (16.4%)

Source: The authors (2024).

To estimate lean body mass, two models were employed. The first is the *James* (8,13) model, which calculates LBM using equation 1.

$$LBW_{James} = \begin{cases} 1.1 * (Weight) - 128 \cdot \left(\frac{Weight}{Height}\right)^2, for\ men \\ 1.07 * (Weight) - 148 \cdot \left(\frac{Weight}{Height}\right)^2, for\ women \end{cases} \quad (1)$$

The second model is the *Janma* (8,14) model, which calculates LBM using equation 2.

$$LBW_{Jamma} = \begin{cases} \frac{9270*(Weight)}{6680+216 \cdot BMI}, for\ men \\ \frac{9270*(Weight)}{8780+244 \cdot BMI}, for\ women \end{cases} \quad (2)$$

BSA was obtained using the model proposed by DuBois (15), according to equation 3

$$BSA\ (m^2) = (W)^{0.425} \cdot (H)^{0.725} \cdot 0.007184 \quad (3)$$

where W=weight and H=Height.

The IBI values, corrected using LBM obtained through the *James* (8,13) model, were calculated as demonstrated in equation 4.

$$IBI_{James} = PBI \cdot SUV_{james}$$
$$IBI_{James} = PBI \cdot \left[SUV \cdot \left(\frac{LBW_{James}}{Weight}\right)\right]$$
$$IBI_{James} = IBI \cdot \left(\frac{LBW_{James}}{Weight}\right) \quad (4)$$

Using a similar deduction to IBI_{James}, the IBI_{Janma} and IBI_{BSA} values were obtained through equations 5 and 6, respectively.

$$IBI_{Janma} = IBI \cdot \left(\frac{LBW_{Janma}}{Weight}\right) \quad (5)$$

$$IBI_{BSA} = IBI \cdot \left(\frac{BSA}{Weight}\right) \quad (6)$$

Individual ^{18}F-FDG PET/CT images were visually analyzed by three skilled nuclear medicine physicians and categorized into five groups: negative bone involvement, mild bone involvement, moderate bone involvement, marked bone involvement and very marked bone involvement.

Visual analysis was conducted exclusively for this study. A blind analysis was performed by two experts. In the event of a disagreement in the category, a third expert carried out a blind analysis to 'break the tie' in the classification.

The non-parametric *Kruskal-Wallis* test, followed by the *Dunn's post-hoc* test was employed to assess whether there is a relationship between the IBI values and the visual analysis of the PET/CT images. Dunn's post-hoc test is a statistical tool used to pinpoint specific group differences after a comprehensive analysis reveals that, overall, at least one group is statistically distinct from the others

Cox proportional hazards regression analysis was used to examine associations between IBI (standard and corrected) and mortality. Statistical significance was considered for p-values < 0.05. The Cox regression analysis was performed using Stata software version 12.0 (StataCorp LP®). Overall survival (OS) was determined as the duration (in months) from the date of diagnosis to the date of death (for deceased patients) or the last consultation (for censored patients). The data were collected from the medical records of the patients included in this study and can be found in the supplementary material that accompanies this manuscript.

This study was approved by the University of Campinas Ethics Committee (CAAE Number: 97966618.5.0000.5405) and was conducted in accordance with the Helsinki Declaration.

3. Results

BSA and LBM corrections for the IBI index were feasible for all patients included in this study.

Figure 1 illustrates the corrected IBI values in two examples of patients who share the same visual classification and have standard IBI values in the same order of magnitude but markedly different body weight.

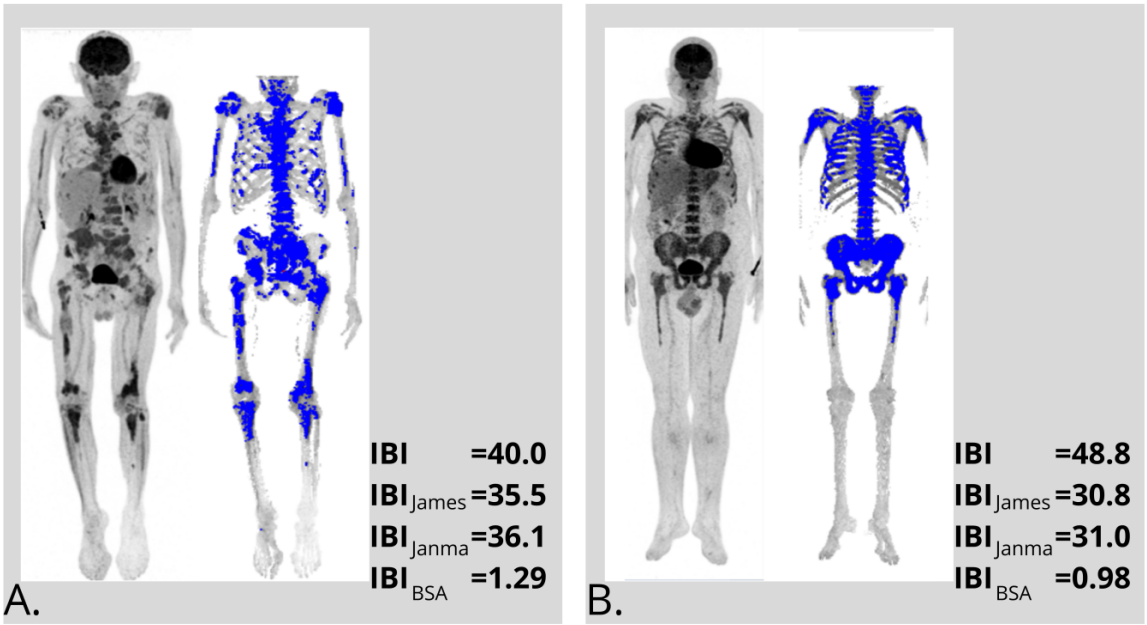

Figure 1. Corrections of Intensity of Bone Involvement (IBI) for two patients diagnosed with multiple myeloma, each exhibiting distinct body weights, both visually categorized with marked bone involvement. IBI was corrected for lean mass (LBM), using the *James* (IBI_{James}) and *Janma* (IBI_{Janma}) models, and for body surface area (IBI_{BSA}). **(A)** represents a male patient weighing 47 kg (BMI=16.7 kg/m^2). **(B)** features a male patient weighing 116 kg (BMI=41 kg/m^2). The left side of **A** and **B** displays maximum intensity projection (MIP) from ^{18}F-FDG PET/CT images, while the highlighted blue areas on the right indicate metabolically active regions where ^{18}F-FDG uptake exceeds hepatic uptake. Notably, after LBM and BSA corrections, the patient in **B**, with a higher body weight and higher standard IBI, presented lower corrected IBIs than the patient on **A**, who had a lower body weight.

The descriptive statistical analysis of the corrected IBI values in relation to their standard values is presented in Table 2. Overlaid histograms of the standard and James- and Janma-corrected IBI values are displayed on the left side of Figure 2, while the distribution of IBI values for BSA correction is presented on the right side.

In the visual analysis conducted by three skilled nuclear medicine physicians, 10 images (13.7%) were classified as negative bone involvement, 23 images (31.5%) as mild bone involvement, 19 images (26.0%) as moderate involvement, 11 images (15.0%) as marked bone involvement, and 10 images (13.7%) as very marked bone involvement. The mean values of the standard IBI and the corrected IBI for each image group are presented in Table 3.

All IBI values (standard and the corrected ones) showed a significant relationship with the visual analysis of the images ($p<0.05$) (Table 4). On the other hand, in the *post-hoc Dunn* test, it was not possible to distinguish the groups with negative/mild and moderate bone involvement in the proposed scenarios.

Table 2. Mean, standard deviation, and amplitude values of the standard IBI and the corrected IBI for 73 MM patients.

	$IBI_{standard}$	IBI_{James}	IBI_{Janma}	IBI_{BSA}
Mean±SD	11.0 ± 20.1	8.5 ± 16.4	8.5 ± 16.2	0.29 ± 0.54
Median	3.79	2.83	2.75	0.10
(Minimum-Maximum)	0.0 - 135.33	0.0 - 112.03	0.0 - 111.29	0.0 – 3.65

Source: The authors (2024).

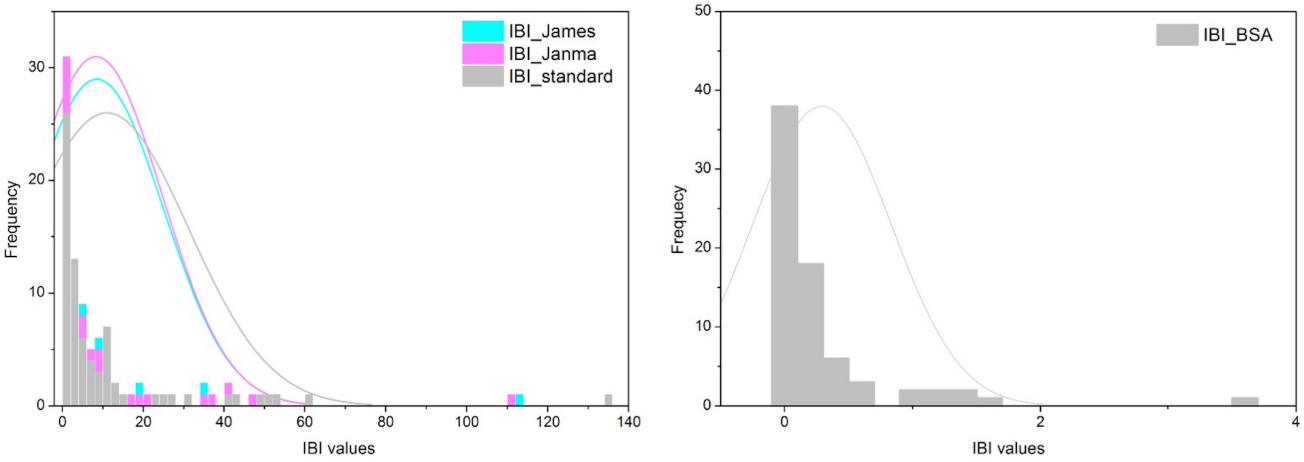

Figure 2. On the left are the overlaid histograms of IBIstandard, IBIJames, and IBIJanma. For the James and Janma corrections, a slight leftward shift of the data in the histogram is observed, reflecting a decrease in the absolute values of the IBI. The histogram for IBI_{BSA} is shown on the right, where a distinct range of values is noticeable, exhibiting a smoother decline in values compared to the others.

Table 3. Mean, standard deviation, minimum and maximum values of the standard IBI and the corrected IBI for all five different image groups.

Group	**$IBI_{standard}$** mean±SD; (min-max)	**IBI_{BSA}** mean±SD; (min-max)	**IBI_{James}** mean±SD; (min-max)	**IBI_{Janma}** mean±SD; (min-max)
Negative *(n=10)*	0.91±1.2; (0.0-3.41)	0.03±0.03; (0.0-0.10)	0.70±0.95; (0.00-2.8)	0.65±0.95; (0.00-2.8)
Mild *(n=23)*	3.2±2.4; (0.4-9.3)	0.08±0.06; (0.01-0.24)	2.4±1.8; (0.23-7.24)	2.3±1.8; (0.23-7.15)
Moderate *(n=19)*	5.3±3.9; (0.8 - 12.0)	0.13±0.10; (0.02-0.33)	3.8±3.0; (0.5-9.5)	3.6±2.9; (0.5-9.5)
Marked *(n=11)*	15.1±11.5; (0.0 - 42.1)	0.40±0.32; (0.0 - 1.2)	11.5±9.5; (0.0 - 34.6)	10.9±9.3; (0.0 - 34.4)
Very Marked *(n=10)*	45.6±36.8; (0.0 - 135.3)	1.21±0.99; (0.0 - 3.7)	36.4±30.8; (0.0 - 112.0)	36.2±30.1; (0.0 - 111.3)

Source: The authors (2024).

Table 4. p-values of Kruskal-Wallis test

	p-value
$IBI_{standard}$	p=1,660×10-7*
IBI_{BSA}	p=2,226×10-7*
IBI_{James}	p=3,620×10-7*
IBI_{Janma}	p=3,932×10-7*

**Post-hoc de Dunn*: Negative/mild bone involvement group differs from the marked group; and the moderate bone involvement group differs from the severe group.
Source: The authors (2024).

Table 5. Univariate Cox regression for overall survival.

	Hazard Ratio (HR)	Standard Error (SE)	z	P>z	[95% Conf. Interval]	
IBI_{BSA}	0.8583125	0.3008874	-0.44	0.663	0.43176783	1.70624
IBI_{James}	0.9957643	0.0112986	-0.37	0.708	0.9738638	1.018157
IBI_{Janma}	0.995882	0.0113342	-0.36	0.717	0.9739133	1.018346
$IBI_{standard}$	0.996859	0.009059	-0.35	0.729	0.9792608	1.014773

Source: The authors (2024).

Neither the standard IBI nor its corrections for BSA and LBM were associated with overall survival (OS) for the MM patients (Table 5).

4. Discussion

The lean body mass and body surface area IBI corrections were feasible in all patients included in this study. In extreme cases, corrected values may change the severity ranking among patients. Regarding these two possible correction approaches, even though both indexes have remarkably reduced dependence on body weight, Sugawara et al (9) recommend using SUV_{LBM} (SUV correction for LBM) rather than SUV_{BSA} (SUV correction for BSA). This recommendation stems from the fact that body surface area has units for area (meters squared), whereas lean body mass has units for mass (kilograms), similar to those for body weight. In other words, the SUV_{LBM} is similar in magnitude to the conventional/standard SUV, whereas the SUV_{BSA}, that is not similar in magnitude, may not be ideally comparable (9).

In this sense, two corrections models for LBM stand out: the *James* (8,13) and the *Janma* (8,14) models. The body mass index (BMI) is used by both models in its equations, since it is more indicative of actual fat content than body weight. Although *James* (8,13) model is the most widely used for SUV correction, having even been implemented in a variety of commercially available PET/CT scanners, its equation might be prone to significant inaccuracy when a patient's BMI exceeds a critical value (approximately 43 for men and 37 for women). For this reason, in order to improve SUV consistency for patients with high BMI, an improved model was developed, which was proposed in the *Janma* equation (8,14).

Concerning the relationship between the IBI values and the visual classification of bone involvement, the corrected IBI values achieved the same performance as the standard IBI, and all of which showed a significant relationship with the visual analysis. So, at first, the index correction does not result in significant differences among the patients evaluated in this work. Furthermore, in all proposed scenarios, the groups with marked and very marked bone involvement achieved significantly higher IBI values than the other groups, corroborating the IBI's ability to make the image analysis more objective and reproducible by enabling the classification of patients in situations of extensive and/or intense disease. However, it was not possible to distinguish the negative/mild and moderate groups from each other, which may be linked to the subjectivity of the visual analysis. Also, the overall survival (OS) analysis, using the IBI values, did not result in statistically significant data.

Since this is a retrospective study, one of its limitations was the impossibility of tracking the data collection methodology regarding the patients' body weight and height included in the clinical records. It is possible that the values are not accurate, for example, with the self-reported weight and height being registered by the bedridden patients instead of being measured by metrology instruments, what may change the precision of lean mass and body surface area estimations. Also, the error associated with IBI and PBI was not calculated. Future studies using phantoms are necessary to estimate the order of magnitude of these uncertainties.

5. Conclusion

In this study, we corrected the IBI index by the LBM and BSA using *James*, *Janma* and *DuBois* models. Corrected IBI showed the same performance as the standard IBI regarding the visual classification of images. Moreover, according to the analysis, the IBI values (both standard and its corrections) were not associated with the overall survival (OS) in the present study.

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