

Original Article

Investigation of factors affecting CT attenuation and glucose metabolism of bone marrow as seen on PET/CT scans

Shiro Ishii, Ryo Yamakuni, Shigeyasu Sugawara, Junko Hara, Yoshiki Endo, Hirotochi Hotsumi, Mahori Hiruta, Honami Kobiyama, Yuki Yaginuma, Kenji Fukushima, Hiroshi Ito

Department of Radiology and Nuclear Medicine, Fukushima Medical University, Fukushima, Japan

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Abstract: The aim of this study is to determine the factors affecting the CT attenuation of bone marrow, and its correlation with ^{18}F -FDG uptake. The mean standardized uptake value (SUV) of vertebral bone marrow (Vertebral-SUV) and femoral bone marrow (Femoral-SUV) as well as CT number of bone marrow (BM-CT number) were measured in 243 patients who had undergone ^{18}F -FDG PET/CT. The correlations among BM-CT number, Femoral-SUV, and Vertebral-SUV were investigated. The relationships of Femoral-SUV, Vertebral-SUV, and BM-CT number with blood parameters, age, blood sugar, and body weight were analyzed by correlation and multi-regression analyses. The Mann-Whitney U test and chi-square test and Binomial logistic analysis were used to examine the relationships between high BM-CT number (≥ 0 HU) and the above parameters. Significant correlations were observed between: BM-CT number and Femoral-SUV ($r = 0.73$, $P < 0.01$); Vertebral-SUV and Femoral-SUV ($r = 0.78$, $P < 0.01$); and BM-CT number and Vertebral-SUV ($r = 0.52$, $P < 0.01$). BM-CT number was correlated with patients' age in both univariable ($r = -0.27$) and multivariable analyses ($\beta = -0.20$). Positive BM-CT number correlated with WBC in both univariable ($P = 0.04$) and multivariable ($P < 0.01$) analyses. Bone marrow glucose metabolism had a tendency to decrease with age, was increased in patients with elevated CRP. In conclusion, CT attenuation of bone marrow correlated well with bone marrow metabolism and also tended to decrease with age. High bone marrow attenuation (≥ 0 HU) could predict elevated serum WBC.

Keywords: PET, FDG, CT number, CT, Bone marrow

Introduction

On ^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography (PET) image, physiological radio tracer uptake in the bone marrow (BM) is typically mild and diffuse, reflecting its low metabolic activity [1]. BM ^{18}F -FDG accumulation has been reported to be influenced by age, serum white blood cell (WBC) count, and the C-reactive protein (CRP) level [2-6]. In examinations of malignant lesions such as bone metastasis, focal ^{18}F -FDG uptake in the BM is considered to indicate abnormalities. However, in cases showing diffuse elevation of ^{18}F -FDG accumulation at the BM, benign changes such as increased activity of the red marrow may be difficult to distinguish from metastasis or invasion of myeloproliferative disorders such as leukemia [1, 7-9]. Moreover, BM uptake of ^{18}F -FDG has been reported to be affected by radiotherapy, anticancer chemotherapy, and administration of hematopoietic cytokines such as granulocyte colony-stimulating factor (GCSF) and erythropoietin [10-14].

CT attenuation values reflect tissue composition and are usually expressed in Hounsfield units (HU), where the CT number of water is 0 HU. Measurement of the CT number is useful for speculating on components such as fat, calcification, and hematoma. The CT attenuation of the femoral BM has been reported to be elevated in anemia and various hematological disorders [15, 16]. In the clinical settings, increments in the CT attenuation of BM which

may indicate hyperactivity of the red marrow, are occasionally observed in patients with an inflammatory response or after GCSF administration. Decreased CT attenuation of BM has also been reported in patients with diseases such as aplastic anemia [15]. Hematopoietic elements, being the most metabolically active and densely populated cells in the BM, are expected to contribute to higher values on both PET and CT scans. Consequently, the activity of the BM and its uptake of ^{18}F -FDG can potentially be deduced from the CT attenuation of BM. We sought to investigate that theory indirectly by correlating the peripheral indicators of BM cellularity with ^{18}F -FDG positron emission tomography (PET)/CT. Thus, this study aimed to examine the factors affecting ^{18}F -FDG uptake and CT attenuation of BM, including age, laboratory data, and anticancer chemotherapy-related factors. In addition, we investigated the relationship between ^{18}F -FDG uptake and CT attenuation of BM. Understanding factors that influence ^{18}F -FDG uptake and CT attenuation of BM may facilitate differentiation between malignancy and non-malignant BM conditions such as inflammation and anemia.

Materials and methods

Patient selection and data collection

This study was a retrospective analysis of 2,200 consecutive patients who underwent ^{18}F -FDG PET/CT between

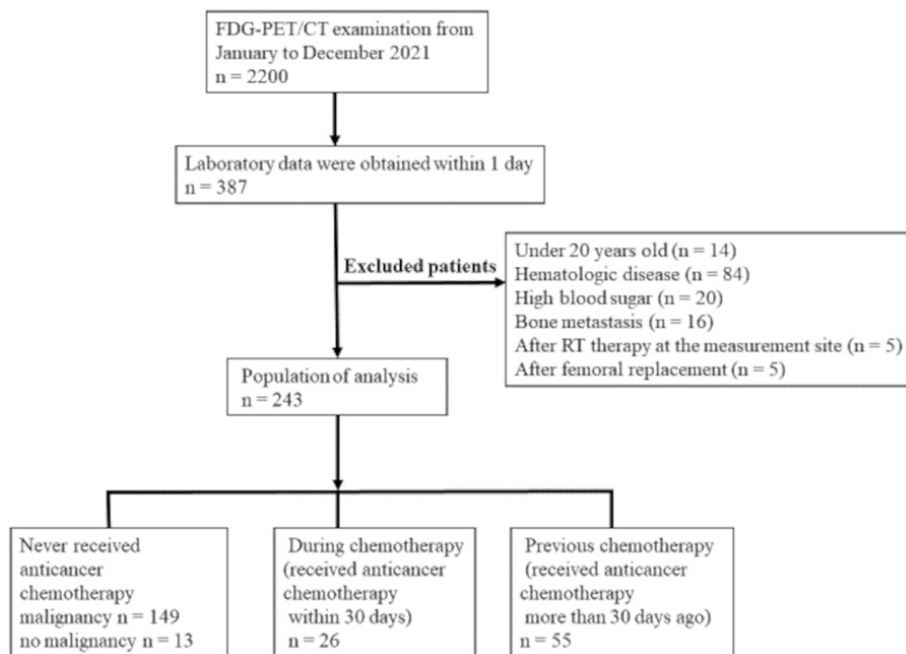


Figure 1. Flowchart of patient selection.

January and December 2021 in our hospital. We enrolled patients whose blood data, including WBC count, hemoglobin (Hgb) level, and platelet (Plt) count, were obtained within one day of the PET/CT examination. We excluded patients with hematologic diseases, such as malignant lymphoma and bone metastasis, those aged under 20 years, those with a high blood sugar level (> 150 mg/dL), and those who had undergone radiotherapy at the measurement site or femoral replacement. Thus, we included 243 patients for analysis; 227 with malignancies, seven each with Takayasu aortitis and cardiac sarcoidosis, and one each with infective endocarditis and erythema multiforme. Of these 243 patients, 162 had no history of anticancer chemotherapy, 26 had received anticancer chemotherapy within 30 days of PET/CT examination, and 55 had received anticancer chemotherapy more than 30 days before (Figure 1).

Patient characteristics including age, sex, surgery, and history of chemotherapy and radiotherapy, as well as blood cell counts including neutrophils, Plts, and lymphocytes were extracted from the patients' medical records. The neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. Similarly, the platelet-to-lymphocyte ratio (PLR) was defined as the absolute Plt count divided by the absolute lymphocyte count. Among the 243 patients, neutrophil and lymphocyte counts were obtained in 218, and CRPs were obtained in 161.

PET/CT protocol

¹⁸F-FDG-PET/CT data were acquired using 128-slice CT with Biograph mCT (Siemens Healthcare, Erlangen, Germany). All patients fasted for at least four hours or

skipped one meal before their examination. They were each injected with 4 MBq/kg of FDG, approximately one hour after which PET/CT examination was started. The acquisition of PET data started from the upper thigh to the head during shallow breathing. The acquisition time was 2-3 min per bed position, with 6-8 bed positions (each 21.8 cm). A 200 × 200 matrix was used for analysis. The PET data were reconstructed using ordered subset expectation maximization containing three iterations and 21 subsets with time of flight, point spread function, and a Gaussian filter of 3 mm full-width at half-maximum. Attenuation correction was performed based on the CT data derived from the CT scan acquired prior to the PET scan. Acquisition parameters for CT were as follows: tube voltage, 120 kVp;

auto mAs (reference tube current, 80 mAs); rotation time, 0.5 s; matrix, 512 × 512; and reconstruction using a 3-mm slice thickness and 2-mm increments. CT data were acquired during expiratory breath holding.

Measurement

The standardized uptake value (SUV) of ¹⁸F-FDG for the BM (BM-SUV) and CT attenuation value were measured by using an elliptical region of interest (ROI) in an axial image of fused PET and CT images. The ROI was placed at the center of the L3-L5 vertebra using a scout tool, and the largest possible femoral BM without adjacent tissue was measured. The ROI of the femoral BM was placed on the caudal side of the greater trochanter where the cortical bone was not visually observed. The SUV of the femur and CT attenuation values were measured simultaneously using the same ROI. CT attenuation values were expressed as HU. The mean SUV of BM was averaged from the values obtained at L3, L4, and L5 (Vertebral-SUV) and from the values for bilateral femoral BM (Femoral-SUV), while the BM-CT number was determined as the mean of CT attenuation for bilateral femoral BM (Figure 2). Measurements were performed using the PACS software (EV Insite, PSP Corporation, Tokyo, Japan) by a board-certified radiologist with 20 years of experience.

Statistical analysis

The correlations among BM-CT number, Femoral-SUV, and Vertebral-SUV were investigated by Pearson's correlation analysis. The relationships of Femoral-SUV, Vertebral-SUV, and BM-CT number with blood parameters (WBC, Plt counts, Hgb, CRP levels, NLR and PLR), patient

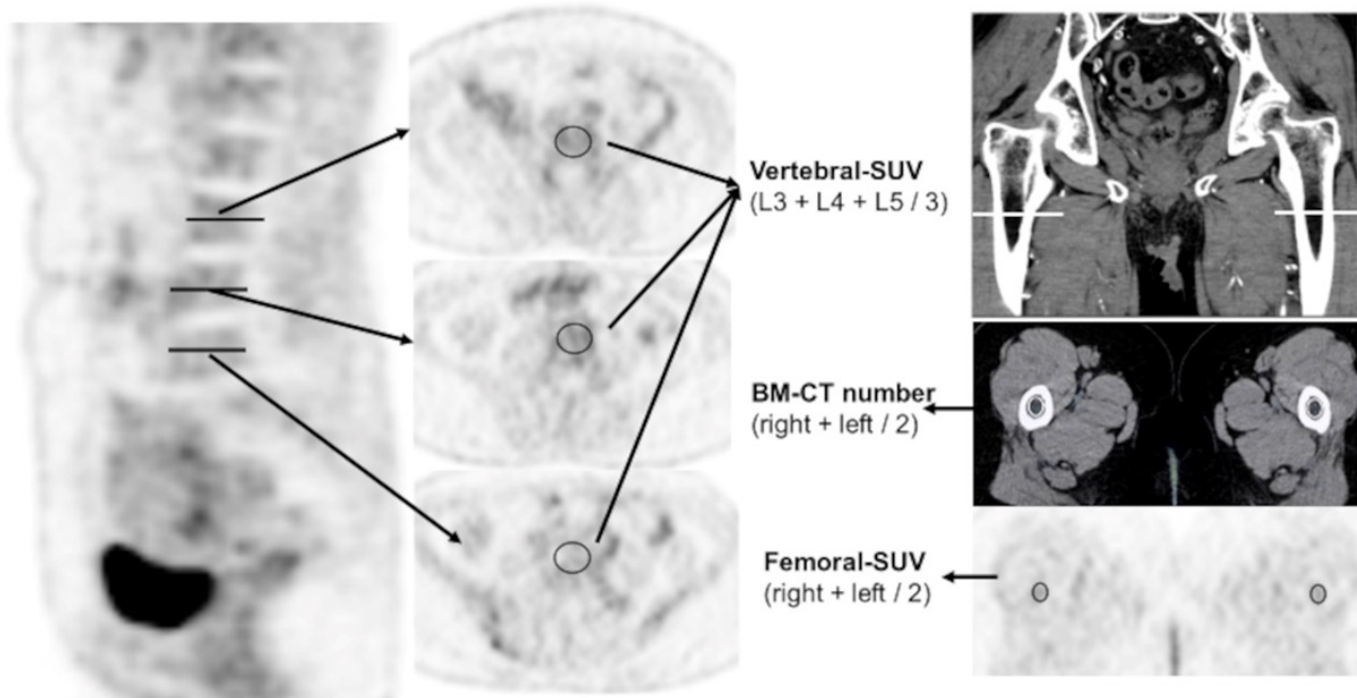


Figure 2. Placement of regions of interest (ROI). The regions of interest were placed at the center of the lumbar spine from L3-5, and the obtained standardized uptake values were averaged (Vertebral-SUV). The ROI for femoral bone marrow was placed on the caudal side of the greater trochanter, where the cortical bone was not visually observed in the same place in Femoral-SUV and BM-CT number.

age, blood sugar level, and body weight were also analyzed by Pearson's correlation analysis for patients who had never received anticancer chemotherapy. Multi-regression analysis was performed with Femoral-SUV, Vertebral-SUV, BM-CT number as dependent variables. The independent variables were the factors for which significant correlations ($P < 0.05$) were observed in a single-correlation analysis.

The Mann-Whitney U test and chi-square test were used to examine the relationship between high BM-CT number (≥ 0 HU) and blood parameters (WBC and Plt counts and Hgb and CRP levels), patient age, sex, body weight, and blood sugar. Binomial logistic analysis was used to examine the factors that showed a significant correlation ($P < 0.05$) in the Mann-Whitney U test and chi-square test between patients with BM-CT number ≥ 0 HU and those with BM-CT number < 0 HU.

The Kruskal-Wallis H test and Mann-Whitney U test with Bonferroni correction were used to identify significant differences in Femoral-SUV, Vertebral-SUV, and BM-CT number among patients with malignancy who had never been treated by anticancer chemotherapy ($n = 149$), those who had received anticancer chemotherapy within 30 days before the PET/CT examination and had not received GCSF administration within 2 weeks previously ($n = 23$), and those who had received anticancer chemotherapy more than 30 days before the PET/CT examination ($n = 55$).

Vertebral-SUV, Femoral-SUV, and BM-CT number were evaluated by an intra-class correlation coefficient (ICC 1, 2). Statistical analysis was performed by SPSS version 28.0 (SPSS, Chicago, Ill, USA).

Results

In Pearson's correlation analysis, a strong correlation was observed between BM-CT number and Femoral-SUV ($r = 0.73$, $P < 0.01$), as well as between Vertebral-SUV and Femoral-SUV ($r = 0.78$, $P < 0.01$), while a substantial correlation was observed between the BM-CT number and Vertebral-SUV ($r = 0.52$, $P < 0.01$) (**Figure 3**).

The results of the single-correlation and multivariable analyses of SUVs, BM-CT number, laboratory data, and patient age are shown in **Table 1**. A moderate correlation was observed between age and Vertebral-SUV ($r = -0.40$), while a weak correlation was observed between age and Femoral-SUV ($r = -0.32$), as well as between age and BM-CT number ($r = -0.27$). WBC count was weakly correlated with Femoral-SUV ($r = 0.25$), and Hgb level was weakly correlated with Femoral-SUV ($r = -0.21$) and Vertebral-SUV ($r = -0.21$). CRP level was moderately correlated with both Vertebral-SUV ($r = 0.53$) and Femoral-SUV ($r = 0.50$) (**Figure 4**).

Multi-regression analyses showed that Vertebral-SUV was negatively correlated with age ($\beta = -0.25$) and positively correlated with the CRP level ($\beta = 0.46$). Femoral-SUV was negatively correlated with age ($\beta = -0.25$) and Plt count (β

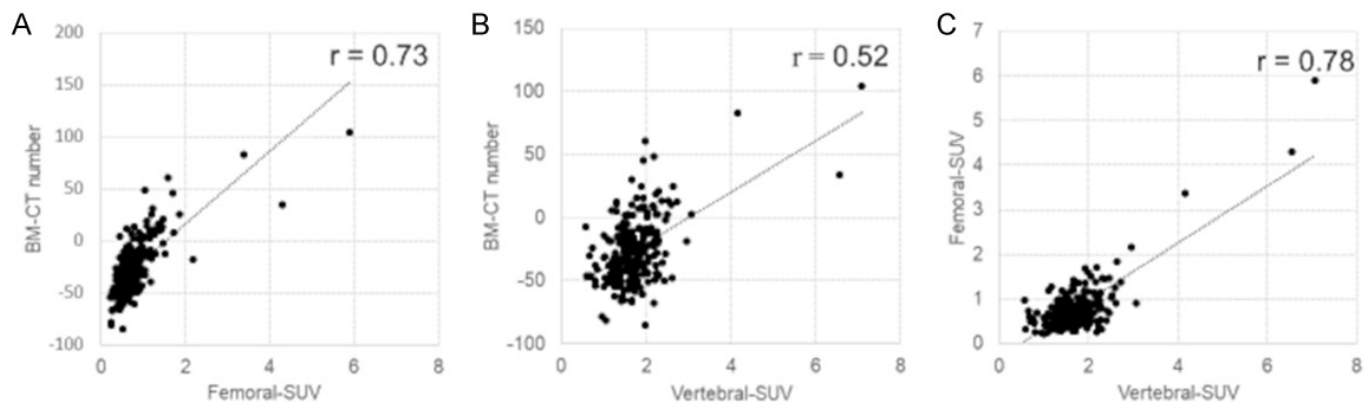


Figure 3. Correlations between Femoral-SUV and BM-CT number (A), Vertebral-SUV and BM-CT number (B), Vertebral-SUV and Femoral-SUV (C).

Table 1. Single correlation coefficients and standardized regression coefficients in multiple regression analysis of vertebral SUV, femoral SUV and BM-CT number, between age, blood sugar, body weight and blood parameters

Variables	Univariate analysis Pearson's coefficient (r)			R ² (adjusted)	Multivariable analysis Standardized regression coefficient (β)		
	Vertebral-SUV	Femoral-SUV	BM-CT number		Vertebral-SUV	Femoral-SUV	BM-CT number
Age	-0.40**	-0.32**	-0.27**	0.34	-0.25**	-0.25**	-0.20**
BS level	-0.04	< 0.01	-0.18				
BW	0.03	-0.01	0.28**				0.25**
WBC count	0.11	0.25**	0.10			0.18	
Hgb level	-0.21**	-0.21**	-0.02		-0.03	-0.13	
Plt count	0.13	0.20*	0.18*			-0.28*	0.16*
CRP level	0.53**	0.50**	0.18		0.46**	0.49**	
NLR	0.02	0.09	0.11				
PLR	0.05	0.09	0.14				

SUV, standardized uptake value; BM, bone marrow; CT, computed tomography; BS, blood sugar; BW, body weight; WBC, white blood cell; Hgb, hemoglobin; Plt, platelet; CRP, C-reactive protein; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio. *P < 0.05. **P < 0.01.

= -0.28), and positively correlated with CRP level (β = 0.49). BM-CT number was negatively correlated with age (β = -0.20) and positively correlated with body weight (β = 0.25) (Table 1).

Significant differences in age (P = 0.01), body weight (P < 0.01), WBC count (P = 0.04), and CRP level (P = 0.04) were observed in the univariable analysis between the patients with BM-CT number ≥ 0 HU and < 0 HU; among these variables, only the WBC count (P < 0.01) showed significance in the multivariable analysis (Table 2).

Significant differences in Vertebral-SUV were observed between patients who received anticancer chemotherapy more than 30 days previously and those who had never received anticancer chemotherapy (P < 0.01); however, no significant differences were observed in BM-CT number and Femoral-SUV among the three groups (Table 3; Figure 5).

The ICC (1, 2) was 0.984, 0.987, 0.978 for the measurements of Vertebral-SUV, Femoral-SUV and BM-CT number respectively.

Discussion

The results of the present study showed that ¹⁸F-FDG uptake in the BM was correlated with age and the CRP level. BM-CT attenuation was also correlated with age and high BM-CT number (≥ 0 HU) was associated with an elevated WBC count. BM-CT attenuation was well correlated with BM-SUV; therefore, the BM-CT attenuation may be used as an indicator of BM-SUV. However, in the clinical setting, high BM-CT attenuation is also seen in BM edema due to liver, renal or heart failure; in such cases, the BM-CT attenuation may not be proportional to the BM-SUV.

The present study confirms previous findings that FDG uptake in bone marrow decreases with age; a trend observed in both healthy individuals and patients with various disorders [5, 6]. The present study similarly demonstrated a decrease in BM-CT attenuation with age, suggesting a potential reduction in red marrow associated with aging.

FDG uptake and CT attenuation of BM

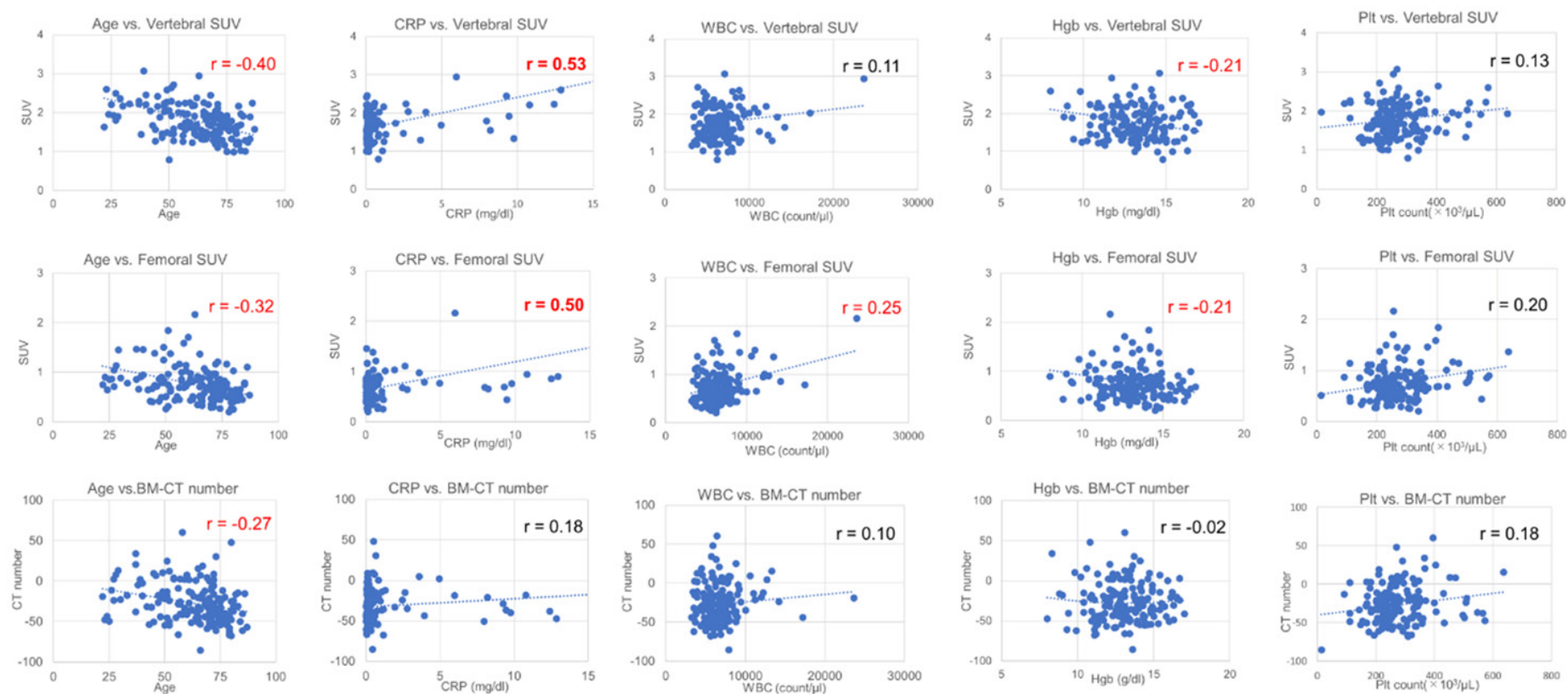


Figure 4. The relationships of Femoral-SUV, Vertebral-SUV, and BM-CT number with blood parameters. A moderate correlation was observed between age and Vertebral-SUV ($r = -0.40$), while weak correlations were observed between age and Femoral-SUV ($r = -0.32$) and between age and BM-CT number ($r = -0.27$). The WBC count was weakly correlated with Femoral-SUV ($r = 0.25$), and Hgb level was weakly correlated both with Femoral-SUV ($r = -0.21$) and Vertebral-SUV ($r = -0.21$). CRP level was moderately correlated with Vertebral-SUV ($r = 0.53$) and Femoral-SUV ($r = 0.50$).

Table 2. Single and multi-regression analysis of the parameters associated with a high BM-CT attenuation value (≥ 0 HU)

Variable	High BM-CT number (≥ 0 HU)	Low BM-CT number (< 0 HU)	P* (Univariable analysis)	P** (Multivariable analysis)
Age (years)	59.5 (27-80)	68 (22-87)	0.01	0.82
Sex (male/female)	16/24	92/111	0.60	
Blood sugar (mg/dL)	102 (45-135)	103 (76-149)	0.71	
Body weight (kg)	64.5 (35.6-103.4)	55.7 (30.8-114.1)	< 0.01	0.57
WBC count ($\times 10^3/\mu\text{L}$)	6.35 (2.10-2.68)	5.80 (1.80-1.72)	0.04	< 0.01
Hgb (mg/dL)	12.6 (8.3-16.7)	12.9 (7.6-17.0)	0.38	
Plt count ($\times 10^3/\mu\text{L}$)	267.5 (28.0-636.0)	240.0 (13.6-572.0)	0.18	
CRP (mg/dL)	0.50 (0.03-21.67)	0.17 (0.01-22.60)	0.04	0.82
NLR	3.4 (0.9-45.5)	2.4 (0.4-91)	0.01	0.43
PLR	195.6 (61.3-854.5)	165.5 (13.2-4000)	0.08	

Values are presented as median (range). CT, computed tomography; WBC, white blood cell; Hgb, hemoglobin; Plt, platelet; CRP, C-reactive protein; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio. *Results of Mann-Whitney U and chi-square tests. **Results of binomial logistic analysis.

Table 3. Characteristics and statistical results of the patients grouped according to their chemotherapy history

Variables	Groups			P value**
	A: No prior chemotherapy*	B: During chemotherapy*	C: Previous chemotherapy*	
Vertebral-SUV	1.69 (0.79-3.07)	1.49 (0.69-2.53)	1.40 (0.56-2.11)	0.04 (A vs B) < 0.01 (A vs C) 0.74 (B vs C)
Femoral-SUV	0.68 (0.21-1.85)	0.70 (0.24-1.13)	0.63 (0.24-1.63)	0.76
BM-CT number	-31.0 (-85.3-60.5)	-22.7 (-81.5-13.6)	-33.2 (-78.6-25.1)	0.35
Age (years)	66 (22-87)	69 (44-79)	65.8 (24-86)	0.41
Male/female	74/75	11/12	20/35	0.24***
BS (mg/dL)	103.1 (76-149)	102.0 (45-147)	103.4 (78-139)	0.92
BW (kg)	59.3 (35.4-114.1)	54.1 (40.8-85.5)	56.5 (30.8-83.5)	0.18
WBC count ($\times 10^3/\mu\text{L}$)	6.20 (3.20-1.72)	4.47 (1.80-11.10)	4.78 (1.80-1.89)	< 0.01 (A vs B) 0.04 (A vs C) 0.74 (B vs C)
Hgb (mg/dL)	13.2 (8.0-17.0)	10.9 (7.8-15.0)	12.4 (7.6-15.4)	< 0.01 (A vs B) < 0.01 (A vs C) 0.03 (B vs C)
Plt count ($\times 10^3/\mu\text{L}$)	255.7 (13.6-572.0)	221.0 (58.0-444.0)	214.3 (28.0-364.0)	< 0.01 (A vs C) 0.01 (A vs B) 1.00 (B vs C)
CRP (mg/dL)	0.23 (0.01-12.9)	0.15 (0.01-8.4)	0.18 (0.02-4.68)	0.44

Values are presented as median (range). SUV, standardized uptake value; BM, bone marrow; CT, computed tomography; BS, blood sugar; BW, body weight; WBC, white blood cell; Hgb, hemoglobin; Plt, platelet; CRP, C-reactive protein. *No prior chemotherapy: patients who had never received anticancer chemotherapy; during chemotherapy: patients who had received anticancer chemotherapy within 30 days previously; previous chemotherapy: patients who had received anticancer chemotherapy more than 30 days previously. **Results of the Kruskal-Wallis H test and Mann-Whitney U test with Bonferroni correction. ***Results of the chi-square test.

Consistent with the findings of previous reports, a relatively strong correlation was observed between BM-SUV and CRP level, and a weak correlation was observed between BM-SUV and WBC count [7, 8]. We speculated that the correlation between WBC count and BM-SUV would be higher in the present study compared to the previous studies due to a shorter interval between PET/CT examination and blood test (within 1 day vs. within 5 or 7 days). However, the correlation between WBC count and BM-SUV was low, and one possible reason for this is the

small number of patients with abnormal WBC counts. The WBC count was correlated with BM-CT attenuation ≥ 0 HU ($P < 0.01$), therefore, high BM-CT attenuation may indicate an inflammatory response.

A weak correlation was observed between Hgb level and BM-SUV ($r = 0.21$) in single-correlation analysis, but no significant correlation was observed in the multivariable analysis. Several studies have reported mixed results regarding the association of Hgb level with BM-SUV [7-9].

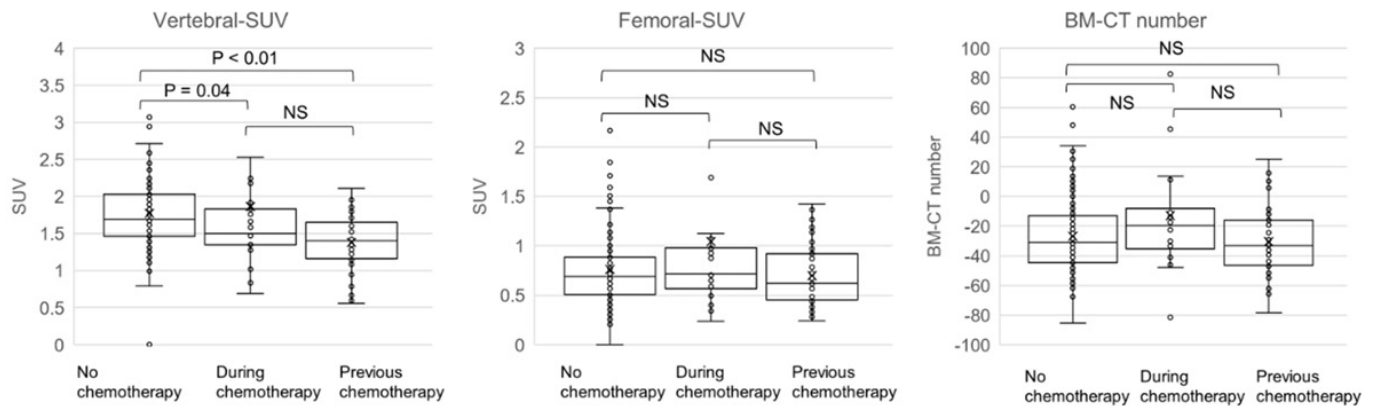


Figure 5. Comparison of SUV and CT number of bone marrow among patients with no anti-cancer chemotherapy, during chemotherapy and previous history of chemotherapy. Compared with patients who had never received anticancer chemotherapy, there were significant differences in Vertebral-SUV in patients who had received anticancer chemotherapy more than 30 days previously ($P < 0.01$) and in patients during chemotherapy with anticancer drugs ($P = 0.04$), but no significant differences were observed in the BM-CT number and Femoral-SUV among the three groups.

One conference presentation suggested that anemic patients have higher BM-SUV than non-anemic patients [16]. On the other hand, previous studies have reported a significant association between intravascular CT attenuation and peripheral blood Hgb levels [17, 18]. Furthermore, Maldjian et al. reported a correlation between high femoral BM-CT attenuation (> 20 HU) and anemia [19]. Therefore, an increased number of erythrocytes, the precursor cells of red blood cells, may elevate the BM-CT attenuation in anemic patients, but the results did not indicate such an elevation. Although BM-CT attenuation may increase in acute or subacute anemia, most of the anemic patients in our study had chronic anemia, which may explain why no significant correlation was found between anemia and BM-CT attenuation. High BM-CT attenuation (> 20 HU) was observed in 10 of 243 patients in this study. Among these 10 patients, seven were anemic (Hgb: < 11.6 in females, 13.7 in males), including three who were administered G-CSF within 2 weeks, one with Takayasu arteritis, and one with infective endocarditis. However, the remaining three patients had no abnormal blood cell count or a history of G-CSF administration within two weeks, and the reason why they had high BM-CT attenuation is unknown.

Almost no correlations were observed between Plt count and BM-SUV, Plt count and BM-CT attenuation. Moreover, no previous reports have described a significant correlation between Plt count and BM-SUV, which may be due to the long lifespan of Plts and the small number of megakaryocytes in the BM.

NLR and PLR are novel biomarkers for assessing inflammation and prognosis in various diseases [20, 21]. However, neither NLR nor PLR significantly correlated with BM-SUV or BM-CT attenuation. Although both these indices and BM-SUV have been reported to be associated with patient prognosis, the low correlation between these indices and BM-SUV may be attributed to differences in

the type of inflammation being reflected, or due to the heterogeneity of the patients included in the study [22-24].

Vertebral-SUV was higher in patients with no prior cancer chemotherapy than in those who had undergone or were currently undergoing cancer chemotherapy. However, Femoral-SUV did not differ significantly among the three groups. This may reflect the heterogeneity of BM distribution [25]. Chemotherapy has been shown to increase BM-SUV, and there are also reports of an increase in BM-SUV within 15 days post-chemotherapy [2, 26]. Increased BM-SUV may depend on the effect on hematopoietic cells and due to BM regeneration. Increased BM-SUV in patients during chemotherapy is thought to be caused by the activation of hematopoietic cells, while the decreased BM-SUV after chemotherapy may be the result of a reduced population of normal hematopoietic cells. However, in the present study, the patients who had undergone chemotherapy showed significantly lower WBC counts than those who had not received chemotherapy, which may also be associated with the decreased BM-SUV. Moreover, the activation of inflammation by untreated or residual malignant lesions may have contributed to the increase in BM-SUV in patients with no prior chemotherapy, potentially accounting for the differences in BM-SUV [27, 28].

Recent reports have shown that elevated BM-SUV in patients with malignant lesions correlated with clinical outcomes such as prognosis, disease progression, and distant metastasis [22-24]. In the present study, a strong correlation was demonstrated between BM-CT attenuation and BM-SUV. Future studies are needed to determine whether BM-CT attenuation is beneficial for predicting such important clinical outcomes.

A limitation of the current study was its single-center retrospective review conducted predominantly on patients with malignancy or with a history of various malignant lesions. Although it would have been preferable to obtain

blood data on the same day as the PET/CT examination, in the present study, we opted to collect blood data within one day of the PET/CT examination, given the potential for selection bias.

Conclusions

BM glucose metabolism had a tendency to decrease with age, was increased in patients with elevated CRP, and was decreased in patients who had undergone chemotherapy. BM-CT attenuation correlated well with BM metabolism and also tended to decrease with age. High BM attenuation (≥ 0 HU) could predict elevated serum WBC.

Acknowledgements

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Shiro Ishii, Department of Radiology and Nuclear Medicine, Fukushima Medical University Hospital, Fukushima Medical University, 1, Hikarigaoka, Fukushima 960-1295, Japan. Tel: +81-(0)24-547-1111; Fax: +81-(0)24-549-3789; E-mail: shirou@fmu.ac.jp

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