

# FDG PET/CT for Initial Staging of Diffuse Large B-Cell Lymphoma: Is Diffuse Bone Marrow Uptake a Reflection of Disease Involvement?

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## Abstract

**Objectives:** Bone marrow assessment is a diagnostic challenge in staging diffuse large B-cell lymphoma (DLBCL). Diffuse bone marrow uptake (BMU) can be observed on FDG PET/CT performed for initial staging of DLBCL, but remains difficult to analyze. The aim of this study was to evaluate the meaning of this diffuse BMU, and especially to assess its correlation with bone marrow involvement (BMI).

**Methods:** Patients who underwent FDG PET/CT for initial staging of DLBCL were analyzed. Diffuse BMU was assessed using a visual qualitative analysis according to liver uptake (grade 1=below liver uptake, 2=equal to liver uptake, 3=above liver uptake), and a semi-quantitative analysis, by measurement of maximum standardized uptake value (SUV) in the sacral promontory. We compared the BMU with BMI, parameters of disease extension and inflammatory markers.

**Results:** 86 patients (median age 59, range: 19-91, 54 men, 32 women) were included. BMU grade was 1, 2 and 3 in 45, 28 and 13 cases respectively. Bone marrow was considered involved in 13 patients. No statistical correlation was found between diffuse BMU and BMI, using qualitative ( $p=0.594$ ) or semi-quantitative method ( $p=0.116$ ). Diffuse BMU visual grading was correlated with inflammatory markers: biological systemic symptoms ( $p=0.003$ ), CRP ( $p=0.002$ ) and fibrinogen ( $p=0.020$ ).

**Conclusions:** Our study suggests that a diffuse BMU seen on FDG PET/CT at initial staging of DLBCL is not representative of bone marrow involvement, but can be due to inflammatory changes.

**Keywords:** Diffuse large B-cell lymphoma; Positron emission tomography; <sup>18</sup>F-fluorodeoxyglucose; Bone marrow involvement; Diffuse bone marrow uptake

## Introduction

It is now well established that positron emission tomography (PET) using <sup>18</sup>F-fluorodeoxyglucose with computed tomography (FDG PET/CT) has a major role in management of diffuse large B-cell lymphoma (DLBCL), especially for therapeutic evaluation but also for initial staging [1]. Indeed, pre-treatment FDG PET/CT is able to detect an additional number of DLBCL sites compared to conventional staging methods, resulting in a modification of stage in about 15-20% of patients with an impact on management in about 5-15% [2].

Bone marrow assessment is a key point in staging lymphomas. Indeed, bone marrow infiltration, which is found in 10-30% of patients, upgrades the disease to stage IV, affecting both treatment and prognosis [3-6]. Iliac crest bone marrow biopsy (BMB) remains the standard procedure for the detection of bone marrow involvement (BMI) [7]. However, this is an invasive procedure, which allows the analysis of only a very limited area, and therefore associated with a high rate of false-negative results [8,9]. Several studies evaluated FDG PET/CT for the detection of BMI in non-Hodgkin's lymphoma (NHL), with discordant results. Recently, Hong et al. concluded in a limited value of PET/CT to detect BMI in patients with DLBCL; half of their patients with positive BMB had negative PET/CT [10]. On the opposite, recent meta-analyses showed a real interest: one of them suggested PET/CT could be more interesting for detection of BMI in aggressive NHL, with a pooled sensitivity of 74%, than in indolent NHL, where it was only 46% [11]. Another one reported pooled sensitivity and specificity for the detection of DLBCL BMI of 88.7% and 99.8% respectively, suggesting a positive FDG-PET could obviate the need for BMB [12]. However, most of these studies have only investigated focal FDG uptakes [13].

On the other hand, diffuse bone marrow uptake (BMU) is also frequently observed at initial staging and can be difficult to interpret. In a previous paper, we showed that diffuse BMU at initial staging of Hodgkin lymphoma (HL) was more likely due to bone marrow inflammatory change than to BMI [14]. The question arises whether this is the case in DLBCL, knowing that DLBCL is a less inflammation provider disease than HL.

So, the aim of our study was to clarify the meaning of FDG PET/CT diffuse BMU in pre-treatment staging, and especially in comparison with bone marrow involvement, disease extension parameters and inflammatory markers.

## Materials and Methods

### Patients

We analysed retrospectively the data from patients who underwent FDG PET/CT for initial staging of histologically proven DLBCL at the University Hospital of Brest between February 2006 and May 2012. All

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patients underwent FDG PET/CT before the first line of chemotherapy. Patients with medical history of lumbar or pelvic irradiation were excluded, as well as patients who received injection of granulocyte colony stimulating factor (G-CSF) during the previous month. Patient characteristics, including Ann Arbor stage, clinical and biological symptoms, presence of bone foci on FDG PET/CT, leukocyte count, C-reactive protein (CRP), fibrinogen, lactate dehydrogenase (LDH),  $\beta$ 2-microglobulin, and BMB results, were collected.

### FDG PET/CT acquisition

All scans were performed on a Gemini GXLi PET/CT scanner (Philips, Eindhoven, The Netherlands). Patients were fasting at least 4 hours, with a blood glucose level which had to be less than 8 mmol/l before the injection of approximately 370 MBq (10 mCi) (4-6 MBq/kg) of  $^{18}\text{F}$ FDG. PET and CT imaging were performed after a period of approximately 60 min, during which patients remained in a quiet room. No muscle relaxants were administered, and patients were allowed to breathe normally during PET and CT acquisitions. PET data were acquired in a three-dimensional (3D) mode from skull base to upper thigh, reconstructed using a row action maximum-likelihood algorithm (RAMLA) iterative, with or without the attenuation correction, using CT data. The Gemini scanner consists of a six-slice multidetector-row spiral CT scanner with a transverse field of view (FOV) of 600 mm. The CT parameters; a collimation of  $6 \times 3$  mm, tube voltage of 120 kV, and effective tube current of 100 mAs are standard for PET/CT studies and allow a good differentiation between the tissues, with a good spatial resolution while ensuring that the patient does not receive a high radiation dose. The acquired images (PET, CT and PET/CT fusion) were reviewed in axial, sagittal and coronal reformatting.

### Bone marrow uptake analysis on FDG PET/CT imaging

BMU was evaluated using visually and semi-quantitative method. Diffuse BMU level was visually evaluated in homogeneous areas, mainly thoracic spine, graded according to liver uptake (1=below liver uptake, 2=equal to liver uptake, 3=above liver uptake). Presence or absence of bone focal uptakes was also reported.

The semi-quantitative method consisted in a calculation of the maximum standardized uptake values (SUV) using a region of interest (ROI) drawn manually on the sacral promontory, using CT data for anatomical location.

### Statistical analysis

The visual BMU level and sacral SUV were statistically compared to patient characteristics like age, parameters reflecting extent of disease (Ann Arbor staging, LDH,  $\beta$ 2-microglobulin), presence of bone foci on FDG PET/CT, bone marrow biopsy, and parameters reflecting inflammatory activation (clinical and biological symptoms, leukocyte count, CRP and fibrinogen).

Comparison between groups of BMU level was performed using a Fisher's exact test for qualitative parameters and non-parametric Kruskal-Wallis test for quantitative parameters. The analysis of SUV was performed with Mann-Whitney test for qualitative data and Spearman's rank correlation test for quantitative data.

Performance of FDG PET diffuse BMU to detect bone/bone marrow involvement was also assessed. We took into account a composite gold standard for BMI, determined on the basis of histology, imaging (MRI, CT or FDG PET for bone/bone marrow assessment) and follow-up. Indeed, we considered the results of unilateral BMB,

but also presence of bone focal lesions on imaging. In particular, we considered that patients with  $^{18}\text{F}$ -FDG PET bone focal uptakes had bone marrow involvement, if targeted biopsy was positive or if follow up demonstrated response to chemotherapy (even if iliac crest bone marrow biopsy was initially negative).

Therefore, diffuse BMU was considered as a true-positive (TP) to detect bone/bone marrow involvement, if the involvement was confirmed by histopathology or by the presence of focused lesions on conventional imaging or FDG PET which were modified after treatment (progression or response of initial focal lesion region confirmed in the follow-up). The absence of diffuse BMU was considered to be false-negative (FN) if bone/bone marrow involvement was positive by histopathology or by imaging method plus follow-up. A false-positive (FP) was a diffuse BMU and negative findings on histopathology or imaging modalities. A true-negative (TN) was defined as the absence of diffuse BMU with negative findings on histopathology or imaging modalities.

## Results

### Patient characteristics

86 patients (32 female, 54 male, median age 59, range: 19-91 years) were analysed. Ann Arbor stage and presence of clinical and biological symptoms were collected for all patients. Leukocyte count (n=80), CRP (n=79), fibrinogen (n=70), LDH (n=82),  $\beta$ 2 microglobulin (n=32) and BMB results (n=31) were also collected. All those characteristics are summarized in Table 1.

### BMI evaluation

4 of the 31 patients (13%) who underwent BMB presented a lymphomatous involvement. Among the 4 positive BMB, 3 consisted of large cells, and 1 of small cells.

We observed bone focal uptakes for 10 patients (12%), one of which was in the group of positive BMB, one had a guided biopsy confirming disease, and 8 had decreased or disappeared focal uptakes

Characteristics	Distribution
Sex (n=86)	
Male	54 (63%)
Female	32 (37%)
Ann Arbor classification (n=86)	
I	24 (28%)
II	14 (16%)
III	14 (16%)
IV	34 (40%)
Systemic symptoms	
A/B (n=80)	66 (82%) /14 (18%)
a/b (n=78)	30 (38%) /48 (62%)
Bone foci on $^{18}\text{F}$ -FDG PET (n=86)	
Yes	10 (12%)
No	76 (88%)
Bone marrow involvement on biopsy (n=31)	
Yes	4 (13%)
No	27 (87%)
<b>Parameters</b>	<b>in Mean <math>\pm</math> SD</b>
Leukocyte count/mm <sup>3</sup> (n=80)	7797 $\pm$ 2579
CRP, mg/L (n=79)	33.3 $\pm$ 48.6
Fibrinogen, g/L (n=70)	4.61 $\pm$ 1.64
LDH, IU/L (n=82)	596 $\pm$ 557
$\beta$ 2-microglobulin, mg/L (n=32)	2.85 $\pm$ 1.38
CRP: C-reactive protein; LDH: Lactate dehydrogenase; SD: Standard deviation	

Table 1: Patient characteristics.

on follow-up. So, according to the defined gold standard, bone marrow was considered involved for 13 patients (15%).

### Qualitative analysis of BMU

Diffuse BMU was visually graded according to liver uptake as grade 1 for 45 patients (52%), grade 2 for 28 patients (33%) and grade 3 for 13 patients (15%). Figure 1 shows an example of each grade. Table 2 shows the repartition of patient characteristics in these 3 groups.

No statistical correlation was found between BMU level and BMI ( $p=0.594$ ). Among the 13 patients with BMI, 7 were in group 1, 3 in group 2 and 3 in group 3. Figures 2 and 3 show examples of discordant results between BMU and BMI. There wasn't either any correlation between diffuse BMU and presence of bone foci ( $p=0.587$ ) (Figure 4) or with BMB results ( $p=0.414$ ). No statistical correlation was found between BMB positivity and the presence of bone foci ( $p=0.999$ ); 1 patient among the 4 (25%) with positive BMB and 3 among the 27 (11%) with negative BMB had bone foci.

About disease extension parameters, we found a correlation between BMU level and LDH ( $p=0.034$ ), but not with Ann Arbor stage ( $p=0.300$ ) or  $\beta$ 2-microglobulin ( $p=0.115$ ). On the other hand, we found a statistical correlation with nearly all inflammatory markers; biological systemic symptoms ( $p=0.003$ ), CRP ( $p=0.002$ ) (Figure 5) and fibrinogen ( $p=0.020$ ). We also found a correlation between diffuse BMU and patient age ( $p=0.037$ ).

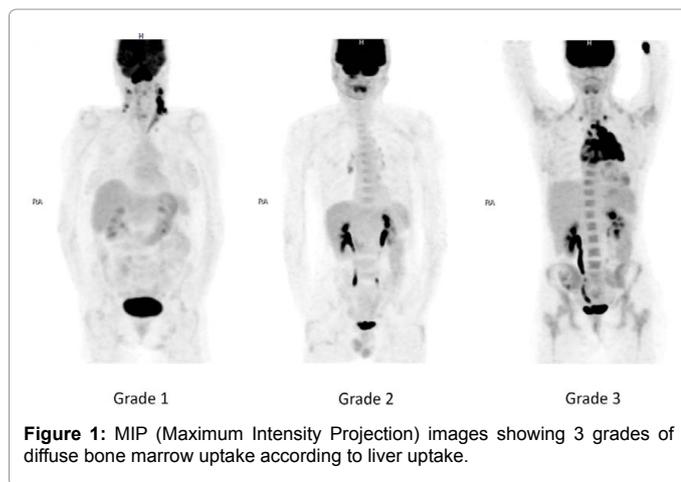


Figure 1: MIP (Maximum Intensity Projection) images showing 3 grades of diffuse bone marrow uptake according to liver uptake.

### Semi-quantitative analysis of BMU

Maximum sacral SUV was measured for all patients ( $n=86$ ). Mean SUV max was  $1.56 \pm 0.66$ . Demographic data according to SUV is summarized in Table 3. Qualitative evaluation using BMU level and semi-quantitative evaluation using sacral SUV were correlated ( $p=0.008$ ), as represented in Figure 6.

When we used binary results to analyse biological parameters (normal vs increased), we only found a correlation between SUV and CRP level ( $p=0.044$ ), without any other link with other inflammation parameters ( $p=0.327$  for clinical symptoms,  $p=0.110$  for biological symptoms,  $p=0.529$  for fibrinogen and  $p=0.298$  for leukocyte count). When we used quantitative linear values of each parameter, we did not find any correlation, even with CRP ( $p=0.103$ ).

About markers of disease extension, no correlation was found between SUV and Ann Arbor stage ( $p=0.151$ ), LDH level ( $p=0.484$ ), or  $\beta$ 2-microglobulin level ( $p=0.764$ ). Using quantitative linear data, LDH or  $\beta$ 2-microglobulin values were not correlated with SUV neither (respectively  $p=0.234$  and  $p=0.477$ ). Sacral SUV was not correlated to the presence of bone foci on FDG PET/CT ( $p=0.174$ ) or with BMI ( $p=0.116$ ), as shown in Figure 7.

### Performance of FDG PET/CT in assessment of BMI

According to the defined gold standard and considering diffuse BMU grade 3 as a positive scan, sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) of FDG PET/CT to detect BMI were, respectively 23%, 86%, 23% and 86%. Accuracy was 77%. When we considered diffuse BMU both grades 2 and 3 as a positive scan, Se, Sp, PPV and NPV were, respectively 46%, 52%, 15% and 84%. Accuracy was 51%.

### Discussion

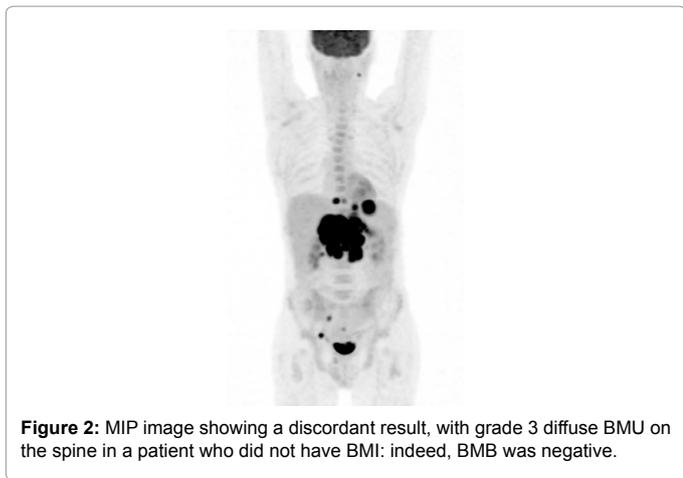
In this study, we assessed the diagnostic value of diffuse BMU at initial staging of DLBCL. Our results suggest that diffuse BMU is not representative of BMI but seems to be correlated with inflammatory changes. FDG PET diffuse bone marrow uptake can be seen quite frequently at initial staging of malignant lymphomas, mainly in HL, but also in aggressive NHL, which leads in difficulties in significance. Is this the reflection of a diffuse BMI, or only inflammatory activation?

In our study, we focused on the most frequently type of aggressive NHL, the DLBCL. For now, BMB remains the gold standard for the

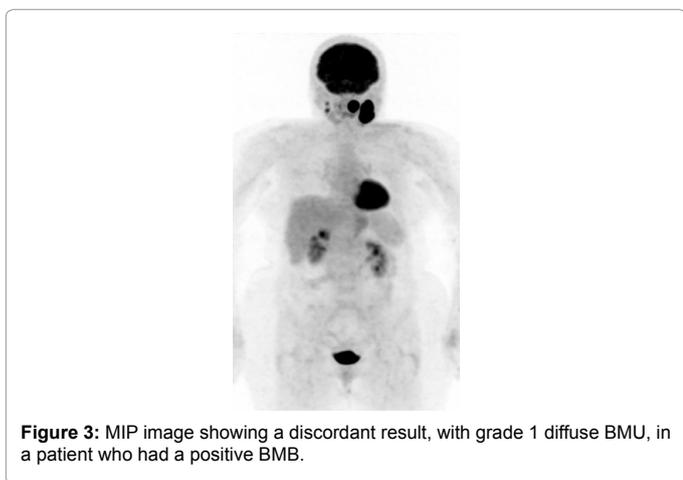
	Demographic Parameters	BMU grade 1	BMU grade 2	BMU grade 3	Univariate Analysis
Clinical parameters	Age (mean $\pm$ SD)	63 $\pm$ 13	55 $\pm$ 17	52 $\pm$ 15	$p=0.037^*$
	Ann Arbor classification (I/II/III/IV)	15/9/5/16	7/4/6/11	2/1/3/7	$p=0.550$
	Clinical systemic symptoms (A/B)	37/5	21/5	8/4	$p=0.202$
Bone marrow involvement	Bone foci on $^{18}$ F-FDG PET (no/yes)	38/7	26/2	12/1	$p=0.587$
	Positive BMB (no/yes)	10/1	12/1	5/2	$p=0.414$
	Bone marrow involvement (no/yes)	38/7	25/3	10/3	$p=0.594$
Biological parameters	Leukocyte count/mm <sup>3</sup> (mean $\pm$ SD)	7505 $\pm$ 2560	7752 $\pm$ 2455	8792 $\pm$ 2840	$p=0.263$
	CRP, mg/L (mean $\pm$ SD)	19.6 $\pm$ 31.9	34.3 $\pm$ 51.1	76.7 $\pm$ 65.1	$p=0.002^*$
	Fibrinogen, g/L (mean $\pm$ SD)	4.25 $\pm$ 1.62	4.58 $\pm$ 1.57	5.62 $\pm$ 1.48	$p=0.020^*$
	LDH, IU/L (mean $\pm$ SD)	476 $\pm$ 414	601 $\pm$ 629	974 $\pm$ 669	$p=0.034^*$
	$\beta$ 2-microglobulin, mg/L (mean $\pm$ SD)	2.70 $\pm$ 1.19	2.61 $\pm$ 1.40	4.23 $\pm$ 1.44	$p=0.115$
	Biological systemic symptoms (a/b)	19/20	11/15	0/13	$p=0.003^*$
	Sacrum SUV (mean $\pm$ SD)	1.40 $\pm$ 0.38	1.51 $\pm$ 0.41	2.26 $\pm$ 1.22	$p=0.008^*$

BMU: Bone marrow uptake; SD: Standard deviation; BMB: Bone marrow biopsy; CRP: C-reactive protein; LDH: Lactate dehydrogenase; SUV: Standardized uptake value.

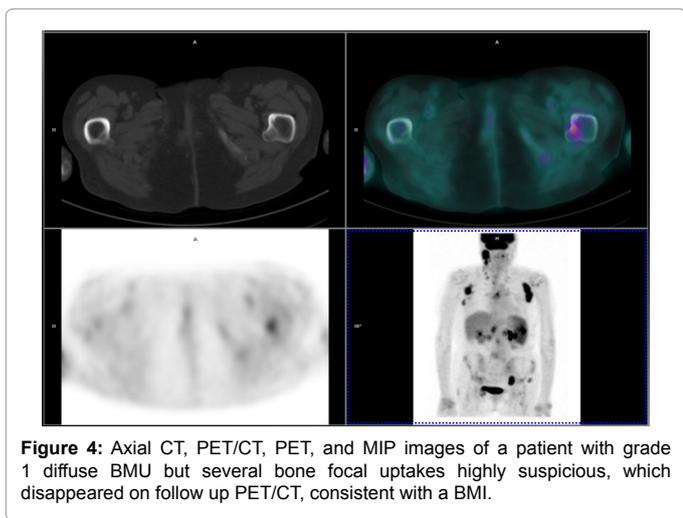
Table 2: Correlation between BMU visual grading and demographics.



**Figure 2:** MIP image showing a discordant result, with grade 3 diffuse BMU on the spine in a patient who did not have BMI: indeed, BMB was negative.



**Figure 3:** MIP image showing a discordant result, with grade 1 diffuse BMU, in a patient who had a positive BMB.

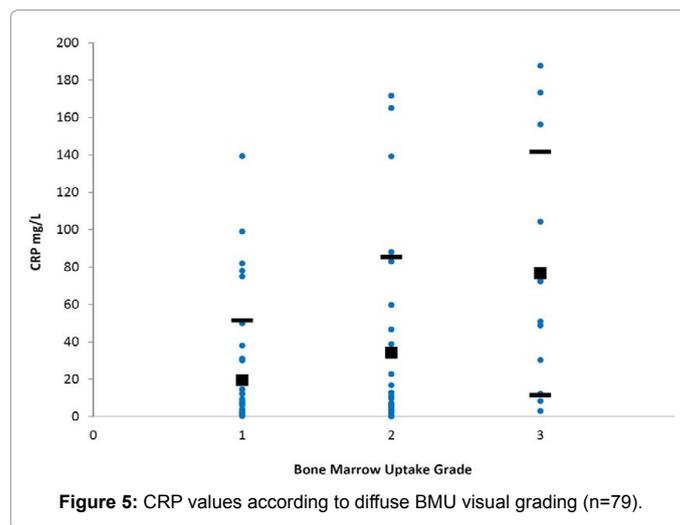


**Figure 4:** Axial CT, PET/CT, PET, and MIP images of a patient with grade 1 diffuse BMU but several bone focal uptakes highly suspicious, which disappeared on follow up PET/CT, consistent with a BMI.

assessment of BMI [1,7] but it is an invasive and painful procedure, with a few adverse events, principally haemorrhage, rare but which can be serious [15]. Furthermore, the analysis is limited to a very small fraction of the bone marrow and BMI at locations other than the iliac crest can be missed. In HL and NHL, unilateral BMB is false-negative compared to bilateral iliac biopsy in up to 80% of the patients and many studies have yet showed an increase from 5% to 26% in disease detection when

bilateral BMB was performed for patients with lymphoma and from 11% to 22% in patients with lymphoma and other neoplastic disease [8,9,16-19]. Therefore, routine non-invasive procedure would be of interest to improve bone marrow assessment in lymphoma.

Many studies have already evaluated FDG PET and bone marrow involvement in NHL/DLBCL [9,10,13,18,20-26]. Most of them only investigated focal uptakes to assess BMI.



**Figure 5:** CRP values according to diffuse BMU visual grading (n=79).

	Demographic Parameters	Sacrum SUV (mean ± SD)	Univariate Analysis
Clinical parameters	Age (mean ± SD)	58.3 ± 15.4	1.56 ± 0.66
	Ann Arbor classification		
	Stage I		1.45 ± 0.53
	Stage II		1.38 ± 0.34
	Stage III		1.49 ± 0.48
Stage IV		1.76 ± 0.85	p=0.151
Clinical systemic symptoms	A	1.58 ± 0.69	p=0.327
	B	1.43 ± 0.53	
Bone marrow involvement	Bone foci on <sup>18</sup> F-FDG PET		
	No	1.53 ± 0.61	p=0.174
	Yes	1.86 ± 0.90	
	Positive BMB		
No	1.64 ± 0.46	p=0.360	
Yes	2.58 ± 1.83		
Biological parameters	Bone marrow involvement		
	No	1.48 ± 0.44	p=0.116
	Yes	2.05 ± 1.25	
	Leukocyte count/mm <sup>3</sup>		
	Normal	1.52 ± 0.54	p=0.298
	Increased	1.88 ± 1.15	
	CRP, mg/L		
	Normal	1.40 ± 0.44	p=0.044*
	Increased	1.69 ± 0.75	
	Fibrinogen, g/L		
Normal	1.53 ± 0.59	p=0.529	
Increased	1.66 ± 0.78		
LDH, IU/L			
Normal	1.48 ± 0.43	p=0.484	
Increased	1.68 ± 0.82		
β2-microglobulin, mg/L			
Normal	1.52 ± 0.44	p=0.764	
Increased	1.46 ± 0.40		
Biological systemic symptoms			
a	1.41 ± 0.34	p=0.110	
b	1.70 ± 0.80		

**Table 3:** Correlation between sacrum SUV and demographics.

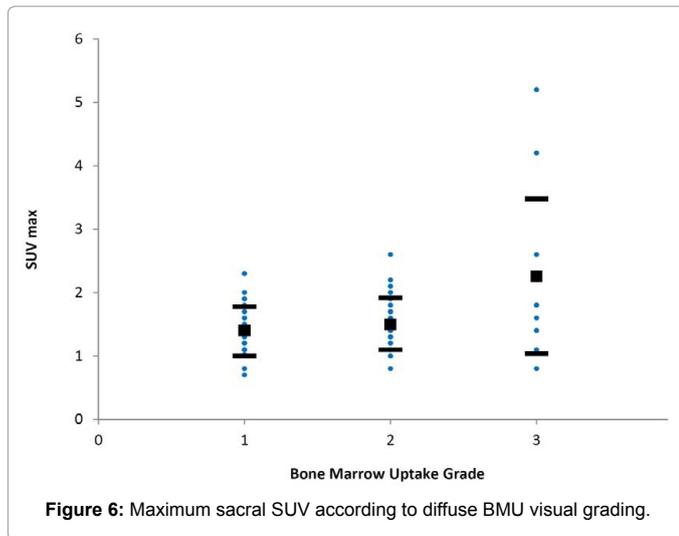


Figure 6: Maximum sacral SUV according to diffuse BMU visual grading.

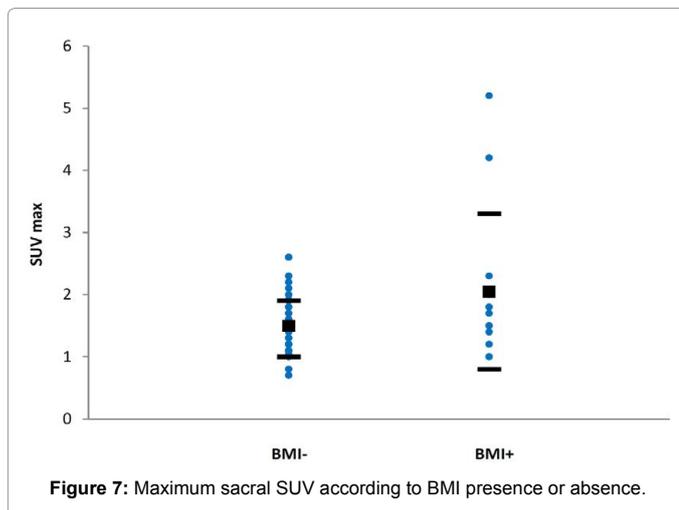


Figure 7: Maximum sacral SUV according to BMI presence or absence.

Schaefer et al. still evaluating FDG focal uptakes suggested that FDG PET/CT was superior to BMB, CT or both combined [9]. Furthermore, 18 patients had guided-biopsy of FDG-avid lesions, and all biopsies were positive for lymphomatous infiltration. Recently, Berthet et al. analyzed 142 patients with DLBCL, and concluded that uni- or multi-focal bone marrow uptake provides better diagnostic performance and prognostic stratification than does BMB [13]. So, FDG focal uptakes appear to be representative of BMI, with good PPV, but with a lower NPV. Indeed, recent recommendations of the International Conference on Malignant Lymphoma stated that in DLBCL, a positive PET-CT at initial staging was sufficient to affirm BMI. However, they mainly focused on focal FDG uptake but not on diffuse uptake [27].

In our study, we assessed the diagnostic value of diffuse BMU, raising the hypothesis it could also reflect BMI. About that, a study of 130 patients, analyzing both focal and diffuse uptakes, suggested that BMB is still needed in case of diffuse BMU [26]. More recently, Adams et al. analyzed only diffuse BMU in HL and NHL (239 patients with aggressive NHL), and their results suggested that a BMB is likely to be positive in the majority of NHL cases with diffusely increased bone marrow FDG uptake [28]. These results are discordant with ours. Indeed, diffuse BMU was not correlated with BMI in our study, using as well qualitative visual analysis ( $p=0.594$ ) than semi-quantitative

analysis ( $p=0.1164$ ). Even when we compared diffuse BMU with BMB results only, there was no significant correlation. One limitation of our study is that only 31 of the 86 (36%) patients underwent a BMB. However, according to our gold standard including histology, imaging and follow-up, 13 of 86 patients had BMI (15%), which corresponds to literature data, reporting from 10% to 30% of BMI in DLBCL [3-6]. About disease extension parameters, we only found a correlation with LDH ( $p=0.0342$ ), but not with B2 microglobulin or Ann Arbor stage. So, our results suggested that diffuse BMU at initial staging of DLBCL is not representative of BMI.

However, we found statistically significant correlations with biological systemic symptoms ( $p=0.003$ ), CRP ( $p=0.002$ ) and fibrinogen ( $p=0.020$ ) when compared with visual analysis. These data were concordant with the results of Inoue et al., who suggested that a FDG BMU greater than or equal to that of the liver indicates BM activation, and that the most likely cause is inflammation [29]. These results are also concordant with those previously reported at initial staging of Hodgkin lymphoma (HL), despite the fact that DLBCL is a less inflammation provider disease than HL [14]. As previously described, these data may suggest a role of inflammatory factors/cytokines on hematopoietic stimulating factors [30,31].

This study has some limitations. First, as we said earlier, all patients did not have BMB. However, we are confident that focal bone marrow uptake is a real reflection of BMI, and, according to recent guidelines, BMB is needed only if PET is negative, and is not recommended systematically at initial staging for all patients. Second, it was a monocentric study, which may limit generalization of our results. Third, there were quite few patients in this retrospective study. However, we found a significant number of patients with diffuse bone marrow FDG uptake who did not have bone marrow involvement, which contrasts with results of the study by Adams et al. [28].

## Conclusion

In conclusion, our study suggests that a diffuse BMU seen on FDG PET/CT at initial staging of DLBCL is not representative of bone marrow involvement, but can be due to inflammatory changes.

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