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ORIGINAL ARTICLE

Bone Marrow Infiltration in Diffuse Large B-Cell Lymphoma Patients: Impact of ^{18}FDG-PET/CT in Detection and Prediction of Therapy Outcome

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ABSTRACT

Objective: to assess the utility of ^{18}FDG-PET/CT in the detection of bone marrow (BM) infiltration and the prediction of therapy outcomes in patients with diffuse large B-cell lymphoma (DLBCL). **Methods:** This retrospective study included 111 patients with pathologically confirmed DLBCL. They underwent ^{18}FDG-PET/CT imaging twice at initial staging and 2 to 12 months following completion of the recommended therapy. **Results:** ^{18}FDG-PET/CT is more accurate than bone marrow biopsy (BMB) for the identification of BM infiltration and exhibited 100% sensitivity (SN), specificity (SP), positive predictive value (PPV), negative predictive value (NPV), and accuracy for BM infiltration detection. Patients with avid ^{18}FDG BM uptake has a bad prognosis compared to those with no BM FDG uptake, as it is significantly associated with lower rates of complete metabolic response (CMR) (66% vs. 85.9%; p = 0.019), a higher relapse rate (38.7% vs. 9.1%; p = 0.001), lower four-year relapse-free survival (RFS) (37.4% vs. 90.3%; p = 0.001), a lower five-year overall survival (OS) rate (0% vs. 77.1%; p = 0.034), and a higher death rate (21.3% vs. 6.2%; p = 0.018). Also, patients with axial, multifocal, and diffuse FDG BM uptake have a bad prognosis, lower RFS and OS rates. **Conclusions:** ^{18}FDG PET/CT imaging provides whole-body mapping for detecting BM infiltration with high SN, SP, and accuracy; it can replace routine BMB in the staging of DLBCL. Avid ^{18}FDG BM uptake is a poor prognostic sign associated with a higher relapse rate and lower rates of CMR and OS.

Keywords: DLBCL; Bone marrow infiltration; Bone marrow biopsy; and ^{18}FDG-PET/CT

INTRODUCTION

Approximately 30% of adult non-Hodgkin's lymphoma (NHL) cases are diffuse large B cell lymphoma (DLBCL), which is the most prevalent and aggressive type of NHL **[1]**. Detection of BM infiltration is crucial, as it influences staging and clinical management **[2]**. The gold standard for the identification of BM infiltration is BMB. However, it is invasive, can have harmful side effects, may be disturbing for patients, and may miss BM infiltration if it is patchy **[3, 4]**. Early PET studies proved clearly that BM infiltration in patients with DLBCL was more often metastatic, with discrete foci of increased 18FDG uptake at one or more sites throughout the medullary skeleton, while diffuse 18FDG uptake was less common **[5]**. Focal BM uptake on 18FDG-PET/CT, with or without diffuse BM uptake, was more accurate than BMB for evaluating BM infiltration. However, BM infiltration could remain undetected in up to 6% of patients with low-volume

diffuse FDG uptake **[6, 7]**. However, it is now accepted that PET reliably detects marrow disease in more patients than BMB **[5]**. A comprehensive review discovered strong evidence for the accuracy and complementary role of PET/CT for detecting BM infiltration in newly diagnosed DLBCL. Additionally, more studies are needed to establish the relative contributions of BMB and PET in determining prognosis **[8]**. We aim to assess the utility of 18FDG-PET/CT in the detection of BM infiltration and the prediction of therapy outcomes in DLBCL patients.

METHODS

This retrospective study included 111 patients with pathologically confirmed DLBCL participated. They underwent whole-body 18FDG-PET/CT imaging twice, at initial staging with a maximum 14-days gap between the PET/CT and BMB and the second 2 to 12 months following the completion of the recommended therapy.

***Ethical approval*:** This study was authorized by the institutional review board (approved no. IRB #: 10600-19-32023). All patients provided written informed consent to share in this research.

***Inclusion criteria*:** Patients must be over 18 years old, and have pathologically confirmed DLBCL, either with or without symptoms of bone marrow invasion.

***Exclusion criteria*:** Patients who match at least one of the following criteria are excluded; patients with other types of lymphoma or an unidentified histological type, a second synchronous primary cancer, severe abdominal infections, uncontrolled diabetic mellitus, or those who are expected to live for less than six months. Also, pregnant women are among the excluded patients.

***Whole-body 18FDG-PET/CT scan*:** The baseline and follow-up scans were done using an integrated PET/CT system (Philips Medical Systems with a 16-slice CT). Patients were also instructed to avoid strenuous activity for a few days before the study to lessen 18FDG uptake by skeletal muscles and follow a low-carb diet 24 hours prior to receiving an FDG injection. Before 18FDG injection, all patients were informed to fast for four hours, and the peripheral blood glucose level should be verified to be less than 150 mg/dL. Oral diabetic drugs could be used as advised, with the exception of prescriptions containing metformin, which should be stopped 48 hours before the study to lower the intestinal background activity produced by such medications. The day before the study, diabetic patients with type 1 diabetes mellitus should fast after midnight (except from drinking water) and scheduled in the morning before taking their insulin. Rescheduling of the exam was indicated when there was hypoglycemia accompanied by symptoms or the glucose level was greater than 200 mg/dL. A pregnancy test was performed as necessary on females who were fertile. Intravenous injection of 185–555 MBq of 18F–FDG was performed. The patient was kept sitting, recumbent, in a quiet room (which reduces muscle uptake). The patient also promptly evacuated their bladder just before imaging. In some instances, the use of intravenous hydration, diuretics, and/or bladder catheterization was necessary to reduce the radiation exposure and artifacts resulting from the physiological accumulation of the radiopharmaceutical in the ureters and bladder. The imaging began 45–60 minutes after the tracer injection and covered from the head to the mid-thigh for nearly six bed positions according to the patient length, with each bed position acquired for two minutes. Both PET and CT scans were reconstructed and reformatted in the axial, sagittal, and coronal plans. Additionally, fusion images were created by combining PET and CT images. Attenuation correction of the PET images was done using CT data. Scans were interpreted by experienced (more than 15 years of experience) radiologists and nuclear medicine specialists (at least one in each modality) while being unaware of the patient's history. If there was a discrepancy between them, another nuclear medicine physician and/or radiologist read the scan, and the final consensus result was taken into account.

***Follow-up Protocol*:** Following completion of the recommended therapy, patients were monitored for six to twelve months. They underwent a comprehensive medical examination and laboratory evaluation (including measurements of a complete blood picture, liver and kidney function tests, and tumour markers). A follow-up 18FDG-PET/CT imaging was also done to track the disease's progression over time.

***Bone marrow biopsy*:** a unilateral iliac crest biopsy was performed on each patient. Those with a negative iliac crest biopsy but avid ^{18}FDG bone/BM uptake on a PET/CT scan underwent a second PET/CT-guided biopsy to confirm or rule out BM infiltration. The sites of the second PET/CT-guided biopsy were the sternum (9 patients), contralateral iliac bone (4 patients), humerus (7 patients), and femora (5 patients). BMB specimens were evaluated morphologically by a hematopathologist. Immunohistochemistry of BMBs was done to

determine the immunophenotyping of the lymphoma and to quantify BM involvement.

***Evaluation of response*:** The clinical and laboratory data, as well as the comparison of the baseline and follow-up ^{18}FDG-PET/CT scans, were used to evaluate the overall response. Lugano criteria were applied to evaluate the effectiveness of treatment.

STATISTICAL ANALYSIS

The mean, standard deviation and median were used to describe quantitative data, while absolute frequencies (numbers) and relative frequencies (%) were used to express qualitative data.

The Shapiro-Wilk test was used to assess the normality of continuous variables. Mann-Whitney Two groups of non-normally distributed variables were compared using a U test. To compare matched data,

McNemar's test was employed. When appropriate, Fisher's exact test or Pearson's chi-square test were used to compare the percentage of categorical variables. The Chi-square test for trend was used to compare the trend of change in the distribution of relative frequencies between ordinal data. Utilizing diagnostic performance based on sample 2x2 contingency tables created using BMB as the GS reference test, it was determined whether the PET/CT was valid for the diagnosis of BM infiltration. The accuracies, sensitivities (SN), specificities (SP), positive predictive values (PPV), negative predictive values (NPV), and their corresponding 95% confidence intervals were calculated. The time from the start of chemotherapy to the date of relapse that was proven or the most recent follow-up in which the patient was free from relapse was used to compute relapse-free survival (RFS). The time from diagnosis to death or the most recent follow-up contact (censored) was used to compute overall survival (OS). Clinicopathological factors were taken into consideration while stratifying RFS and OS. The Kaplan-Meier plot was used to estimate these time-to-event distributions, and a two-sided exact log-rank test was used to compare them. Every test had two sides. A p-value of <0.05 was considered significant. SPSS 22.0 for Windows (IBM Corp., Armonk, NY, USA) and MedCalc 13 for Windows (MedCalc Software bvba, Ostend, Belgium) were used for all statistical calculations.

RESULTS

One hundred eleven patients with pathologically confirmed DLBCL were comprised in this retrospective study with a mean age of 44.4±15.7 years (range 16–73 years), a male to female ratio of 5/3, and a mean follow-up period of 44.6±9.7 months. All patients were treated with recommended therapy. Forty-seven patients (47.8%) had evidence of avid FDG uptake on ^{18}FDG-PET/CT imaging and proved to have BM infiltration; out of them, lymphomatous BM infiltration was proved in 22 patients (47.8%) by a positive iliac crest biopsy, and 25 patients (53.2%) had a negative iliac crest biopsy but a positive second PET/CT-guided biopsy in bones other than the iliac crest. **(Table 1).**

18FDG-PET/CT imaging was found to be more accurate than iliac crest BMB for the identification of BM infiltration, with 100% SN, SP, and accuracy, however BMB had 46.8% SN (detected BM infiltration in only 22 out of 47 patients). The most frequently affected bones were the skull, vertebrae, pelvic bones, humerus, and femora (44, 26, 20, 20, and 20 patients, respectively). The skull showed the highest accuracy for detecting lymphomatous BM infiltration by PET/CT imaging, while scapular infiltration had the lowest accuracy (62.0%) **(Table 2).**

Four patterns of ^{18}FDG BM uptake were seen: unifocal, bifocal, multifocal, and diffuse, with the multifocal pattern being the most frequently encountered (17.1%), while the bifocal pattern was the least commonly seen (1.8%). Both unifocal and diffuse uptake patterns were comparable (found at 11.7% each) with the axial rather than the appendicular skeleton more commonly affected [19 patients (17.1%) versus 8 patients (7.2%) respectively]. Lymph nodes followed by BM, were the most commonly affected organs [97 patients (87.4%) and 47patients (42.3%), respectively]. Spleen affection was seen in 20.7% of patients, while liver and pulmonary affection were equally affected (11.7% each). The brain, lung, and the rest of the abdominal and pelvic organs were involved in a low percentage, ranging from 0.9% to 5.4%, in association with LNs infiltration and/or BM infiltration **(Table 3)**.

Among our patients' high rates of CMR, RFS, and five-year OS was seen (77.5%, 71.4%, and 48.3% of patients, respectively)**.** Positive BM infiltration on PET/CT had a bad prognostic value as it was significantly associated with a lower rate of CMR (66% versus 85.9% of patients with a normal scan; p = 0.019), higher rates of relapse (38.7% vs. 9.1%; p = 0.001), lower rates of four-year RFS (37.4% vs. 90.3%, respectively; p = 0.001), higher death rates (21.3% compared to 6.2%; p = 0.018), and lower rates of five-year OS (0% vs. 77.1%, respectively, p-value = 0.034) **(Table 4, Fig C &D).**

The site of abnormal FDG BM uptake had an impact on the outcome. Patients with appendicular BM infiltration had higher four-year RFS and five-year OS than patients with axial bone BM infiltration (75% versus 51.9%, p<0.001, and 100% versus 60.5% p-value = 0.011 respectively). Also, the pattern of abnormal BM uptake which represents the disease extent has its own impact: unifocal pattern has statistically higher 4-years RFS and 5-years OS than the multifocal and diffuse patterns (79.5% versus 51.9 and 0%, p=0.003 and 100% versus 0% and 51.9%) so, the response to treatment, RFS, and 5-year OS could be predicted according to the findings on PET/CT. **(Figure 1E, F, G, and H).**

Table 1: Clinicopathological parameters and therapy outcome of the studied patients with DLBCL

Total Patients No.=111				**Total Patients No.= 111**			
Parameters	**Item**	**No.**	**%**	**Parameters**	**Item**	No.	%
Age Group	Mean±SD	44.4±15.7		**Stage**	Stage I	7	6.3%
	Median (Range)	47(16 – 73)			Stage II	25	22.5%
	≤60 years	93	83.8%		Stage III	11	9.9%
	>60 years	18	16.2%		Stage IV	68	61.3%
Sex	Male	69	62.2%		Stage I-II	32	28.8%
	Female	42	37.8%		Stage III-IV	79	71.2%
ECOG PS	ECOG 1-2	84	75.7%	**Extranodal sites**	≤1 site	92	82.9%
	ECOG 3-4	27	24.3%		>1 site	19	17.1%
Serum LDH	Mean±SD	373.6±385.9		**IPI**	Score 0	16	14.4%
	Median (Range)	289 (97 – 3238)			Score 1	31	27.9%
	Normal	54	48.6%		Score 2	36	32.4%
	Elevated	57	51.4%		Score 3	18	16.2%
ALP	Mean±SD	135.5±144.8			Score 4	8	7.2%
	Median (Range)	93(40 – 1146)			Score 5	2	1.8%
	Normal	89	80.2%		Low	47	42.3%
	Elevated	22	19.8%		Low-Intermed.	36	32.4%
ESR	Mean±SD	39.7±25.1			Intermed-High	18	16.2%
	Median (Range)	32(10 – 110)			High	10	9%
	Normal	44	39.6%	**Metabolic Response (No.=111)**	CR	86	77.5%
	Elevated	67	60.4%		PR	18	16.2%
CBC	Normal	64	57.7%		SD	7	6.3%
	Anemia	30	27%	**Relapse (No=86)**	Absent	69	80.2%
	Pancytopenia	15	13.5%		Present	17	19.8%
	Leukocytosis	2	1.8%	**Mortality (No.=111)**	Alive	97	87.4%
B Symptoms	A	62	55.9%		Died	14	12.6%
	B	49	44.1%	**F. up duration (months)**	Mean±SD	44.6±9.7	
BMB	Negative	64	57.7%		Median (Range)	44.5 (11– 81)	
	Positive	47	42.3%				

Categorical data were expressed as numbers (%), whereas continuous variables were expressed as mean ± SD and median (range).

Table 2: Diagnostic performance of PET/CT in the detection of BM infiltration sites among the studied patients with DLBCL

PET/CT Findings	TP	FP	TN	FN	SN% (95%CI)	SP% (95%CI)	PPV% (95%CI)	NPV% (95%CI)	Acc% (95%CI)	p-value[a]
Bone marrow involvement	47	0	64	0	100% (92.5-100)	100% (94.4-100)	100%	100%	100% (96.7-100)	1.00
Skull	44	0	64	3	93.6% (82.5-98.7)	100% (94.4-100)	100%	95.5% (87.7-98.5)	97.3% (92.3-99.4)	<0.001
Vertebrae	26	0	64	21	55.3% (40.1-69.8)	100% (94.4-100)	100%	75.3% (68.9-80.7)	81.1% (72.5-87.9)	<0.001
Sacrum	9	0	64	38	19.1% (9.1-33.3)	100% (94.4-100)	100%	62.7% (59.4-65.9)	65.8% (56.2-74.5)	<0.001
Pelvic bone	20	0	64	27	42.6% (28.3-57.8)	100% (94.4-100)	100%	70.3% (64.9-75.2)	75.7% (66.6-83.3)	<0.001
Sternum	9	0	64	38	19.1% (9.1-33.3)	100% (94.4-100)	100%	62.7% (59.4-65.9)	65.8% (56.2-74.5)	<0.001
Clavicles	5	0	64	42	10.6% (3.5-23.1)	100% (94.4-100)	100%	60.4% (57.9-62.7)	62.2% (52.5-71.2)	0.012
Ribs	8	0	64	39	17% (7.6-30.8)	100% (94.4-100)	100%	62.1% (59-65.1)	64.9% (55.2-73.7)	0.001
Scapula	6	0	64	41	12.8% (4.8-25.7)	100% (94.4-100)	100%	60.9% (58.3-63.5)	62% (52.2-71.2)	0.005
Humerous	20	0	64	27	42.6% (28.3-57.8)	100% (94.4-100)	100%	70.3% (64.9-75.2)	75.7% (66.6-83.3)	<0.001
Femur	20	0	64	27	42.6% (28.3-57.8)	100% (94.4-100)	100%	70.3% (64.9-75.2)	75.7% (66.6-83.3)	<0.001

Qualitative data were expressed as a number (percentage); TP: True Positive; FP: False Positive; TN: True Negative; FN: False Negative; SN: Sensitivity; SP: Specificity; PPV: Positive Predictive Value; NPV: Negative Predictive Value; Acc: Accuracy; %CI: 95% Confidence Interval; a: McNemar's test; p-value< 0.05 is significant.

Table (3): The sites infiltrated with DLBCL in the studied patients based on PET/CT findings.

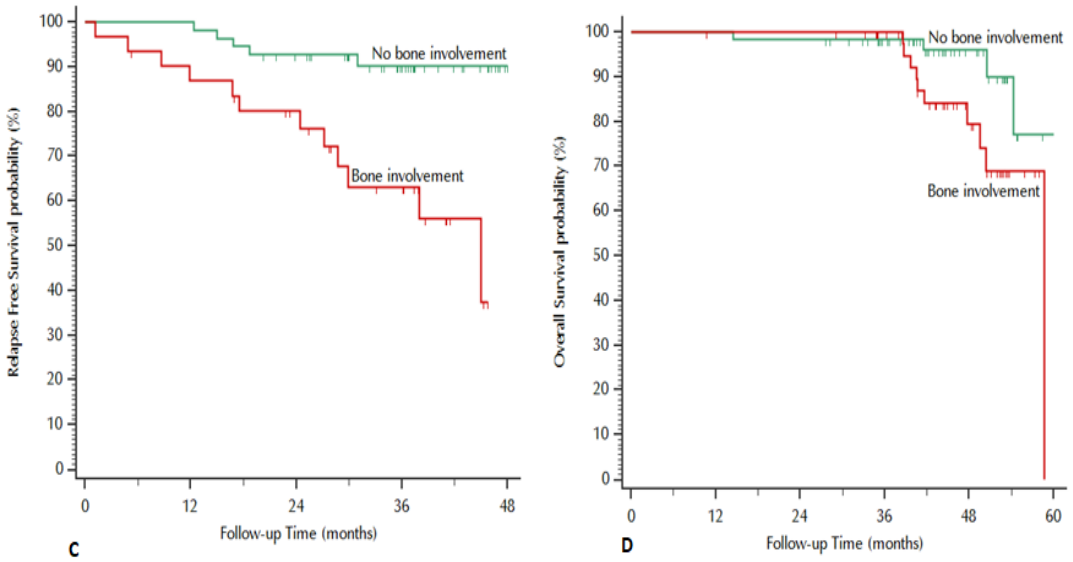
Site	PET/CT findings	N =111	%	Site	PET/CT findings	N =111	%
Nodal sites	Absent	14	12.6%	**Para spinal**	Absent	110	99.1%
	Supradiaphragmatic.	28	25.2%		Present	1	0.9%
	Infradiaphragmatic.	27	24.3%	**Skin**	Absent	108	97.3%
	Supra & Infra	42	37.8%		Present	3	2.7%
Extra nodal Sites	Absent	55	49.5%	**Soft Tissue**	Absent	107	96.4%
	Present	56	50.5%		Present	4	3.6%
Spleen	Absent	88	79.3%	**Renal**	Absent	107	96.4%
	Present	23	20.7%		Present	4	3.6%
Liver	Absent	98	88.3%	**Bone**	Absent	64	57.7%
	Present	13	11.7%		Present	47	42.3%
Lung	Absent	98	88.3%	**Skeleton Type**	Absent	64	57.7%
	Present	13	11.7%		Axial	19	17.1%
Stomach	Absent	105	94.6%		Appendicular	8	7.2%
	Present	6	5.4%		Axial&Append.	20	18%
Brain	Absent	108	97.3%		Absent	64	57.7%
	Present	3	2.7%	**Uptake Pattern**	Absent	64	57.7%
Pancreas	Absent	107	96.4%		Unifocal	13	11.7%
	Present	4	3.6%		Bifocal	2	1.8%
Peritoneum	Absent	110	99.1%		Multifocal	19	17.1%
	Present	1	0.9%		Diffuse	13	11.7%
Nasopharynx	Absent	107	96.4%	**SUV**	Mean±SD	13.5±8.5	
	Present	4	3.6%		Median (Range)	11 (4- 46)	

Continuous variables were expressed as mean ± SD & median (range); Categorical variables were expressed as number (percentage).

Table (4): Relationship between therapy outcome and lymphomatous BM infiltration in PET/CT among the studied DLBCL patients

Therapy Outcome	All studied patients		Bone infiltration n PET/CT				p-value
			Absent		Present		
	No.	%	No.	%	No.	%	
Metabolic Response	(N=111)		(N=64)		(N=47)		
CR	86	77.5%	55	85.9%	31	66%	0.019[b]
PR	18	16.2%	5	7.8%	13	27.7%	
SD	7	6.3%	4	6.2%	3	6.4%	
Relapse	(N=86)		(N=55)		(N=31)		
Absent	69	80.2%	50	90.9%	19	61.3%	0.001[b]
Present	17	19.8%	5	9.1%	12	38.7%	
Relapse Free Survival							
Mean RFS (months)	42.2		45.7		34.9		<0.001[e]

Therapy Outcome	All studied patients		Bone infiltration n PET/CT				p-value
			Absent		Present		
(95%CI)	(39.5 – 45.0)		(43.3 – 48.0)		(29.7 – 40.2)		
1-year RFS	94.1%		98.2%		86.9%		
2-year RFS	87%		92.7%		80%		
3-year RFS	80.9%		90.3%		63.2%		
4-year RFS	71.4%		90.3%		37.4%		
Mortality	(N=111)		(N=64)		(N=47)		
Alive	97	87.4%	60	93.8%	37	78.7%	0.018[b]
Died	14	12.6%	4	6.2%	10	21.3%	
Overall Survival							
Mean OS (months)	66.3 months		73.9 months		54.3 months		0.034[e]
(95%CI)	(56.7 – 75.9)		(66.5 – 81.3)		(51.7 – 56.9)		
1-year OS	100%		100%		100%		
2-year OS	99.1%		98.4%		100%		
3-year OS	99.1%		98.4%		100%		
4-year OS	88.2%		96%		79.5%		
5-year OS	48.3%		77.1%		0%		



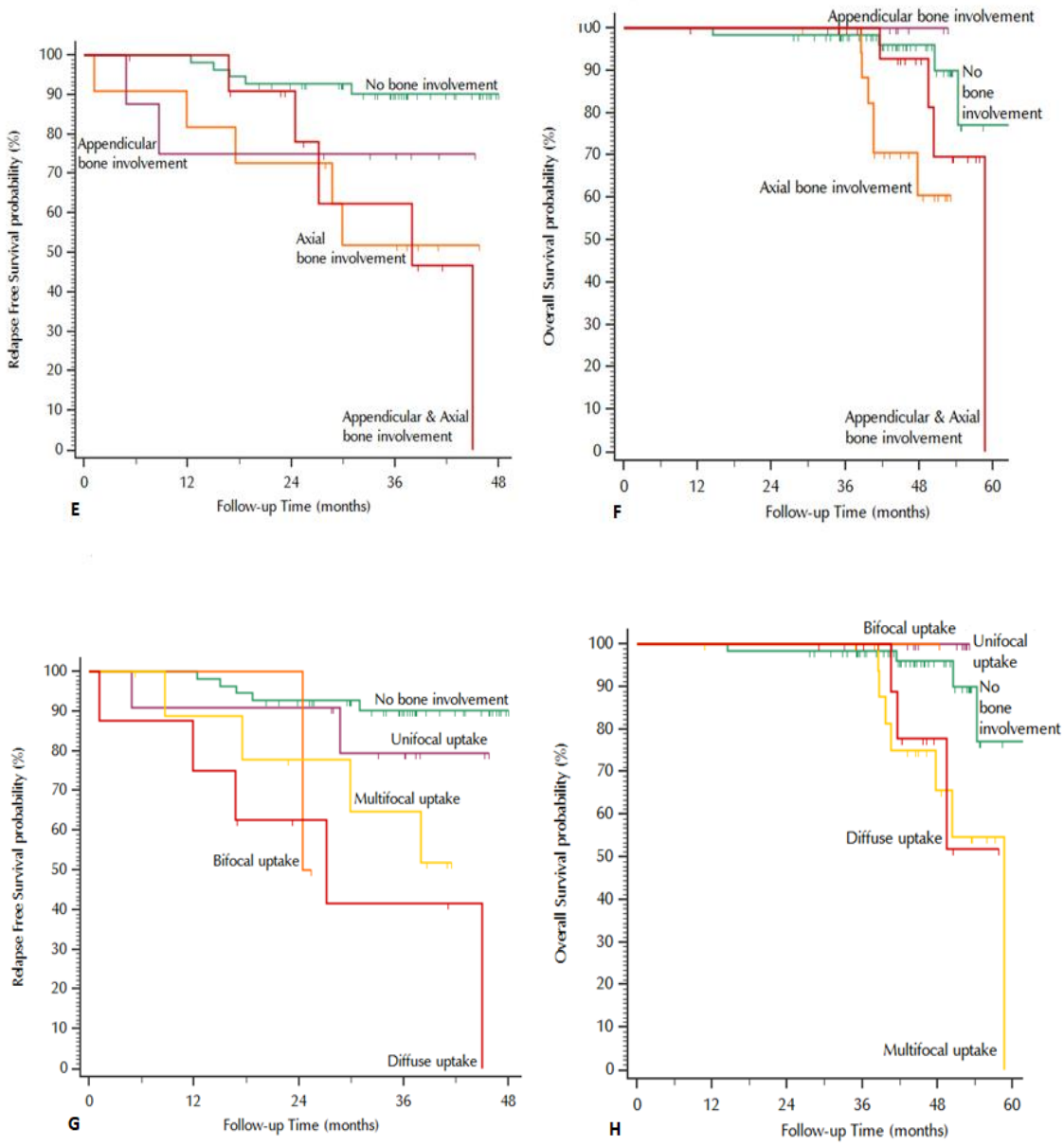


Figure 1: Kaplan-Meier Survival plots for all studied patients with DLBCL (**N** = 111): Bone involvement and/or BM infiltration in PET/CT are stratified by **(C** and **D)**. The type of the involved skeleton was stratified by (**E** and **F**), while (**G** and **H**) stratified the uptake pattern.

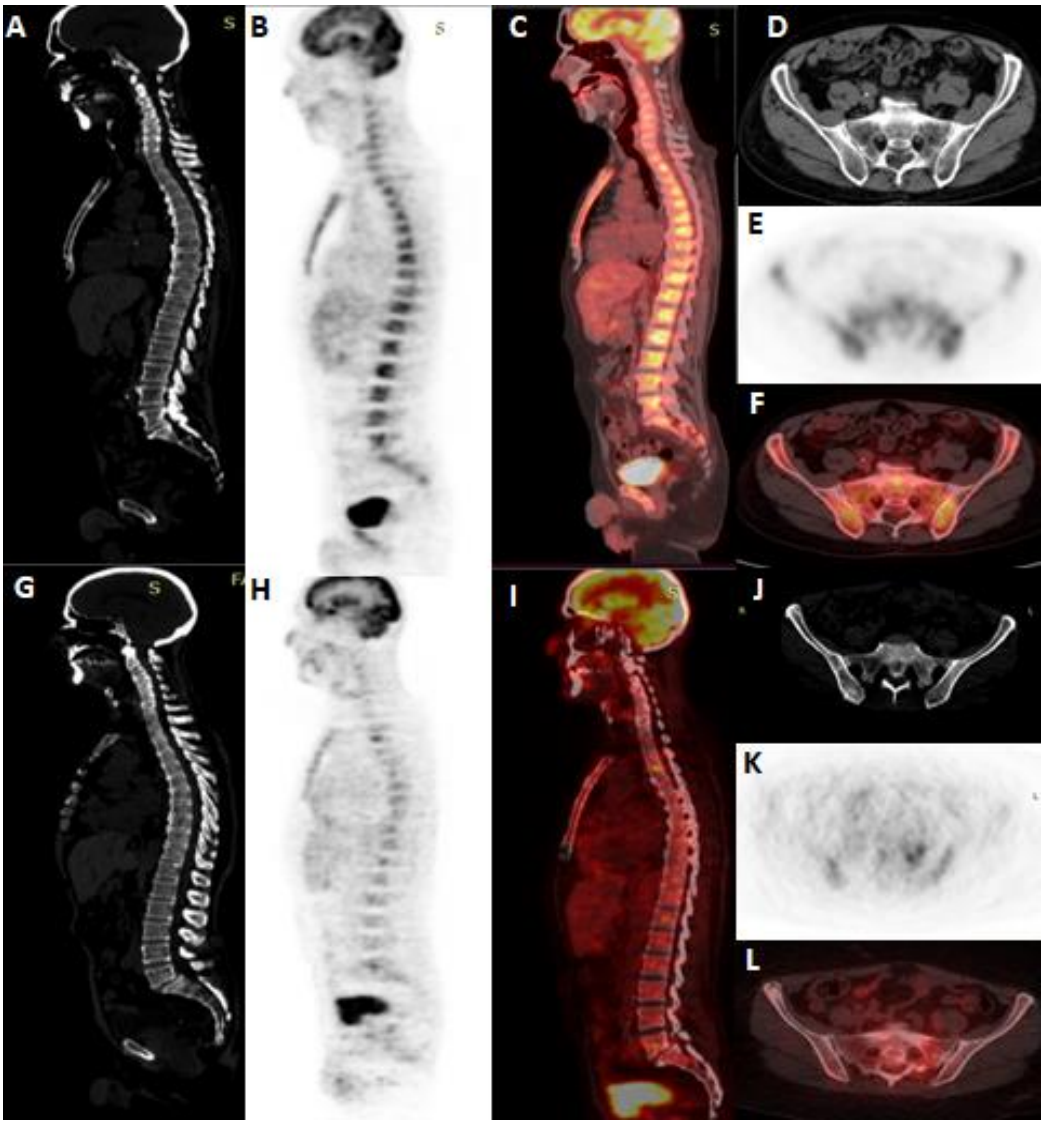


Figure (2): 52-year-old male with pathologically confirmed DLBCL and negative iliac crest biopsy for BM infiltration, the sagittal images (**A, B**, and **C**), as well as the axial cuts of the pelvis (**D, E,** and **F**), revealed metabolically active FDG avid widespread mixed lytic and sclerotic osseous deposits (predominantly sclerotic) involving most of the axial and appendicular skeleton. Sternal biopsy confirmed Positive BM infiltration. The lower raw images of the same cuts (**G, H, I, J, K**, and **L**) showed mild regression in the activity of previously reported lesions, with a reduction of SUVmax from 9.8 to 6.7 in the most active lesion (LV2).

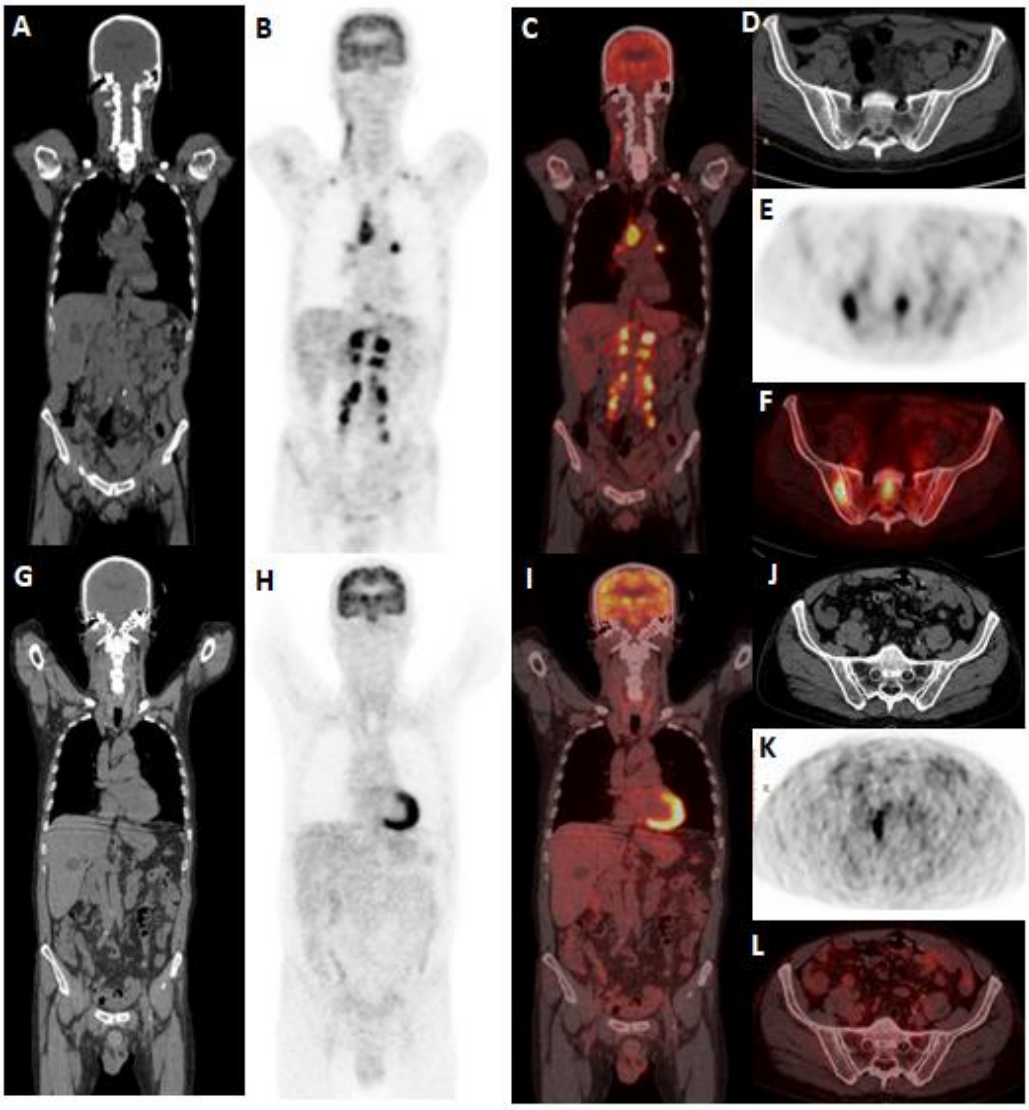


Fig. 3: A 66-year-old male with DLBCL. The sagittal images **(A, B, and C),** as well as the axial cuts of the pelvis **(D, E, and F)**, revealed metabolically active FDG avid wide-spread LNs infiltration at the axillary, mediastinal, and many abdominal and pelvic LNs groups. Also, there is active FDG uptake at the sacrum and right iliac bone. The follow-up PET/CT scan **(the lower raw G, H, I, J, K, and L images of the same cuts)** showed almost complete resolution of the previously mentioned nodal and osseous lesions, reflecting a complete metabolic response. A hypodense small hepatic focal lesion was noted in both studies, likely attributed to a simple hepatic cyst.

DISCUSSION

^{18}FDG-PET/CT had a major role in malignant lymphoma management since the mid-1990s. Detecting lymphoma manifestations at staging was one of the first uses for PET in oncology and has demonstrated high SN **[9]**. To choose the best plan of treatment for Hodgkin lymphoma and DLBCL, reliable and precise staging is essential. The 2014 Lugano criteria, which updated the well-known Ann Arbor classification, recommend ^{18}FDG-PET as the gold standard method for evaluating all ^{18}FDG-avid lymphomas, owing to its high SN for the diagnosis of involved LNs and extra-nodal disease **[10, 11]**. Also, **Gómez et al.** reported that ^{18}FDG-PET is highly recommended for staging DLBCL due to its greater SN in detecting nodal and extra-nodal lymphomatous infiltration **[12]**. Evaluation of lymphomatous BM infiltration is crucial for staging

because its infiltration upstages the disease to stage IV. Histologic examination of the BM can be done via a small sample of BMB from the posterior iliac crest, which is an invasive procedure. Unlike, ^{18}F-FDG PET/CT is a noninvasive method that enables visualization of the entire BM **[13]**. When infiltration is found in sites other than the posterior iliac crest, the blind BMB does not rule out BM infiltration **[14]**. The SN of PET/CT decreases when a BMB is simply applied as the reference standard **[15]**. Historically, a BMB has been the most reliable method for identifying lymphomatous BM infiltration. However, BMB has many drawbacks, including the potential to miss a patchy pattern of lymphomatous BM infiltration **[16]**. According to **Cheson et al.,** an ^{18}FDG-PET/CT showing bone or BM infiltration is sufficient to indicate a late disease stage, and the BMB is not necessary **[10]**. On the other side, **Adams et al.** stated that BMB cannot be substituted for ^{18}FDG-PET/CT when evaluating patients with DLBCL **[17]**. The percentage of positive iliac crest BMB (+ve BMB) varies greatly between different studies. **Chen et al.** reported a 7.2% +ve BMB rate that lies in the lower range of previous studies (6.0% to 16.4%) **[18, 19, 20]**, which is somewhat lower than the rate of the current study (19.8%). As a result of this heterogeneity, the predictive significance of BMB may be interpreted differently.

The present study showed that ^{18}FDG-PET/CT is more sensitive, specific, and accurate than BMB for the recognition of DLBCL BM infiltration. +ve FDG BM uptake was depicted in 47 out of 47 patients with 100% SN and 100% NPV, while BMB was positive in 22 out of 47 patients with 46.8% SN. The 100% NPV means no patients who had positive BM infiltration were missed by PET/CT. This may suggest that a BMB could be omitted safely in negative PET patients. In contrast, Adams et al., in a meta-analysis, suggested that BM infiltration cannot be excluded in cases with negative PET results, as PET/CT can miss BM infiltration in nearly 3.1% of patients **[17]**. It should be remembered that the SN of ^{18}FDG-PET in the detection of BM infiltration in aggressive non-Hodgkin lymphoma is lower than Hodgkin lymphoma **[21, 22]**. Also, Alzahrani et al.'s analysis of data from one Canadian and two Danish centers reported lower values of NPV and SN (60% and 91%, respectively) **[20]**. A combined analysis of the Positron Emission Tomography Guided Therapy of Aggressive Non-Hodgkin's Lymphomas and (PETAL and OPTIMAL>60 research groups reported similar results **[23]**. In this regard, the limited SN of PET scans could be attributed to the observation that +ve BMB results in DLBCL usually come along with diffusely enhanced skeletal ^{18}FDG uptake that sometimes interpreted as negative scan. In contrast, BMB appears warranted only when results could have a direct effect on treatment choice, for example, in cases with limited-stage disease but without other risk factors. Importantly, a BMB should be excluded in all patients where infiltration has already been confirmed with ^{18}FDG-PET **[9]**.

To evaluate the state of BM in DLBCL patients, our study provided a detailed description of ^{18}FDG BM uptake patterns. Four patterns of +ve ^{18}FDG BM were seen as multifocal (19), bifocal (2), unifocal (13), and diffuse (13) with the multifocal pattern being the most prevalent 40% (19/47), which is comparable to that reported by **Lim et al. [24]** and the Danish-Canadian study [**20**] but with different rates (64% and 17.1%, respectively) that could be related to the patient's number in each study. The BM infiltration prognostic value based on ^{18}FDG-PET/CT is currently poorly understood. Some studies found that +ve ^{18}FDG BM uptake had a great predictive value for DLBCL patients **[25-28]**. On the contrary, other researchers came to the opposite result [21, 28, 29]. These studies employed a different interpretation of the diffuse BM pattern, which more or less led to different conclusions. Patients with +ve ^{18}FDG BM uptake in the current study exhibited significantly poorer four-year RFS and five-year OS rates than patients with -ve ^{18}FDG BM uptake, demonstrating the prognostic usefulness of PET/CT. **El Karak et al.** reported that the mean progression-free survival (PFS) of patients with or without BM infiltration on PET was 16.2 months and 21.2 months, respectively. Additionally, there was a significant difference in the risk of death between patients with positive and negative BM infiltration detected by PET; the mean OS of patients with or without BM infiltration on PET was 19.2 months and 23.3 months, respectively [**30**]. Patients who had either +ve BMB or +ve ^{18}FDG BM results in Danish-Canadian research had worse outcomes compared to those who had negative results from both tests [**20**]. **Lim et al.** found that in a subgroup of patients with positive BMB, the survival of 35 patients with +ve ^{18}FDG BM was substantially worse than that of 24 patients with -ve ^{18}FDG BM [**24**]. Instead of using PET to determine BM infiltration, **Chen et al.** investigated the predictive usefulness of PET/CT-based BM uptake patterns. According to their findings, focal +ve PET patients had a significantly worse prognosis than normal PET patients, however, 3y-PFS for +ve BMB and -ve BMB revealed no

statistically significant difference. Moreover, they showed that focal +ve PET can differentiate patients with a bad prognosis from those with -ve BMB. In multivariate analysis of PFS, it was found that only stage III/IV and focal +ve PET were to be independent predictors of PFS. In conclusion, the focal BM pattern has a higher predictive value than BMB **[18]**. Unlike **Chen-Liang's and Khan's** results, **Chen Yumei et al.** didn't achieve the result that BMB was independently prognostic for PFS and OS [**22, 28, and 18**]. In the current study, the focal and diffuse +ve PET could independently predict the RFS and OS. But in the **Chen Yumei et al.** study **[18]**, focal +ve PET failed to independently predict OS. The relatively small number of deaths during follow-up in their study (10.4%, 20/193) may be the main cause for this result. They also found that there is no significant difference in patients' survival between diffuse +ve PET and -ve PET, which may be due to the small portion of +ve BMB in diffuse +ve PET patients.

LIMITATIONS

Is the small number of patients with lymphomatous BM infiltration. We did not repeat the BMB for patients (64 patients), who were negative for both unilateral iliac crest biopsy and ^{18}FDG BM uptake. We relied on qualitative visual analysis to categorize BM lesions as positive or negative, while quantitative measurements of BM on the ^{18}FDG-PET/CT scan may help in better stratification of BM infiltration, and finally, a short follow-up period, especially for those with BM infiltration.

CONCLUSIONS

^{18}FDG PET/CT imaging provides whole-body mapping for detecting BM infiltration with high SN, SP, and accuracy; it can replace routine BMB in the staging of DLBCL. Avid ^{18}FDG BM uptake is a poor prognostic sign associated with a higher relapse rate and lower rates of CMR and OS. It is necessary to conduct additional prospective studies with a larger sample size to understand the clinical significance of PET/CT in evaluating BM infiltration.

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List of abbreviations:

NHL: Non-Hodgkin's lymphoma
PET–CT: Positron emotion tomography/computerized tomography
^{18}FDG: Florodeoxyglucose
BM: Bone marrow
+ve : Positive
-ve: Negative
+ ve ^{18}FDG BM : Positive FDG Bone marrow uptake
-ve ^{18}FDG BM: Negative FDG Bone marrow uptake
DLBCL: Diffuse large B-cell lymphoma
BMB: Bone marrow biopsy
+ve BMB: Positive Bone marrow biopsy
-ve BMB: Negative Bone marrow biopsy
GS: Gold standard
SPSS: Statistical Package for the Social Sciences;
SN: Sensitivity
SP: Specificity
PPV: Positive predictive value
NPV: Negative predictive value
LNs: Lymph node
CMR: Complete metabolic Response
PMR: Partial metabolic response
SD: Stable disease
RFS: Relapse free survival
OS: Overall survival
PFS Progression Free Survival

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