Prognostic value of bone marrow ^{18}F-FDG uptake on PET/CT in lymphoma patients with negative bone marrow involvement

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Abstract

Objective: The study evaluated the significance of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake of bone marrow (BM) for predicting progression-free survival (PFS) in lymphoma patients without BM involvement. **Subjects and Methods:** Ninety-five patients with histopathologically proven lymphoma, 7 Hodgkin's lymphoma and 88 non-Hodgkin's lymphoma, who underwent ^{18}F-FDG positron emission tomography/computed tomography (PET/CT) and BM biopsy for staging work-up and 40 normal subjects were retrospectively enrolled. Maximal ^{18}F-FDG uptake of lymphoma (Lmax), mean ^{18}F-FDG uptake of BM (BM SUV) and BM-to-liver uptake ratio (BLR) were measured. Prognostic value of BM SUV and BLR for predicting PFS were assessed. **Results:** Of the 95 patients, 35 (36.8%) were histopathologically or clinically diagnosed with BM involvement of lymphoma. There were significant differences of BLR among lymphoma patients with/without BM involvement and normal subjects ($P<0.05$). For all patients, high risk indicated by International Prognostic Index (IPI) score and Lmax were significantly associated with PFS on multivariate analysis ($P< 0.05$). For 60 patients without BM involvement, BM SUV and BLR were independent prognostic factors for PFS along with performance status and Lmax ($p<0.05$). Among patients without BM involvement, high ^{18}F-FDG uptake of BM was associated with significantly worse PFS than low ^{18}F-FDG uptake of BM, with no significant difference in PFS apparent compared to patients with BM involvement. **Conclusion:** In lymphoma patients without BM involvement, ^{18}F-FDG uptake of BM was significantly associated with worse PFS. Patients with high ^{18}F-FDG uptake of BM showed similar prognosis to those with BM involvement.

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Introduction

In patients with lymphoma, accurate evaluation of the extent of lymphoma is imperative in selecting optimal treatment and predicting prognosis [1, 2]. Currently, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) is the standard popular means of evaluating the extent of lymphoma and treatment response, and is part of the standard staging assessment [3-5]. For Hodgkin's lymphoma (HL), ^{18}F-FDG PET/CT is a more sensitive way of detecting bone marrow (BM) involvement than BM biopsy and focal BM ^{18}F-FDG uptake is indicative of BM involvement [4, 6]. For non-Hodgkin's lymphoma (NHL), ^{18}F-FDG PET/CT has lower sensitivity (50.0-68. 8%) in detecting BM involvement, which may be insufficient to replace BM biopsy [6-8]. Many NHL patients with BM involvement display only diffusely increased BM ^{18}F-FDG uptake without any focal ^{18}F-FDG uptake [9]. Because the degree of BM ^{18}F-FDG uptake is also related with BM activation in response to infection or malignancy, diffusely increased ^{18}F-FDG uptake of BM can be found in some of patients with negative BM involvement, making it hard to differentiate from BM involvement of NHL [10-13].

Inflammatory and immune responses to malignancy have been associated with progression of various types of cancers, and prognostic values of biomarkers reflecting the systemic inflammatory response, such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and C-reactive protein (CRP), have been studied in lymphoma patients [14-16]. Considering that ^{18}F-FDG uptake of BM can reflect a systemic inflammatory response to malignancy, BM ^{18}F-FDG uptake in a lymphoma patient might be associated with prognosis, even the patient lacks evidence of BM involvement. However, most of the previous studies explored the diagnostic capability of ^{18}F-FDG PET/ CT to detect BM involvement, and only a few studies have evaluated the prognostic value

of ^{18}F-FDG uptake of BM in patients with lymphoma [10, 12].

In the present study, we evaluated the relationship between ^{18}F-FDG uptake of BM, serum inflammatory markers and prognostic value of BM ^{18}F-FDG uptake, in lymphoma patients with negative BM involvement. Furthermore, we classified those patients into two subgroups according to ^{18}F-FDG uptake of BM (high and low ^{18}F-FDG uptake) and compared the prognosis in those two subgroups to the prognosis in patients with BM involvement.

Subjects and Methods

Patients

This retrospective study was approved by the institutional review board of our university and followed the principles of the Declaration of Helsinki. Due to the retrospective nature of the study, the requirement to obtained informed consent was waived. We retrospectively enrolled 95 patients with histopathologically proven lymphoma in our medical center between January 2011 and December 2014. The 95 enrolled patients included 7 with HL and 88 with NHL. The characteristics of the patients are listed in Table 1. Patients who were diagnosed with primary central nervous system lymphoma or mucosa-associated lymphoid tissue lymphoma, who had concurrent liver or infectious disease, or who had a history of another malignant disease were excluded. All patients underwent staging work-up of physical examina-tions, blood tests, including blood cell counts and serum CRP and lactate dehydrogenase (LDH) levels, contrast enhanced CT, ^{18}F-FDG PET/CT, and BM biopsy. Untargeted BM biopsy was performed in the unilateral iliac crests. Immunohistochemical staining as well as hematoxylin and eosin staining were performed to detect BM involvement. After staging work-up, all patients underwent chemotherapy, radiotherapy, and/or immunotherapy according to the histopathology types and stage of lymphoma, and their clinical condition. After the initial treatment, physical examinations and regular imaging studies including contrast-enhanced CT and ^{18}F-FDG PET/CT were performed and disease status was determined for each clinical follow-up visit according to the results of the imaging examinations. Disease progression was defined as an increase of size of known involved lesion and/or appearance of new involved lesion according to the International Harmonisation Project revision of the International Working Group criteria [17].

For comparison, 40 normal subjects (median age, 54 years; range, 35-77 years) comprising 18 men and 22 women were also included in the study. All had undergone ^{18}F-FDG PET/CT for cancer screening in our medical center between January and December 2014. None of them had a history of malignant, infectious, or liver disease and there were no abnormal PET/CT findings.

The ^{18}F-FDG PET/CT scan

Fluorine-18-FDG PET/CT studies were obtained using a dedicated Biograph mCT 128 scanner (Siemens Healthcare, Knxville, TN, USA). After at least 6 hours fasting, 4.07 MBq/kg of ^{18}F-FDG was intravenously administered. Before the ^{18}F-FDG injection, blood glucose test was performed. Blood glucose was $\leqslant$150mg/dL in all patients. Approximately 60 minutes after ^{18}F-FDG injection, PET/CT scan from the skull base to the proximal thigh was performed. At first, a CT scan was done to generate attenuation correction map at 100mA and 120kVp without contrast enhancement. Positron emission tomography data were then acquired at a 1.5 minutes per one bed position. The PET images were reconstructed with an iterative algorithm using TrueX and time-of-flight reconstruction.

^{18}F-FDG PET/CT image analysis

All PET/CT images were retrospectively reviewed by two nuclear medicine physicians who were blinded to the BM biopsy results and clinical outcomes. Disagreements between the readers were resolved by a consensus reading. At first, PET/CT images were visually assessed and extent of lymphoma was determined. Fluorine-18-FDG uptake of BM was evaluated and focal BM ^{18}F-FDG uptake was considered as positive BM involvement. Focal ^{18}F-FDG uptake of BM was defined as one or more circumscribed areas of increased ^{18}F-FDG uptake showing greater intensity of ^{18}F-FDG uptake than normal liver and no anatomical lesions to suggest benign bone pathology [12]. Thereafter, a spheroid-shaped volume of interest (VOI) was drawn over each lesion of lymphoma and the maximum standardized uptake value (SUV) of lymphoma for each patient was measured (Lmax). In patients without focal ^{18}F-FDG uptake on BM, ^{18}F-FDG uptake of BM was measured as follows. Seven VOI were drawn over the bilateral iliac bones and vertebral bodies of five vertebrae (mostly T11, T12, L3, L4, and L5 spines, unless a pathologic lesion such as compression fracture or severe osteoarthritic changes was present). Mean SUV for each VOI was measured using an automatic isocontour set at 75% of maximum SUV, because the mean SUV using 75% cut-off value of the maximum SUV produces substantial agreement between observers [18, 19]. Mean SUV of the seven VOI was calculated and defined as BM SUV. To measure ^{18}F-FDG uptake of normal liver, 2 cm-sized spheroid-shaped VOI was drawn in the right lobe of the liver, where lymphoma involvement was not detected, and mean SUV of VOI was measured. Afterwards, BM SUV-to-normal liver uptake ratio of ^{18}F-FDG uptake (BLR) was calculated.

Statistical analysis

The Kruskal-Wallis test with post-hoc analysis was performed to compare BM SUV and BLR between patient groups. For evaluation of correlation of ^{18}F-FDG uptake of the BM with hematologic parameters, serum inflammatory markers, and BM cellularity on BM biopsy, Spearman's rank correlation coefficients were calculated. The predictive value of variables for progression-free survival (PFS) was assessed using a Cox proportional hazards regression model for univariate and multivariate analyses. All continuous variables included in the survival analysis were dichotomized according to the optimal cut-off values determined by maximally selected chi-square statistics.For multivariate analysis, variables that showed statistical significance in univariate

Table 1. *Characteristics of the 95 enrolled patients*

Characteristic		Number of patients (%)	Median (range)
Age (years)			
Sex	Male	57 (60.0%)	
	Female	38(40.0%)	
Subtype	Diffuse large B-cell lymphoma	47 (49.5%)	
	Peripheral T-cell lymphoma	9 (9.5%)	
	Follicular lymphoma	8 (8.4%)	
	Marginal zone B-cell lymphoma	8 (8.4%)	
	Hodgkin's lymphoma	7 (7.4%)	
	Anaplastic large cell lymphoma	5 (5.3%)	
	NK/T-cell lymphoma	4 (4.2%)	
	Mantle cell lymphoma	4 (4.2%)	
	Angioimmuno-blastic T-cell lymphoma	3 (3.1%)	
Stage	I	23 (24.2%)	
	II	21 (22.1%)	
	III	10 (10.5%)	
	IV	41 (43.2%)	
BM involvement on BM biopsy or ^{18}F-FDG PET/CT		35 (36.8%)	
Extranodal involvement		41 (43.2%)	
Presence of B symptoms		27 (28.4%)	
ECOG PS	0-1	82 (86.3%)	
	2-3	13(13.7%)	
IPI	0-1 (low)	34 (35.8%)	
	2 (low intermediate)	15 (15.8%)	
	3 (high intermediate)	14 (14.7%)	
	4-5 (high)	32 (33.7%)	
LDH (IU/L)			349.0 (143.0-7323.0)
CRP (mg/dL)			8.2 (0.1-348.1)
WBC (×10^{12}cells/L)			6.05 (0.81-100.90)
Hemoglobin (g/dL)			12.1 (6.1-16.4)
NLR			2.44 (0.15-114.66)
PLR			135.58 (3.55-1187.08)
Lmax			11.00 (1.52-47.43)
BM SUV*	25 patients with BM involvement		1.62 (0.94-4.74)
	60 patients with no BM involvement		1.44 (0.82-2.97)
BLR*	25 patients with BM involvement		0.88 (0.60-3.92)
	60 patients with no BM involvement		0.73 (0.44-1.94)

**Measured in 85 patients without focal ^{18}F-FDG uptake on the BM. BM, bone marrow; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; LDH, lactate dehydrogenase; CRP, C-reactive protein; WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet to lymphocyte ratio; Lmax, maximum standardized uptake value of lymphoma; BM SUV, mean standardized uptake value of bone marrow; BLR, BM SUV to liver uptake ratio.*

analysis were included. Survival time for PFS was defined as the time from the day of the initiation of the first-line treatment to the day of detection of disease progression. Hazard ratios with Wald 95% confidence intervals (CIs) were provided for Cox models. For the internal validation, a bootstrap method using 1,000 bootstrap replications was performed. A P-value of <0.05 was considered statistically significant. Survival curves according to the ^{18}F-FDG uptake of BM were estimated by the Kaplan-Meier method and compared by using the log-rank test. In a comparison of PFS between three patient subgroups (those with BM involvement, those with high ^{18}F-FDG uptake of BM and negative BM involvement, and those with low ^{18}F-FDG uptake of BM and negative BM involvement), Bonferroni correction was used to account for multiple testing, and P-value of less

than 0.0167 (0.05/3=0.0167) was considered to be a significant difference. Statistical analyses were performed using IBM SPSS statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA) and R 2.13.0 software (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

Of all patients, 8 patients (8.4%) showed BM involvement of lymphoma on BM biopsy and focal BM ^{18}F-FDG on PET/CT, and 25 patients (26.3%) had BM involvement on BM biopsy but no focal BM ^{18}F-FDG uptake. Two patients (2.1%) had negative results on BM biopsy but showed focal ^{18}F-FDG uptake of the BM and were clinically diagnosed with BM involvement. Overall, 35 patients (36.8%) were histopathologically or clinically diagnosed with BM involvement of lymphoma. Bone marrow SUV and BLR were measured in 85 patients without focal ^{18}F-FDG uptake on the BM, consisted of 25 patients with BM involvement and 60 patients with negative BM involvement (Table 1). During the mean follow-up period of 22.5±12.3 months, 36 patients (37.9%) experienced disease progression.

The BM SUV and BLR of 25 patients with BM involvement and no focal ^{18}F-FDG uptake and 60 patients with negative BM involvement (Figure 1) were compared with those of 40 normal subjects (mean BM SUV, 1.31±0.21; mean BLR, 0.60±0.10). The Kruskal-Wallis test revealed significant differences of BM SUV (P=0.01) and BLR (P<0.001) between the three groups (Figure 2). On post-hoc analysis, BM SUV and BLR in both patient groups were significantly higher than those in the 40 normal subjects (P<0.05). BLR of the 25 patients with BM involvement was significantly higher than that in 60 patients with negative BM involvement (P<0.05); however, there was no significant difference of BM SUV between the two patient groups (P>0.05).

Prognostic factors predicting PFS

The significance of prognostic factors for predicting PFS in all patients on univariate and multivariate analyses are shown in Table 2. The optimal cut-off values determined by the maximal chi-square method for age, LDH, CRP, NLR, PLR, and Lmax were 60 years, 450 IU/L, 3.0mg/dL, 3.0, 120, and 7.0, respectively. On univariate analysis, stage, BM involvement, extranodal involvement, presence of B symptoms, Eastern Cooperative Oncology Group performance status (ECOG PS), International Prognostic Index (IPI) score, serum CRP level, and Lmax were significantly associated with PFS (P<0.05 for all) and were selected for multivariate analysis. On multivariate analysis, high risk on IPI (P=0.03), and Lmax (P=0.01) were independent prognostic factors for PFS.

Subgroup analysis for patients without BM involvement

To evaluate the clinical implication of ^{18}F-FDG uptake of the BM, subgroups analysis was performed in 60 patients with no

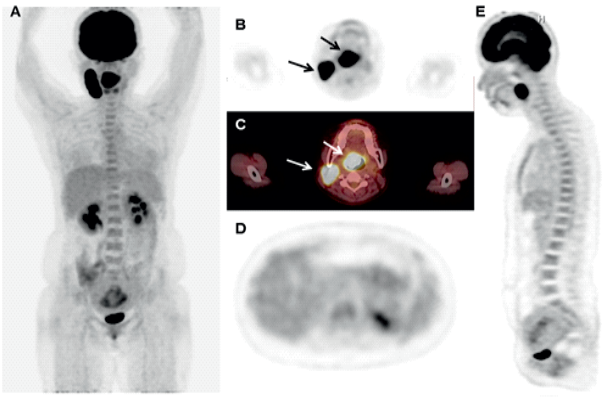

Figure 1. Maximum intensity projection (A), transaxial, (B) and (D), and sagittal (E) ^{18}F-FDG PET images and transaxial fused PET/CT images (C), of a 28 year old woman with diffuse large B-cell lymphoma. Lymphoma involvement is seen in the right palatine tonsil and right neck area with Lmax of 39.18 (arrows in (B) and (C)). No other region showed lymphoma involvement on ^{18}F-FDG PET/CT with negative result on BM biopsy. Diffusely increased ^{18}F-FDG uptake of BM is shown with BM SUV of 1.82 and BLR of 0.95. Serum CRP level, NLR, and PLR were 23.82mg/dL, 3.84, and 166.10, respectively. The patient underwent chemotherapy that consisted of doxorubicin, cyclophosphamide, vincristine, and prednisone with rituximab, achieving complete response after 6 cycles of chemotherapy. However, lymphoma was recurred 13.4 months after the treatment.

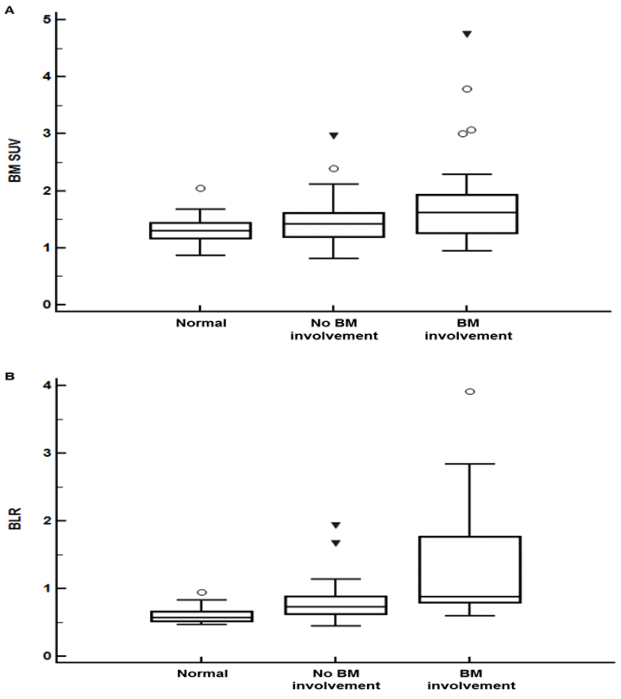

Figure 2. Distribution of BM SUV (A) and BLR (B) in 40 normal subjects (normal), 60 lymphoma patients with no BM involvement (no BM involvement), and 25 lymphoma patients with BM involvement (BM involvement) using box and whisker plot.

or clinical evidence of BM involvement. Of these, 7 patients (11.7%) had BM SUV exceeding liver ^{18}F-FDG uptake (BLR> 1.0). The relationships of ^{18}F-FDG uptake of the BM with hematologic (white blood cell count and hemoglobin level) and inflammatory (serum CRP level, NLR, and PLR) markers, and BM cellularity on BM biopsy were assessed (Table 3).

Table 2. *Significance of prognostic factors for PFS on univariate and multivariate analyses.*

Variables		Univariate analysis		Multivariate analysis	
		P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)
Age	⩽60 years		1.00		
	>60 years	0.8	1.10 (0.57-2.11)		
Sex	Female		1.00		
	Male	0.7	0.86 (0.44-1.70)		
Stage	I-II		1.00		1.00
	III-IV	0.03	2.18 (1.10-4.33)	0.5	1.66 (0.35-7.93)
ECOG	0-1		1.00		1.00
	2-3	0.002	3.56 (1.58-7.99)	0.2	2.01 (0.68-5.96)
BM involvement	No		1.00		1.00
	Yes	0.03	2.08 (1.08-4.02)	0.3	1.64 (0.61-4.40)
Extranodal involvement	No		1.00		1.00
	Yes	0.008	2.62 (1.29-5.32)	0.8	1.17 (0.44-3.12)
B symptoms	No		1.00		1.00
	Yes	0.02	2.21 (1.14-4.29)	0.4	0.57 (0.16-2.02)
IPI	0-1		1.00		1.00
	2-3	0.7	0.87 (0.35-2.16)	0.4	0.52 (0.13-2.09)
	4-5	0.009		0.03	2.02 (1.21-4.04)
LDH	⩽450 IU/L		1.00		
	>450 IU/L	0.2	1.63 (0.81-3.26)		
CRP	⩽3.0 mg/dL		1.00		1.00
	>3.0 mg/dL	0.01	2.60 (1.21-5.60)	0.4	1.40 (0.59-3.30)
NLR	⩽3.0		1.00		
	>3.0	0.3	1.48 (0.75-2.94)		
PLR	⩽120.0		1.00		
	>120.0	0.3	0.73 (0.38-1.39)		
Lmax	⩽7.0		1.00		1.00
	>7.0	0.01	3.04 (1.26-7.34)	0.01	3.14 (1.29-7.67)

ECOG PS, Eastern Cooperative Oncology Group performance status; BM, bone marrow; IPI, International Prognostic Index; LDH, lactate dehydrogenase; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; Lmax, maximum standardized uptake value of lymphoma.

Table 3. *Correlation of ^{18}F-FDG uptake of BM on PET/CT with hematologic and inflammatory markers and BM cellularity in a subgroup of 60 patients without BM involvement.*

	White blood cells	Hemoglobin	NLR	PLR	CRP	BM cellularity
BM SUV	P = 0.02 r = 0.296 (0.045 – 0.511)	P = 0.2 r = -0.176 (-0.412 – 0.082)	P = 0.04 r = 0.262 (0.009 – 0.484)	P = 0.08 r = 0.232 (-0.024 – 0.459)	P < 0.001 r = 0.467 (0.242 – 0.645)	P = 0.2 r = 0.173 (-0.111 – 0.430)
BLR	P = 0.003 r = 0.420 (0.186 – 0.609)	P = 0.1 r = -0.291 (-0.507 – 0.041)	P = 0.005 r = 0.355 (0.111 – 0.559)	P = 0.003 r = 0.401 (0.164-0.594)	P = 0.001 r = 0.597 (0.405-0.739)	P = 0.07 r = 0.261 (-0.019 – 0.503)

r, Spearman's correlation coefficient. Data in parentheses are 95% confidence intervals with a bootstrap method. BM, bone marrow; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; CRP, C-reactive protein; BM SUV, mean standardized uptake value of bone marrow; BLR, BM SUV to liver uptake ratio.

Bone marrow SUV was significantly associated with white blood cells count (P=0.02), NLR (P=0.04), and serum CPR level (P<0.001), and BLR was significantly correlated with white blood cell count (P=0.003), NLR (P=0.005), PLR (P=0.003), and serum CRP levels (P=0.001). No significant correlation was shown between BM ^{18}F-FDG uptake, hemoglobin, and BM cellularity (P>0.05).

In a subgroup of 60 patients without BM involvement, survival analysis was performed with including BM SUV and BLR as variables (Table 4). The cut-off values determined by the maximal chi-square method were 1.50 for BM SUV and 0.70 for BLR. On univariate analysis, ECOG PS, IPI score, serum CRP level, NLR, Lmax, BM SUV, and BLR were significant prognostic factors for PFS (P<0.05 for all). On multivariate analysis, ECOG PS (P=0.02), Lmax (P=0.02), BM SUV (P=0.04), and BLR (P=0.03) were significantly associated with worse PFS.

Survival analysis according to BM involvement and BM ^{18}F-FDG uptake

Because BM SUV and BLR were independent prognostic factors for PFS in patients without BM involvement, we further performed survival analysis between patients with BM involvement and two subgroups of patients without BM involvement (high and low BM SUV or BLR) with correction for multiple testing. For BM SUV, patients with BM involvement (P=0.004) and patients with BM SUV of >1.50 and negative BM involvement (P=0.01) had significantly worse PFS than those with BM SUV of ⩽1.50 and negative BM involvement. No significant difference in PFS was observed between patients with BM involvement and those with BM SUV of >1.50 and no BM involvement (P=0.6; Figure 3a). Likewise, for BLR, patients with BM involvement (P=0.004) and patients with BLR of >0.70 and negative BM involvement (P=0.01) had significantly worse PFS than those with BLR of ⩽0.70 and negative BM involvement, and no significant difference in PFS was seen between patients with BM involvement and BLR of >0.70 (P=0.3; Figure 3b).

Discussion

In the present study, BM SUV and BLR were independent prognostic factors predicting PFS in lymphoma patients without BM involvement. The ^{18}F-FDG uptake of BM in lymphoma patients was higher than that in normal subjects and significantly correlated with serum inflammatory markers. Furthermore, interestingly, patients who showed high ^{18}F-FDG uptake of BM with negative lymphoma involvement showed similar prognosis as patients with BM involvement, which were significantly worse than those with low BM ^{18}F-FDG uptake and negative BM involvement.

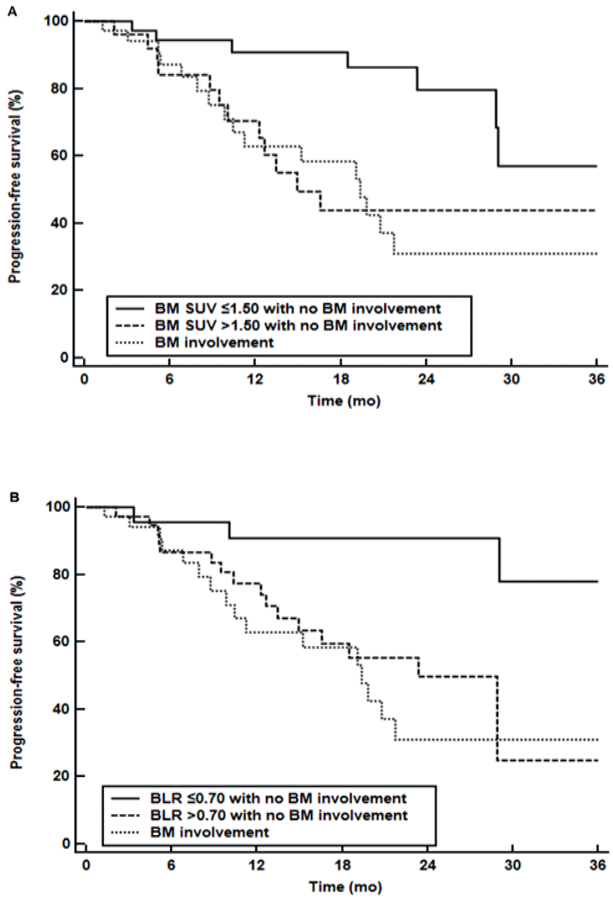

Figure 3. Kaplan-Meier curves for PFS stratified according to BM SUV (A) and BLR (B).

Table 4. *Significance of prognostic factors for PFS on univariate and multivariate analyses in a subgroup of 60 patients without BM involvement.*

Variables		Univariate analysis		Multivariate analysis	
		P-value	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)
Age	⩽60 years		1.00		
	>60 years	0.6	1.25 (0.50-3.12)		
Sex	Female		1.00		
	Male	0.9	0.92 (0.36-2.31)		
Stage	I-II		1.00		
	III-IV	0.4	1.53 (0.57-4.07)		
ECOG PS	0-1		1.00		1.00
	2-3	0.04	3.79(1.06-13.57)	0.02	5.04 (1.25-20.30)
Extranodal involvement	No		1.00		
	Yes	0.3	1.85 (0.64-5.34)		
B symptoms	No		1.00		
	Yes	0.3	1.87 (0.53-6.56)		
IPI	0-1		1.00		1.00
	2-3	0.3	0.58 (0.16-2.00)	0.3	0.51 (0.13-2.03)
	4-5	0.04	2.55 (1.05-7.63)	0.3	2.04 (0.40-10.47)
LDH	⩽450 IU/L		1.00		
	>450 IU/L	0.8	0.85 (0.20-3.69)		
CRP	⩽3.0 mg/dL		1.00		1.00
	>3.0 mg/dL	0.04	2.88 (1.02-8.14)	0.9	0.99 (0.29-3.78)
NLR	⩽3.0		1.00		1.00
	>3.0	0.02	3.07 (1.18-8.01)	0.5	1.48 (0.52-4.25)
PLR	⩽120.0		1.00		
	>120.0	0.4	1.53 (0.57-4.12)		
Lmax	⩽7.0		1.00		1.00
	>7.0	0.04	8.78 (1.17-66.20)	0.02	11.12 (1.38-89.61)
BM SUV	⩽1.50		1.00		1.00
	>1.50	0.01	3.26 (1.28-8.35)	0.04	3.17 (1.11-9.05)
BLR	⩽0.70		1.00		1.00
	>0.70	0.01	5.41 (1.49-19.82)	0.03	4.80 (1.31-20.39)

BM, bone marrow; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; LDH, lactate dehydrogenase; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; Lmax, maximum standardized uptake value of lymphoma; BM SUV, mean standardized uptake value of bone marrow; BLR, BM SUV-to-liver uptake ratio.

In general, only mild ^{18}F-FDG uptake is observed in BM of normal subjects. On the contrary, ^{18}F-FDG uptake of BM in lung cancer patients is significantly higher than that in those with benign lung nodules and correlates with serum inflammatory markers [18, 20, 21]. Also, the inter-individual variation of BM SUV in patients with various types of disease can be reduced with the correction by the normal liver ^{18}F-FDG uptake, which was BLR in the study [11]. Similarly, previous studies revealed that some lymphoma patients without BM involvement can display diffusely increased BM ^{18}F-FDG uptake, linked to anemia or inflammatory change [6, 9, 13]. In our study, BM SUV and BLR in lymphoma patients were higher than in normal subjects, regardless of BM involvement, and 11.7% of lymphoma patients without BM involvement showed BLR>1.0. Furthermore, BM SUV and BLR in patients without BM involvement significantly correlated with serum inflammatory markers including white blood cells count, NLR, and serum CRP levels, suggesting that ^{18}F-FDG uptake of BM can represent the degree of the systemic inflammatory response [18, 21].

Diverse innate and adaptive immune cells are present within the tumor microenvironment, and inflammation in the tumor microenvironment can enhance tumor initiation, progression, and metastases [22, 23]. Because serum inflammatory markers like serum CRP and NLR, which represent systemic inflammatory response to cancer cells are significant predictors for clinical outcome in lymphoma patients [14, 24], we speculated that BM ^{18}F-FDG uptake could be significantly associated with PFS in lymphoma patients. In a subgroup of lymphoma patients without BM involvement, BM ^{18}F-FDG uptake was significantly associated with PFS. Even though patients had no histopathological or clinical evidence of BM involvement, if BM ^{18}F-FDG uptake in them shows diffusely increased ^{18}F-FDG uptake, their clinical outcome can be as poor as that of the patients with BM involvement.

Hitherto, most previous studies have evaluated the prognosis of lymphoma patients only according to the status of BM ^{18}F-FDG uptake and results of BM biopsy, showing worse prognosis in patients with both focal ^{18}F-FDG uptake of BM on PET/CT and BM involvement on BM biopsy, and have usually considered diffusely increased ^{18}F-FDG uptake of BM as a negative finding [12, 13]. However, the present study suggests that degree of diffuse ^{18}F-FDG uptake in BM could have prognostic value for predicting PFS. The previous study by Yang et al. (2015) [10] also measured maximum and mean SUV of BM and assessed the prognostic value of BM ^{18}F-FDG uptake in lymphoma patients. The above authors enrolled 34 patients with lymphoma-associated hemophagocytic lymphohistiocytosis and showed that patients with high maximum or mean SUV of BM had significantly worse survival than those with low maximum or mean SUV. However, 25 out of 34 patients in their study had BM involvement by BM examinations, and BM ^{18}F-FDG uptake might have been affected by lymphoma involvement. In our study, survival analysis was performed in a subgroup of lymphoma patients with negative BM involvement, and in this subgroup ^{18}F-FDG uptake of BM still showed significant association with PFS. Bone marrow biopsy in our study was performed only in bilateral iliac bones. Considering the possibility of sampling errors of BM biopsy [9, 25], BM involvement might have been underestimated by BM biopsy and hidden BM involvement might have influenced ^{18}F-FDG uptake of BM and prognosis.

The present study had several limitations. First, the study was retrospective and enrolled a small number of patients with heterogeneous lymphoma subtypes at various stages in a single institution. Further prospective studies with more patients are necessary to confirm results. Second, increased BM ^{18}F-FDG uptake in HL caused by red marrow hyperplasia has been reported [26]. Fluorine-18-FDG uptake of BM in our study might have been affected by the status of red marrow, although no significant correlation was shown between BM ^{18}F-FDG uptake and hemoglobin level. Lastly, BM biopsy was performed only in bilateral iliac bones and BM involvement might have been missed by the biopsy. Patients with diffusely increased BM ^{18}F-FDG uptake might have harbored lymphoma involvement [6,7,8]. However, BM biopsy at a local level reportedly provides an acceptable histopathological substrate of BM ^{18}F-FDG uptake [9].

In conclusion, in lymphoma patients with negative BM involvement, BM ^{18}F-FDG uptake was significantly associated with white blood cells count, NLR, and serum CRP level and was an independent prognostic factor for PFS. Even though lymphoma patients only showed diffuse BM ^{18}F-FDG uptake without evidence of BM involvement, this study suggests that ^{18}F-FDG uptake of BM can be a predictor for prognosis.

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The authors declare that they have no conflicts of interest

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