

Original Article

# Femoral marrow MRI is a non-invasive, non-irradiated and useful tool for detecting bone marrow involvement in non-Hodgkin lymphoma

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Femoral marrow magnetic resonance imaging (MRI) is a non-invasive, non-irradiated and useful modality for evaluating bone marrow (BM) conditions. Human adult femoral BM is almost uniformly fatty marrow and has the largest volume of a single bone. MRI has an extremely high resolution for fat and water, which allows high-contrast imaging of cellular infiltration into fat tissue. In hematological diseases, femoral BM MRI can clearly detect cell infiltration, which is symmetrically imaged from the proximal to the distal direction of abnormal signal areas. Thus, we investigated the significance of femoral MRI for non-Hodgkin lymphoma (NHL). We analyzed the data of 69 NHL patients who received femoral MRI at diagnosis in this single-center retrospective cohort study. The median patient age was 73 years. MRI patterns were mainly classified as uniform patterns or nonuniform patterns. We also classified the range of cellular marrow as high-grade or low-grade based on whether it had spread to over half of the femur. Both overall survival (OS) and progression-free survival (PFS) were significantly influenced by abnormal femoral marrow MRI. In particular, the patients with cellular femoral marrow lesions had a worse OS and PFS based on log-rank tests. Multivariable analyses with the Cox proportional hazards model revealed that OS and PFS were significantly influenced by cellular marrow diagnosed by femoral MRI. We concluded that femoral marrow MRI is a useful tool for detecting BM involvement and an independent prognostic factor in NHL patients.

**Keywords:** femoral marrow MRI, non-Hodgkin lymphoma, bone marrow involvement

## INTRODUCTION

Magnetic resonance imaging (MRI) is a non-invasive and non-irradiated diagnostic method. MRI has higher resolution of fatty tissue and cellular tissue than other modalities. Although there have been several studies evaluating bone marrow (BM) involvement in hematological disorders in a clinical setting,<sup>1-3</sup> the significance of MRI for examining BM involvement remains unclear. According to the various guidelines for hematological disorders, BM aspiration and biopsy are still gold standards for determining BM involvement positivity or negativity.<sup>4-8</sup> Because BM aspirate and biopsy are collected from only the sternum or ilium, they do not necessarily reflect the overall condition of the BM. Positron emission tomography-computed tomography (PET-CT) has been recommended as an aid for determining

the stage of malignant lymphoma. However, information on marrow conditions below the pelvis generally cannot be obtained from PET-CT.


BM is the largest hematopoietic organ in mammals. Hematopoiesis in BM continues throughout life and changes according to the distribution of red marrow and yellow marrow.<sup>3</sup> Fatty replacement of functioning hematopoietic marrow occurs in the periphery of the appendicular skeleton. In long bones, such as the femur, fatty marrow spreads from the diaphysis and epiphyses to metaphyses.<sup>9,10</sup> Hematopoietic marrow remains throughout life in only the proximal metaphysis in the femur. During aging, other femur marrow is replaced with yellow marrow.<sup>3</sup> MRI enables the evaluation of the entire BM compartment without invasive examinations, such as BM aspiration and biopsy. We specifically developed the femoral MRI method to visualize the entire

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BM condition.<sup>1</sup> Although MRI is a popular imaging modality, the significance of MRI for hematological disorders, including malignant lymphoma, remains to be elucidated. The purpose of this study was to clarify and confirm the clinical significance of femoral marrow MRI in non-Hodgkin lymphoma (NHL) patients.

## MATERIALS AND METHODS

### Study design and patients

This study was a single-center retrospective cohort study. A total of 69 NHL patients who received MRI at diagnosis agreed to participate in this study, which was approved by the local Ethics Committee at Aizu Medical Center of Fukushima Medical University (FMU) and carried out in accordance with the relevant guidelines and regulations. Written informed consent was obtained from all subjects prior to enrollment. We obtained patient characteristics, imaging data, and laboratory data from clinical records of all patients diagnosed with NHL, including diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), mantle cell lymphoma (MCL), T cell lymphoma, and other lymphomas, from 2012 to 2020. BM aspirate and/or biopsy were performed from the posterior iliac crest at diagnosis. We diagnosed pathological BM involvement in these samples using immunohistochemistry (IHC). Treatments for patients mainly included cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP)/CHOP plus rituximab (R-CHOP) therapy and bendamustine and rituximab (B-R) for NHL.

### MRI

MRI was performed with a 1.5 Tesla MRI system (Avant; Siemens AG, Erlangen, Germany) using a phased-array body coil. Coronal T1-weighted spin-echo (SE) images of the femur were obtained in contiguous 5-mm slices in a 200 x 320 matrix with repetition time (TR), 400 ms; echo time (TE), 20 ms; flip angle 170° and number of signal acquisitions, 2. Tissues with short proton T1 values, such as fatty tissue, have a high signal intensity and appear bright on T1-weighted SE images, whereas those with long T1 values, such as cellular marrow, have a low signal intensity and appear dark. Short TI inversion recovery (STIR) coronal images of the femur were obtained in 5-mm slices in a 200x 320 matrix with TR, 2,500 ms; TE, 20 ms; flip angle 150° and TI, 150 ms. On STIR images, the signal from fatty tissue was not detected, whereas the signal from tissues with a longer T1 value was progressively brighter (Figure 1a).

The abnormal MRI findings on femoral marrow MRI were categorized as uniform patterns (Figure 1b) or nonuniform patterns, including nodular patterns and scattered patterns (Figure 1c). A uniform pattern was characterized by the uniform replacement of fatty marrow. A nodular pattern was defined by nodular areas of fatty marrow replacement with a signal intensity that was lower on T1-weighted SE images (higher on STIR images) than that of muscles. Furthermore, a scattered pattern was defined by multiple

scattered foci of marrow replacement on a background of uninvolved marrow.<sup>1</sup> In addition, we classified the range of cellular marrow lesions as low-grade or high-grade based on whether the T1-low lesion exceeded half of the femur, which can be easily evaluated by many clinicians. MRI results were evaluated in a blinded manner by two independent observers who had no knowledge of patient marrow histology, tumor type, or stage. MRI patterns and ranges were evaluated in a blinded fashion by two hematologists.

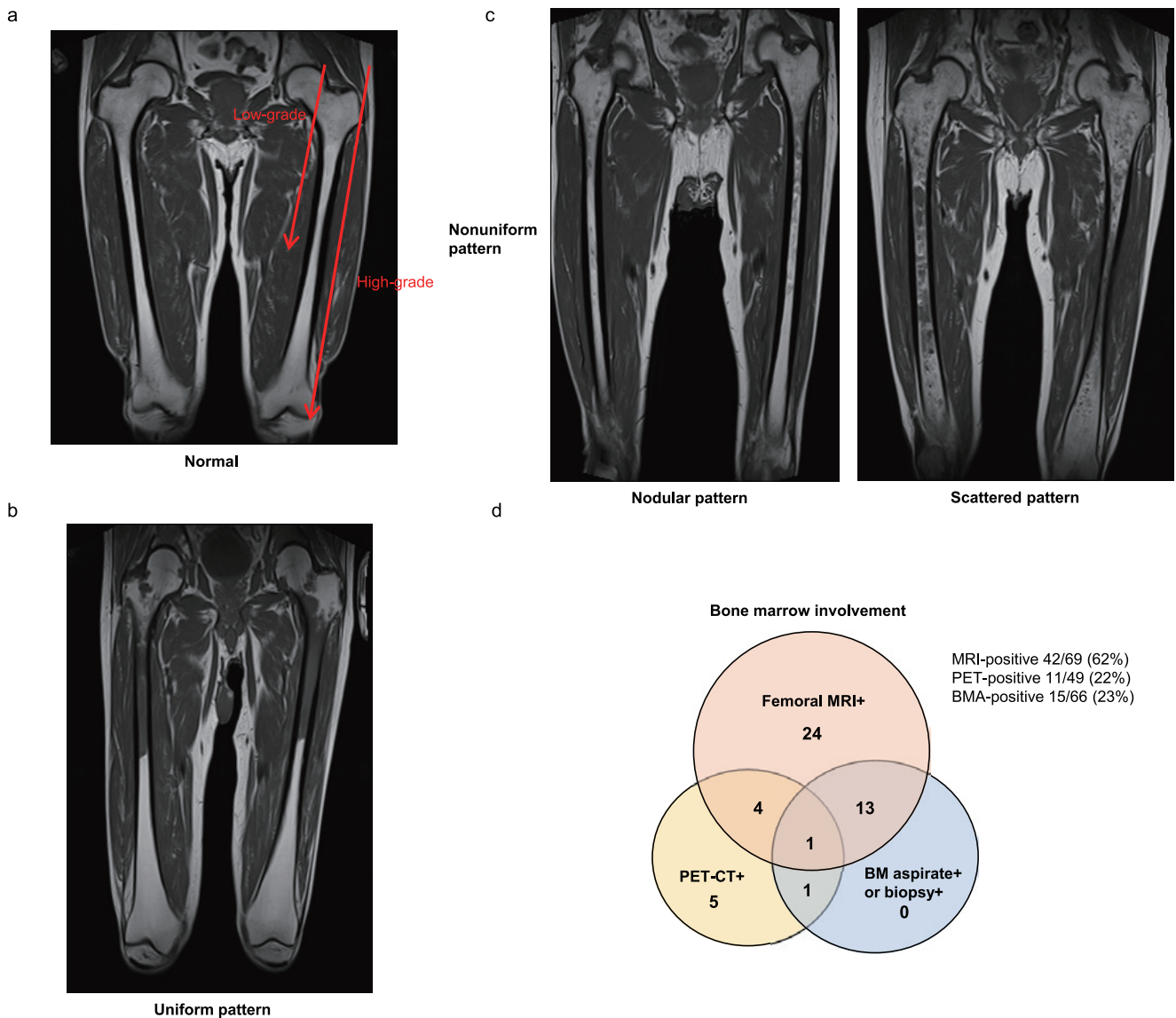
### Statistical analysis

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions that are frequently used in biostatistics.<sup>11</sup> The Kolmogorov-Smirnov test was used to analyze the normality of the distribution of parameters.<sup>12,13</sup> All variables with normal distributions are expressed as the mean  $\pm$  standard deviation, and those with log-normal distributions are expressed as the median with the interquartile range (IQR). Overall survival (OS) was defined as the time from MRI evaluation to death or the date of the last follow-up.<sup>14</sup> Progression-free survival (PFS) was defined as the time from MRI evaluation to relapse, death, or the date of the last follow-up. OS and PFS rates were estimated with the Kaplan-Meier method and compared with the log-rank test.<sup>11,14</sup> Hazard ratios (HRs) and associated 95% confidence intervals (CIs) for potential prognostic factors were calculated using the Cox proportional hazards regression model. Variables with  $p < 0.10$  in univariate analysis were used as independent variables in multivariate analysis. All statistical tests were two-sided, and a significance level of 0.05 was used.

## RESULTS

### Patient characteristics

We enrolled patients who received femoral marrow MRI at NHL diagnosis. The median age of the 69 patients included in this study was 73 years (range, 30 to 89 years), and 45% were women (Table 1). Patients were diagnosed with NHL at Aizu Medical Center, and their stage was evaluated by BM aspiration and/or biopsy, computed tomography (CT), and PET-CT. The proportion of patients with poor Eastern Cooperative Oncology Group (ECOG) performance status (PS) scores (more than 2) was 38%, the proportion of patients with anemia (hemoglobin less than 10 g/dL) was 19%, and the proportion of patients with lactate dehydrogenase (LDH) levels greater than the upper normal limit (UNL) was 54%. Serum levels of soluble interleukin-2 receptor (IL-2R) were elevated above the UNL in almost all NHL patients (84%). At the time of diagnosis, the proportion of patients with intermediate- and high-risk International Prognostic Index (IPI) scores was 74%, and the proportion of



**Fig. 1.** Patterns and ranges of femoral marrow MRI. (a) Representative images of normal femoral MRI, (b) uniform patterns, and (c) nonuniform patterns, including nodular and scattered patterns, are shown. (d) The process for the detection of BM involvement is shown by a Venn diagram.

patients with advanced-stage (III and IV) disease was 77%. Moreover, the proportion of the patients with BM involvement and B symptoms was 22% and 32%, respectively. The lymphoma histology of patients included 42 DLBCL, 15 FL, 5 MCL, 4 T cell lymphoma, and other lymphomas. In addition, the proportion of patients with Ki-67 positivity greater than 50% by IHC was 41%.

**MRI findings and the evaluation of BM involvement**

Of the 69 patients whose MRI findings could be evaluated, 42 patients had abnormal positive MRI results of the femoral marrow on T1-weighted SE and STIR images (Table 2). Among patients who had a uniform pattern, two were classified as low-grade, and one was classified as high-grade. Nonuniform patterns, including scattered and nodular patterns, were observed in a total of 39 patients. Of the 39 patients, there were 16 low-grade patients and 23 high-grade

patients. All uniform pattern MRI findings were observed in symmetrical femoral marrow on the proximal side and was not found only on the distal side in this study.

Our strategy for the detection for BM involvement is shown in a Venn diagram (Figure 1d). In the present study, the proportion of positive BM involvement based on BM aspirate and/or biopsy was 15 (23%). Our data indicated that femoral MRI detected all instances of BM involvement, excluding three patients who had missing BM data. PET-CT detected 11 instances of BM involvement, including five patients who were missed by femoral marrow MRI and BM aspirate and/or biopsy. Conversely, BM involvement in 24 patients was only detected by femoral marrow MRI. Our results suggested that femoral marrow MRI is useful for detecting BM involvement despite being non-invasive and non-irradiated.

Next, we investigated the frequency of cellular femoral

**Table 1.** Patient characteristics.

Characteristic	Patients
Patients, n	69
Age, median [min, max]	73 [30, 89]
Women, n (%)	31 (45)
BMI (<20 kg/m <sup>2</sup> ), n (%)	14 (20)
Performance status, n (%)	
0-1	43 (59)
2-4	26 (38)
Unknown	4 (5.8)
Histology, n (%)	
B cell lymphoma	65 (94)
DLBCL	42 (61)
FL	15 (22)
MCL	5 (5.8)
Others	4 (5.8)
T cell lymphoma	4 (5.8)
IPI, n (%)	
Low risk	16 (23)
Intermediate risk	27 (39)
High risk	24 (35)
Unknown	2 (2.9)
Stage, n(%)	
I	10 (14)
II	7 (10)
III	16 (23)
IV	37 (54)
Bone marrow involvement, n (%)	15 (22)
B symptoms present, n (%)	22 (32)
Extranodal lesion, n (%)	51 (74)
Anemia (Hb <10), n (%)	13 (19)
Serum LDH (≥ Upper normal limit; 240)	37 (54)
Soluble IL-2R high (U/mL) (≥ Upper normal limit; 500)	58 (84)
Ki-67 high (≥50%), n(%)	28 (41)

Abbreviations: DLBCL, diffuse large B cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma

**Table 2.** The frequencies of patterns and ranges of femoral marrow MRI in NHL patients.

Pattern	Normal	Range n, (%)	
		Low-grade	High-grade
Uniform	-	2 (2.9)	1 (1.4)
Nonuniform			
Scattered	-	6 (8.7)	10 (15)
Nodular	-	10 (15)	13 (19)
Normal	27	-	-
Total	27	18	24

marrow in each lymphoma subtype. As shown in Table 3, the number of patients with MRI-negative disease was 17, low-grade was 11, and high-grade was 14 in DLBCL. In our study, all MCL patients had high-grade femoral MRI results.

**Table 3.** The frequency of the femoral marrow MRI range in NHL

Variable	Negative	Low-grade	High-grade	Total
DLBCL	17	11	14	42
MCL	0	0	4	4
FL	8	5	2	15

Abbreviations: DLBCL; diffuse large B cell lymphoma, FL; follicular lymphoma

In FL patients, there were eight MRI-negative patients, five low-grade MRI patients, and two high-grade MRI patients.

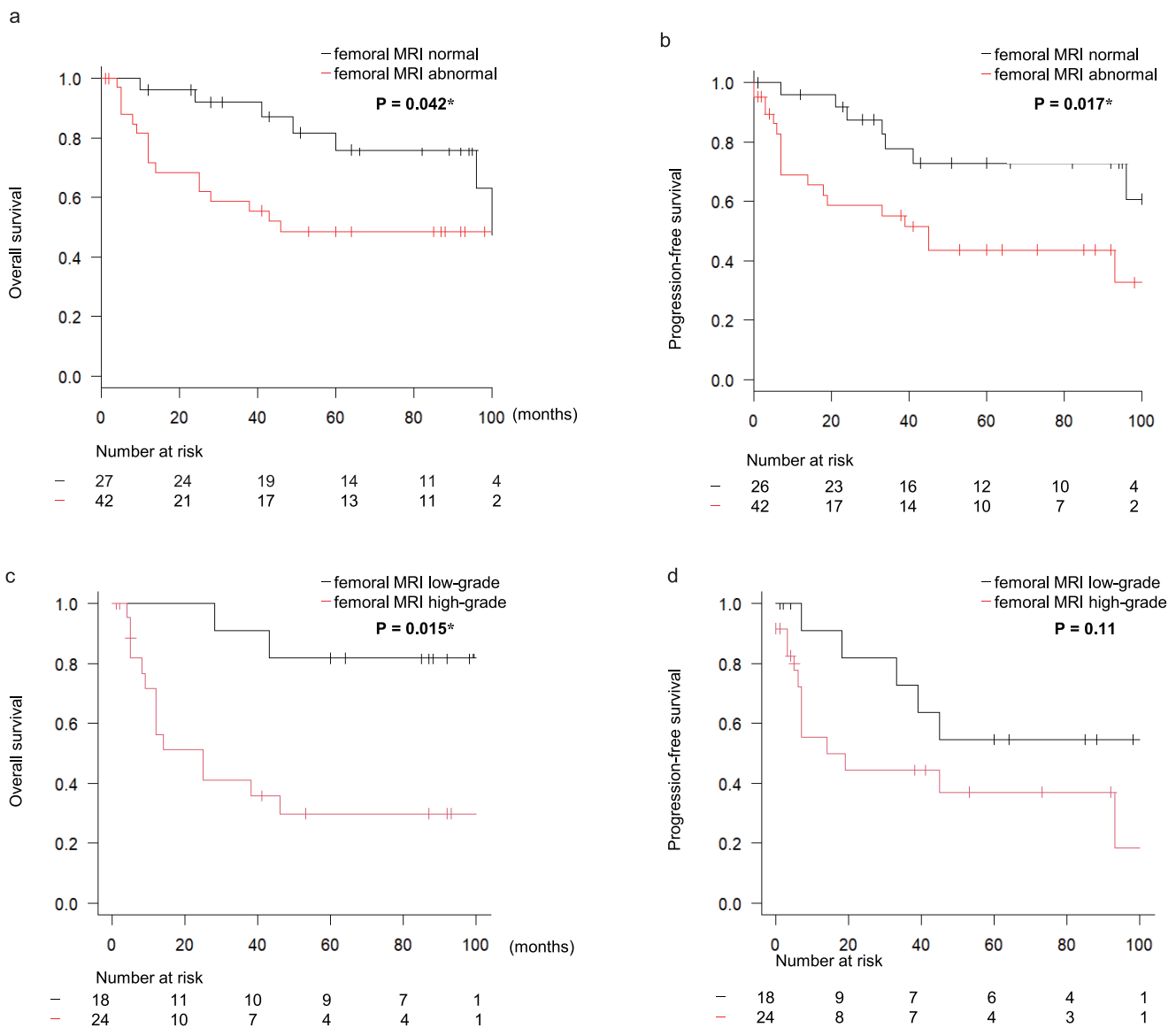
### Survival analysis

In a clinical setting, sampling femoral marrow is difficult in practice. It is not possible to compare MRI findings and pathological findings. Therefore, we tried to clarify the significance of evaluating BM involvement by femoral marrow MRI with log-rank tests. The median follow-up duration of survivors was 41 months (range, 1-133). Both OS and PFS were significantly influenced by abnormal femoral marrow MRI findings. The median OS of patients with normal femoral marrow MRI results was 100 months (range, 96-not achieved; NA), and that of the patients with abnormal findings was 46 months (range, 14-NA) ( $P = 0.043$ ) (Figure 2a). The median PFS of patients with normal femoral marrow MRI findings was also not reached (range, 41-NA), and that of the patients with abnormal findings was 45 months (range, 7-NA) (Figure 2b).

Furthermore, we performed univariate analysis to identify other independent factors related to OS and PFS (Table 4). OS was significantly influenced by PS ( $\geq 2$ ) (HR 3.48, 95% CI 1.47-8.21) ( $P = 0.004$ ), serum LDH ( $>UNL$ ) (HR 5.73, 95% CI 2.24-14.7) ( $P < 0.001$ ) and B symptoms (HR 2.58, 95% CI 1.09-6.08) ( $P = 0.031$ ). PFS was also significantly influenced by serum LDH ( $> UNL$ ) (HR 4.70, 95% CI 2.00-11.1) ( $P < 0.001$ ) and B symptoms (HR 2.67, 95% CI 1.18-6.03) ( $P = 0.013$ ).

Moreover, we performed multivariable analyses of OS and PFS with the Cox proportional hazards model. Each analysis was evaluated by adding age ( $\geq 61$ ), PS ( $\geq 2$ ), serum LDH, B symptoms and MRI high-grade to the independent factors (Table 4). Abnormal MRI findings and serum LDH were identified as independent, significant factors for OS (MRI; HR 3.23, 95% CI 1.16-8.98,  $P = 0.025$ ) (LDH; HR 5.29, 95% CI 1.76-15.9,  $P = 0.003$ ) and PFS (MRI; HR 2.92, 95% CI 1.16-7.37,  $P = 0.023$ ) (LDH; HR 6.07, 95% CI 2.08-17.8,  $P < 0.001$ ). In addition, we analyzed influences of differences in femoral marrow MRI T1-low lesion ranges. We performed log-rank tests for patients stratified by high-grade and low-grade. Patients with high-grade cellular femoral marrow had a significantly worse OS ( $P = 0.015$ ) (Figure 2c) and tended to be worse PFS ( $P = 0.11$ ) (Figure 2d) than the patients with low-grade cellular femoral marrow.

Finally, we considered the difference in lymphoma subtypes and performed log-rank test for patients stratified by high-grade or low-grade and normal MRI ranges (Table 5).



**Fig. 2.** Kaplan-Meier estimates. (a) OS and (b) PFS were stratified by whether the femoral marrow MRI findings were abnormal or normal. (c) OS and (d) PFS were stratified by the grade of the cellular marrow range of femoral MRI.

In DLBCL patients, MRI ranges significantly influenced OS ( $P < 0.001$ ) and PFS ( $P = 0.004$ ). However, FL patients, MRI ranges did not significantly influence OS ( $P = 0.068$ ) or PFS ( $P = 0.91$ ).

## DISCUSSION

In the present study, we examined the significance of femoral marrow MRI. Our data suggested that femoral marrow MRI is non-invasive, non-irradiated, and useful for detecting BM involvement. We characterized the range of cellular femoral marrow in MRI as low-grade or high-grade, which many clinicians can easily evaluate. Especially high-grade cellular marrow in abnormal femoral MRI findings contributed to significantly worse prognosis in NHL patients. In our study, femoral marrow MRI detected all instances of BM involvement diagnosed by BM aspiration and/or biopsy.

In addition, femoral MRI identified patients with BM involvement who were not diagnosed by PET-CT. Femoral marrow MRI can complement BM aspiration and biopsy and PET-CT to detect BM involvement in NHL.

The usefulness of femoral marrow MRI has been reported in several studies;<sup>2,3,15-17</sup> however, there have been few reports on femoral marrow MRI for BM involvement. Recently, most MRI reports related to NHL have determined the stage.<sup>18-21</sup> In the clinic, physicians have difficulty distinguishing nodular patterns or scattered patterns. In our study, differences among these patterns did not contribute to survival analyses. There were few patients with uniform patterns. Therefore, clarifying the clinical significance of femoral MRI patterns may be difficult. To elucidate this point, further large clinical investigations will be required. In the present study, all uniform pattern MRI findings were observed in symmetrical femoral marrow on the proximal

**Table 4.** Table 4. Univariate and multivariate analysis of overall survival and progression-free survival.

Variable	Overall survival		Progression-free survival	
	HR (95% CI)	p-value	HR (95%CI)	p-value
Univariate analysis				
Age ( $\geq 61$ )	1.23 (0.44-3.42)	0.39	1.06 (0.42-2.69)	0.90
Sex	0.67 (0.29-1.56)	0.35	0.79 (0.36-1.75)	0.56
Hb >10	0.61 (0.23-1.66)	0.33	0.53 (0.21-1.35)	0.18
sIL-2R (>UNL)	1.99 (0.46-8.56)	0.35	1.45 (0.43-4.89)	0.55
BMI < 20 kg/m <sup>2</sup>	1.32 (0.45-3.89)	0.61	1.59 (0.54-4.64)	0.40
PS $\geq 2$	3.48 (1.47-8.21)	0.004**	2.18 (0.98-4.86)	0.058
Serum LDH (>UNL)	5.73 (2.24-14.7)	< 0.001***	4.70 (2.00-11.1)	< 0.001***
Abnormal femoral marrow MRI	2.43 (1.01-5.95)	0.042*	2.76 (1.15-6.66)	0.023*
B symptoms	2.58 (1.09-6.08)	0.031*	2.67 (1.18-6.03)	0.018*
Ki-67 $\geq 50\%$	1.07 (0.47-2.47)	0.87	0.68 (0.30-1.55)	0.35
Multivariate analysis				
Age ( $\geq 61$ )	0.86 (0.27-2.64)	0.79	1.04 (0.36-2.98)	0.94
B symptoms	1.12 (0.43-2.92)	0.82	1.33 (0.53-3.36)	0.54
PS ( $\geq 2$ )	1.86 (0.72-4.81)	0.20	0.89 (0.34-2.33)	0.81
Serum LDH (>UNL)	5.29 (1.76-15.9)	0.003**	6.07(2.08-17.8)	< 0.001***
Abnormal femoral marrow MRI	3.23 (1.16-8.98)	0.025*	2.92 (1.16-7.37)	0.023*
MRI low-grade vs high-grade in MRI positive patients				
	6.42 (1.44-28.6)	0.015*	2.33 (0.82-6.57)	0.11

Abbreviations: HR; hazard ratio, CI; confidence interval, UNL; upper normal limit, BM; bone marrow, MRI; magnetic resonance imaging, PET; positron emission tomography  
\*P < 0.05, \*\*P < 0.01, \*\*\*P < 0.001

**Table 5.** Univariate analysis of survival and progression-free survival with the log-rank test with or without high-grade femoral marrow MRI findings.

Variable	Overall survival p-value	Progression-free survival p-value
DLBCL	P < 0.001***	P = 0.004**
FL	P = 0.068	P = 0.91

Abbreviations: DLBCL; diffuse large B cell lymphoma, FL; follicular lymphoma  
\*P < 0.05, \*\*P < 0.01, \*\*\*P < 0.001

side and was not found only on the distal side. These findings may indicate that cellular marrow spreads from the proximal to distal femur.

However, there were some limitations to our study. First, the diagnosis of patterns and ranges of femoral marrow MRI is currently subjective. Objective methods to evaluate these patterns and ranges are needed. We are developing a novel method to assess MRI lesions with artificial intelligence. Next, there were a few numbers of lymphoma subtypes other than DLBCL. In our study, all MCL patients have high-grade cellular femoral marrow. More numbers of patients were required to determine the significance of MRI for the prognosis of MCL patients. Last, there were no time-course analyses of femoral marrow MRI. If femoral MRI findings improve in NHL after treatment, it is unclear what this indicates. Therefore, we need to collect data after treatment and analyze time-course changes in femoral MRI.

In conclusion, we clarified the significance of femoral marrow MRI for evaluating BM involvement and as an independent factor for NHL prognosis. To confirm these findings, further investigations will be performed.

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## CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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