Positive Predictive Value of [18F]FDG PET/CT for the Detection of Bone Marrow Infiltration in Diffuse Large B-Cell Lymphoma: Impact of Focal versus Diffuse Pattern

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Swiss Journal of Radiology and Nuclear Medicine - www.sjoranm.com - Rosenweg 3 in CH-6340 Baar, Switzerland

Abstract

Background: Bone marrow involvement in diffuse large B-cell lymphoma (DLBCL) is a major prognostic factor corresponding to Ann Arbor stage IV disease. While [18F]FDG PET/CT has largely replaced bone marrow biopsy (BMB) in many staging algorithms, the interpretation of bone marrow uptake patterns—particularly focal versus diffuse—remains a clinical challenge.
Purpose: To evaluate the positive predictive value (PPV) of [18F]FDG PET/CT for bone marrow infiltration in DLBCL and to assess the diagnostic impact of focal versus diffuse uptake patterns.
Methods: This retrospective single-center study included 142 newly diagnosed DLBCL patients. Among them, 91 patients with PET-positive bone marrow findings underwent BMB. PET/CT patterns were categorized as focal or diffuse based on uptake relative to hepatic activity. PPV was calculated, and associations between imaging patterns, clinical parameters, and histological confirmation were analyzed.
Results: Bone marrow involvement on PET/CT was observed in 91 patients, with histological confirmation in 67 cases (overall PPV: 73.6%). All patients with focal uptake (18/18) had confirmed marrow infiltration (PPV: 100%), whereas only 49/73 patients with diffuse uptake showed histological involvement (PPV: 67.1%). Focal uptake was strongly associated with confirmed infiltration (OR = 19.5; p = 0.003). In the diffuse pattern subgroup, anemia (OR = 12.5; $p < 0.001$) and leukopenia (OR = 3.7; p = 0.02) were significantly associated with negative biopsy findings, suggesting reactive bone marrow activation.
Conclusion: [[18F]FDG PET/CT demonstrates high predictive value for bone marrow involvement in DLBCL, particularly in the presence of focal uptake. In contrast, diffuse bone marrow hypermetabolism requires cautious interpretation and should be integrated with clinical and biological parameters. These findings support a more selective and individualized approach to bone marrow biopsy in DLBCL staging.

Keywords: Bone Marrow, Diffuse Large B-Cell Lymphoma, Positron-Emission Tomography Computed Tomography

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received: 31.01.2026 - peer reviewed, accepted and published: 31.05.2026

Introduction

Diffuse large B-cell lymphoma (DLBCL) is a common and aggressive subtype of non-Hodgkin lymphoma, accounting for approximately 30% of all cases [1]. It most frequently arises in lymph node chains but may also involve other organs such as the spleen, liver, gastrointestinal tract, central nervous system, or bone marrow [2]. The diagnosis of bone marrow involvement

is a crucial prognostic indicator, as its presence corresponds to stage IV in the Ann Arbor classification, with important prognostic and therapeutic implications [3]. The reference standard for diagnosing bone marrow involvement is unilateral or bilateral bone marrow biopsy (BMB) of the iliac crest. However, BMB is an invasive procedure that may cause discomfort and complications for the patient [4]. In addition to its invasive nature, BMB evaluates only a very small portion of the total bone marrow, and therefore focal bone marrow involvement may be missed [4,5].

Meanwhile, 18F-fluoro-2-deoxy-D-glucose positron emission tomography ([[18F]FDG PET) combined with computed tomography (CT) has become a routinely used modality for the initial staging of FDG-avid lymphomas, outperforming CT alone in this setting [6]. It is used for both nodal and extranodal staging, including the assessment of bone marrow involvement. The main advantages of [18F]FDG PET/CT over BMB are its non-invasive nature and its ability to assess the entire bone marrow compartment. It enables the identification of hypermetabolic areas suggestive of lymphomatous infiltration. The European Society for Medical Oncology (ESMO) considers it the imaging modality of choice for initial staging in patients diagnosed with DLBCL [7]. [18F]FDG PET/CT has demonstrated promising results in terms of sensitivity and specificity, with high accuracy for detecting bone marrow involvement in patients with DLBCL [8].

In recent years, several studies have evaluated the diagnostic accuracy of [18F]FDG PET/CT for detecting bone marrow involvement in newly diagnosed DLBCL, using bone marrow biopsy as the reference standard. However, few studies have specifically analyzed the impact of the bone marrow hypermetabolic pattern observed on [18F]FDG PET/CT on the actual likelihood of histologically confirmed infiltration. The aim of this study was to assess the impact of different bone marrow involvement patterns (focal versus diffuse) on [18F]FDG PET/CT on the probability of biopsy-confirmed infiltration in DLBCL, in order to better define the predictive value of each presentation and to provide guidance for clinical decision-making regarding the systematic use of bone marrow biopsy.

Patients and Methods

This was a retrospective single-center study conducted in newly diagnosed DLBCL patients who had not received chemotherapy or radiotherapy and had no history of other malignancies. Eligible patients were adults (>18 years) with histologically confirmed newly diagnosed DLBCL who showed bone marrow involvement on [18F]FDG PET/CT and underwent bone marrow biopsy (BMB) for confirmation. Patients who had received any treatment prior to initial staging or who had an excessive delay (>14 days) between [18F]FDG PET/CT and BMB were excluded.

All PET/CT examinations were performed using a SIEMENS Biograph 6 TruePoint PET/CT scanner. Patients fasted for 6 hours prior to imaging. Blood glucose levels were measured and maintained below 1.26 g/L (2 g/L in diabetic patients) before intravenous administration of [18F]FDG (3 MBq/kg). The protocol included an initial six-slice helical CT acquisition (110 kVp, 95 mA, pitch 1.75:1, 5 mm slice thickness, 1.5 s rotation time). PET and CT images were acquired from the skull vertex to mid-thigh in three-dimensional mode, without breath-hold, with an acquisition time of 3 minutes per bed position (7 bed positions, each covering 15 cm), and an axial sampling thickness of 3 mm per slice. PET images were reconstructed using an iterative method (OSEM: 8 subsets, 4 iterations), while CT images were reconstructed using filtered back projection. Attenuation correction of PET images was derived from CT data. PET and CT volumes were then fused for precise anatomical-metabolic correlation.

PET/CT images were interpreted by two senior nuclear medicine physicians with more than 10 years of experience. Bone marrow involvement was classified into two patterns: focal (one or more hypermetabolic bone marrow foci with FDG uptake higher than liver uptake) and diffuse (homogeneous diffuse bone marrow hypermetabolism with FDG uptake higher than liver uptake).

Patients with positive [18F]FDG PET/CT findings underwent unilateral BMB at the posterior superior iliac spine. Adequate bone marrow samples (2–3 cm) were obtained by hematologists and analyzed by pathologists. Biopsies were performed within a maximum of 14 days after PET/CT. BMB was considered positive in cases of histologically confirmed DLBCL infiltration.

Data were collected from medical records, entered using Kobo Collect, exported to Excel, and analyzed with SPSS. The Shapiro–Wilk test assessed normality of quantitative variables. Quantitative variables were expressed as mean ± standard deviation; qualitative variables as frequencies and percentages. Analysis focused on patients with PET-positive bone marrow involvement. Positive predictive value (PPV) was calculated as the ratio of positive BMBs to total PET-positive cases. Focal and diffuse patterns were compared regarding biopsy positivity using the chi-square or Fisher's exact test, as appropriate. Statistical significance was set at $p < 0.05$.

Results

Table 1: Demographic, clinical, and biological characteristics of patients diagnosed with diffuse large B-cell lymphoma (n = 142)

	Effectifs	Percentages
Sex		
Female	59	41,5
Male	83	58,5
Male-to-female ratio: 1,4		
Age		
< 60	93	65,5
≥ 60	49	34,5
Mean age: 60,3 ± 8,7		
Primary site		
Nodal	109	76,8
Extranodal	33	23,2
Physical findings		
Lymphadenopathy	112	78,9
Splenomegaly	67	47,2
Hepatomegaly	26	18,3
LDH		
≥ 2N	89	62,7
< 2	52	33,3
IPI score		
≥ 2	63	44,4
< 2	79	55,6
Leukopenia		
Yes	118	83,1
No	24	16,9
Anemia		
Yes	87	61,3
No	55	38,7
Thrombocytopenia		
Yes	133	93,7
No	9	6,3

LDH: Lactate Dehydrogenase; **IPI:** International Prognostic Index

A total of 142 patients diagnosed with DLBCL were included in the study. The population was predominantly male, with 83 men (58.5%) and 59 women (41.5%). Most patients were younger than 60 years (93 patients, 65.5%), while 49 patients (34.5%) were aged 60 years or older, with a mean age of 60.3 years. The primary site of disease was nodal in 109 cases (76.8%) and extranodal in 33 cases (23.2%). Clinically, lymphadenopathy was present in 112 patients (78.9%), splenomegaly in 67 patients (47.2%), and hepatomegaly in 26 patients (18.3%). Biologically, LDH levels ≥ 2× the upper limit of normal times were observed in 89 patients (62.7%). Regarding the International Prognostic Index (IPI), 63 patients (44.4%) had a score ≥ 2, whereas 79 patients (55.6%) had a score < 2. Hematological abnormalities were frequent: leukopenia was found in 118 patients (83.1%), anemia in 87 patients (61.3%), and thrombocytopenia in 133 patients (93.7%).

Table 2: Association between bone marrow involvement pattern on [^{18}F]FDG PET/CT and histological confirmation by bone marrow biopsy.

PET Pattern	BMB + n (%)	BMB – n (%)	Total	PPV (%)	OR (IC95%)	p-value
Focal	18 (100%)	0 (0%)	18	100%		
Diffuse	49 (67.1%)	24 (32.9%)	73	67.1%	19.5 (1.1 – 341)	0.003
Total	67	24	91	73.6%		

Bone marrow involvement was detected on [^{18}F]FDG PET/CT in 91 patients. Among them, histological confirmation by bone marrow biopsy was obtained in 67 patients, corresponding to an overall positive predictive value (PPV) of 73.6%.

Analysis according to the pattern of bone marrow involvement showed that 18 patients had a focal pattern, whereas 73 patients had a diffuse pattern. Bone marrow biopsy confirmed infiltration in all focal cases (18/18), yielding a PPV of 100% for this pattern. In contrast, among the 73 patients with a diffuse pattern, bone marrow infiltration was confirmed in only 49 cases, corresponding to a PPV of 67.1%, indicating a non-negligible proportion of false-positive findings in this group.

Statistical analysis demonstrated a significant association between the PET/CT pattern and histological confirmation of bone marrow infiltration. Patients with a focal pattern had a significantly higher likelihood of biopsy-confirmed bone marrow involvement compared with those presenting a diffuse pattern (OR = 19.5; 95% CI: 1.1–341; p = 0.003). These findings

highlight the strong diagnostic value of the focal pattern and suggest that the diffuse pattern requires more cautious interpretation and systematic histological confirmation.

Table 3: Univariate analysis of factors associated with biopsy-confirmed bone marrow infiltration in patients with positive [^{18}F]FDG PET/CT findings.

	BMB+	BMB –	OR (IC95%)	p-value
Pattern			19.5	0.003
Focal	18	0		
Diffuse	49	24		
LDH ≥ 2× ULN	9	3	1.09	0.89
IPI ≥ 2	7	3	0.82	0.79
Anemia	9	6	0.47	0.18
Leukopeniea	11	5	0.75	0.64
Thrombocytopenia	13	7	0.59	0.34

LDH: Lactate Dehydrogenase; **IPI:** International Prognostic Index

Univariate analysis performed in the 91 patients with bone marrow involvement on [^{18}F]FDG PET/CT showed that the pattern type was the only factor significantly associated with histological confirmation of bone marrow infiltration. In contrast, no statistically significant association was found between bone marrow biopsy positivity and the biological or prognostic parameters studied. Neither elevated LDH (≥ 2× upper limit of normal), nor IPI score (≥ 2), nor the presence of anemia, leukopenia, or thrombocytopenia was significantly associated with confirmed bone marrow infiltration ($p > 0.05$ for all comparisons).

These findings indicate that the pattern of bone marrow hypermetabolism on [^{18}F]FDG PET/CT was the main determinant of histological confirmation of bone marrow involvement in this cohort, reinforcing its role as a major discriminative factor in the diagnostic assessment of DLBCL.

Table 4: Univariate analysis of factors associated with a negative biopsy in the diffuse pattern group (n = 73).

	BMB + (n= 49)	BMB – (n= 24)	OR (IC95%)	OR (IC95%)
Extranodal	38	5	0.08	< 0.001
LDH ≥ 2N ULN	43	7	0.06	< 0.001
IPI ≥ 2	37	7	0.05	< 0.001
Leukopenia	17	16	3.7	0.02
Anemia	18	21	12.5	< 0.001

Univariate analysis performed to identify factors associated with the absence of histological confirmation among patients with a diffuse pattern on [^{18}F]FDG PET/CT showed that the presence of anemia was strongly associated with a negative biopsy (OR = 12.5; $p < 0.001$). Similarly, leukopenia was significantly associated with the absence of confirmed bone marrow infiltration (OR = 3.7; $p = 0.02$). These findings suggest that cytopenias may be involved in reactive bone marrow processes responsible for diffuse, non-infiltrative hypermetabolism. Conversely, in this subgroup, certain parameters were significantly associated with histological confirmation of bone marrow infiltration. Elevated LDH ≥ 2× the upper limit of normal (OR ≈ 0.06; $p < 0.001$), an IPI score ≥ 2 (OR = 0.05; $p < 0.001$), and an extranodal primary site (OR = 0.08; $p < 0.001$) were strongly associated with a positive biopsy.

Discussion

This study confirms that [18F]FDG PET/CT provides decisive information for the assessment of bone marrow infiltration in DLBCL, particularly when bone marrow hypermetabolism is focal. In our cohort, all focal lesions were confirmed by bone marrow biopsy (PPV 100%), supporting the widely accepted view that focal hypermetabolic bone marrow lesions on [18F]FDG PET/CT in FDG-avid lymphomas are highly suggestive of infiltration. This finding is consistent with the Lugano international recommendations [9], which emphasize the high diagnostic value of focal bone marrow uptake on [18F]FDG PET/CT in aggressive lymphomas and suggest that PET/CT may, in many cases, reduce the need for systematic bone marrow biopsy.

In contrast, our results highlight the well-known limitation of the diffuse pattern, despite increased uptake on [18F]FDG PET/CT. Biopsy confirmed infiltration in only about two-thirds of diffuse cases, reflecting the etiological heterogeneity underlying diffuse bone marrow hypermetabolism. Furthermore, analysis of factors associated with false-positive PET/CT findings among diffuse cases revealed that anemia and leukopenia were significantly

associated with the absence of histological confirmation. This is consistent with the findings of Alyamany R. et al. [10], who reported the limited specificity of diffuse bone marrow hypermetabolism on [18F]FDG PET/CT and stressed the importance of correlating imaging findings with clinical and biological data. The difficulty in interpreting diffuse bone marrow uptake is well documented in the literature, as [18F]FDG PET/CT may demonstrate diffuse hypermetabolism related to non-malignant causes such as inflammation or anemia.

Conversely, within the diffuse subgroup, certain tumor burden markers (elevated LDH, high IPI score, extranodal involvement) were associated with positive biopsy results in our study, reinforcing the concept that the diffuse pattern does not have a single interpretation. It may reflect either reactive hypermetabolism or true lymphomatous infiltration. This approach aligns with current practice trends, which aim not merely to replace bone marrow biopsy with [18F]FDG PET/CT, but rather to identify the subgroups in which biopsy retains added value [12].

Our findings support the growing tendency to reduce the systematic use of bone marrow biopsy in newly diagnosed DLBCL when [18F]FDG PET/CT provides clear information, particularly in the presence of focal lesions. Publications and consensus statements [9] emphasize the central role of [18F]FDG PET/CT in the initial staging of FDG-avid lymphomas and indicate that, under defined conditions, it may render bone marrow biopsy unnecessary, while acknowledging that a negative PET/CT does not always exclude low-volume infiltration or certain discordant findings [7,8].

However, these results should be interpreted with caution due to several important methodological limitations. Indeed, bone marrow biopsy was performed only in patients with medullary abnormalities detected on PET, thereby introducing a verification bias. This bias limits the validity of the diagnostic assessment, as it prevents reliable estimation of the sensitivity, specificity, and negative predictive value of [18F]FDG PET/CT in the studied population. Furthermore, the reported positive predictive value (PPV) of 100% in patients with focal osteomedullary involvement should be interpreted cautiously. This estimate is based on a relatively small sample size, resulting in wide confidence intervals and limiting both the precision and generalizability of the findings. Therefore, although these results are promising, they need to be confirmed by studies with larger sample sizes and more robust methodologies.

Nevertheless, this study supports a hierarchical interpretation strategy: focal bone marrow hypermetabolism on [18F]FDG PET/CT appears highly suggestive of infiltration, whereas diffuse uptake should be interpreted in an integrated manner, taking into account biological data and tumor burden markers. Such an approach may help optimize the indication for bone marrow biopsy by targeting situations in which it provides the greatest added value.

Conclusions

This study confirms the major diagnostic value of [18F]FDG PET/CT in the assessment of bone marrow infiltration in diffuse large B-cell lymphoma. A focal pattern of bone marrow hypermetabolism appears highly predictive of biopsy-confirmed infiltration. In contrast, the diffuse pattern demonstrates diagnostic heterogeneity. Analysis of factors associated with discordant findings showed that anemia and leukopenia were significantly linked to the absence of histological confirmation, suggesting a reactive bone marrow mechanism. Conversely, elevated LDH levels, a high IPI score, and extranodal involvement were associated with confirmed infiltration. These findings support an integrated approach combining imaging data with clinical and biological parameters in order to optimize the indication for bone marrow biopsy and improve the diagnostic stratification of patients with DLBCL.

Author Contributions

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Declarations

Consent for publication: The author clarifies that written informed consent was obtained and the anonymity of the patient was ensured. This study submitted to Swiss J. Rad. Nucl. Med. has been conducted in accordance with the Declaration of Helsinki and according to requirements of all applicable local and international standards. All authors contributed to the conception and design of the manuscript, participated in drafting and revising the content critically for important intellectual input, and approved the final version for publication. Each author agrees to be accountable for all aspects of the work, ensuring its accuracy and integrity.

Conflict of interest:

The authors declare that there were no conflicts of interest within the meaning of the recommendations of the International Committee of Medical Journal Editors when the article was written.

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