# Relationship between Fluorine-18 Fluorodeoxyglucose PET/CT uptake and the plasma cell infiltration rate in the bone marrow of multiple myeloma patients

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# Abstract

**Background:** The current study investigated the relationship between maximum standardized uptake values ($SUV_{max}$) on Fluorine-18 Fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) and the plasma cell proliferation percentage in the bone marrow as well as hematological and biochemical test results of patients with multiple myeloma (MM). Moreover, we identified if there exist differences in parameters across different types of paraproteins and stages.

**Material and methods:** Patients clinically and pathologically diagnosed with MM between 2012 and 2019 were selected from the database of the Dokkyo Medical University hospital, Japan. Unsuitable patients were excluded from the current study to avoid false uptake. We examined 60 patients. Hematological and biochemical tests were recorded and evaluated. The percentage of plasma cells in bone marrow aspiration samples was calculated. In PET/CT images, the $SUV_{max}$ of the region of interest of the right posterior ilium (aspiration area) was measured. Relationships were examined using Spearman's correlation coefficient, and differences were identified using the Kruskal-Wallis test with SPSS.

**Results:** A positive correlation was observed between FDG uptake and the percentage of plasma cells ($r=0.672$, $P<0.0001$).

**Conclusion:** Increased FDG uptake by bone marrow correlated with the percentage of plasma cells. Some biochemical and hematological parameters were statistically different according to the stage and types of paraproteins. PET/CT is suitable for evaluating the condition of a patient and the activity of the MM lesion.

**Keywords:** FDG uptake, Multiple Myeloma, PET/CT, Plasma Cell.

# Introduction

Multiple myeloma (MM) is the second most common blood cancer worldwide, accounting for 1% of all cancers. It is characterized as a malignant hematological disorder with the uncontrollable monoclonal proliferation of malignant plasma cells [1,2]. According to Global cancer statistics 2018, MM represented 0.9% of new malignancies and 1.1% of the causes of cancer-related deaths [3].

Positron emission tomography/computed tomography (PET/CT) with the radiopharmaceutical Fluorine-18 Fluorodeoxyglucose (FDG) accumulates in more metabolically active tissues and provides morphological and functional information regarding the human body [4–9]. It is very useful for detecting bone damage; more than 80–90% of MM patients have bone lesions [10,11], which is a myeloma-defining event. PET/CT also has the capacity to identify skeletal and extramedullary lesions with a sensitivity of approximately 80–90% and specificity of 70–100% [12–16].

The International Myeloma Working Group (IMWG) consensus recommends the mandatory use of FDG PET/CT to confirm a suspected diagnosis of MM, smoldering MM, and solitary plasmacytoma and provide useful prognostic information [17,18]. The European Society of Medical Oncology and European Myeloma Network guidelines also recommend low-dose, whole-body CT and FDG PET/CT based on their availability [5,8].

The diagnosis and classification of MM previously required the presence of end-organ damage, known as the CRAB criteria, which pertains to an elevated calcium level, renal dysfunction, anemia, and destructive bone lesions [19].

The Durie-Salmon Staging System (DSSS) shows the relationship between the extent of myeloma and associated damage, and the revised system in 2006 integrated new imaging techniques, such as FDG PET/CT and magnetic resonance imaging [20]. The International Staging System (ISS) is based on serum beta2-microglobulin (b2m) and serum albumin (Alb)

levels. The 2015 revised system includes the chromosomal abnormality t(14;16), t(4,14), del17p and serum lactate dehydrogenase (LDH) levels [21].

The 5-year survival rate of MM in the US was 54%; approximately 75% among those were diagnosed in the early stages and 51% among those were diagnosed at the late advanced stage of the disease. The survival rate of MM has steadily been increasing in the last few decades due to advances in treatment and management [22].

Moreover, in MM patients, the amount of paraprotein levels usually provides much prognostic information [23–25]. Paraprotein is a monoclonal immunoglobulin or a light chain present in the blood or urine. It is produced by a clonal population of mature B cells, most commonly called plasma cells.

The percentage of plasma cells in the bone marrow is an important index of disease activity. According to some reports, increased plasma-cell infiltration causes a higher FDG uptake in bone marrow. However, the FDG accumulation to MM lesion clinically is often uncertain.

In this study, we investigated the relationship between FDG uptake with plasma-cell percentage and other hematological and biochemical test results based on our data.

# Materials and methods

This retrospective study was approved by the Ethics Committee of Dokkyo Medical University. This study was conducted between January 2012 and October 2019. First, we selected 245 patients who had the keyword MM on their report data. We then selected 101 pathologically confirmed cases. Some patients underwent PET/CT scan several times; hence, we excluded repeated cases and chose the cases where PET/CT and aspiration dates were within 1 month. We excluded patients with other malignancies and those who received chemotherapy and hematopoietic treatments in the past 4 weeks or radiation therapy 2–3 months prior to PET/CT scans. Finally, all patients with MM proven by bone marrow aspiration biopsy were retrospectively evaluated. The patient group included either first diagnosed or recurrent cases; thus, it was a mixed group. We examined 60 patients (females : males, 27:33) aged 67.3 ± 10.2 (mean ± standard deviation) years between 37 and 91. Since this was a retrospective study, hematological and biochemical test results such as hemoglobin (Hb), hematocrit (Ht), C-reactive protein (CRP), b2m, creatinine (Cre), Alb, LDH, calcium (Ca), white blood cells (WBC), red blood cells (RBC), paraprotein levels of M-protein, and free light chain were obtained at the nearest timing within 2 weeks before or after the PET/CT scan date. However, some results had longer time gaps (42 patients' data were within 2 weeks, 16 were within 4 weeks, and the remaining 2 were within 6 weeks). Table 1 shows the demographic and clinical properties of patients.

### *18F-FDG PET/CT imaging*

Prior to PET/CT, all patients fasted overnight (for at least 6 hours) and were intravenously administered FDG based on their body mass (4MBq/kg). Blood glucose levels, which should be equal to or less than 200 mg/dL, were measured before the FDG injection.

Patients rested in a warm room during the FDG uptake time of 1 hour. Whole-body imaging was performed using PET/CT scanners (Biograph mCT Flow and Biograph mCT Horizon, Siemens Healthcare, Tokyo, Japan). The PET acquisition time was 2.2 min per field of view. CT scan data were obtained with a peak voltage of 120 kV and tube current of 70 mAs.

To evaluate the maximum standardized uptake values (SUVmax) of bone marrow, the region of interest (ROI) was placed in the right posterior ilium at the level of the sacroiliac joint and the first anterior sacral foramen, which is an aspiration area. The right posterior ilium was selected to standardize the calculation of FDG uptake by bone marrow [12,26,27]. The ROI was manually drawn around the aspiration area and was calculated using the semiautomatic image registration software package (Syngo.Via, Siemens Healthcare, Tokyo, Japan).

***Bone marrow aspiration and plasma cell counting***

The bone marrow was aspirated from the right iliac crest. All hematoxylin and eosin (H&E)-stained bone marrow specimens were examined under a light microscope (BX53 Olympus, Japan) and digital photos were taken using the imaging software (cellSens Standard, Olympus Corporation, Japan). Plasma cells were counted using the application, QuPath 0.2.2, (Centre for Cancer Research and Cell Biology, Queen's University Belfast, UK), which is the most widely used image analyses software program in the world [28]. The infiltration rate of plasma cells represents the number relative to all nucleated hematopoietic cells in bone marrow. Figures 1 and 2 show the plasma cell aspiration samples.

***Statistical analysis***

Statistical analyses were performed using SPSS 27 (SPSS Inc, Chicago, III., USA) [29]. The relationship between FDG uptake and the plasma-cell infiltration rate as well as other hematological and biochemical parameters was analyzed using Spearman's correlation coefficient. The differences in parameters according to the stage and types of paraprotein were calculated using the Kruskal-Wallis test. The results obtained were considered to be significant at a p-value less than 0.05 ($P<0.05$).

# Results

The average $SUV_{max}$ of ROI of the right posterior ilium was between 1.34 and 7.76 (mean 2.74 ± 1.32), and the percentage of plasma cells in the bone marrow of the right posterior ilium was between 11.2 to 66.8 (mean 29.8 ± 11.1). The relationship between FDG uptake and plasma cell infiltration (r=0.672, P<0.0001) in bone marrow was positive (Table 2, Figure 3). We calculated the relationship between PET/CT scans and the parameter results. A correlation was not observed between FDG uptake and b2m (r=0.198, P=0.148) (Table 2, Figure 4).

Moreover, we evaluated the differences between hematological and biochemical parameters according to the types of paraprotein stages using Kruskal-Wallis test; the results showed statistically significant differences in the parameters of Cre (P=0.028) and WBC (P=0.032) with types of paraprotein; and Hb (P=0.011), Ht (P=0.023), RBC (P=0.009), and b2m (P=0.009) with stage (Table 3). As the stages of 15 cases were not recorded in the data, we excluded them in the evaluation of differences according to stage; therefore, the results are based on 45 cases.

# Discussion

The results of the current study revealed a correlation between FDG uptake by bone marrow on PET/CT and the plasma-cell infiltration rate in patients with MM. The retrospective study by Ben et al. found that PET/CT scan results affected the planned management of two-thirds of patients with plasma cell disorders including MM [7]. In a study by Dimitrakopoulou-Strauss, PET/CT prior to and after the first course of chemotherapy appeared to be useful for identifying patients who will respond to treatment [30]. Furthermore, studies have also shown that PET/CT scans are helpful in assessing responses to treatment [31] and allow for better management of patients with MM [32].

B2m is a low molecular weight protein found on the surface of all nucleated cells, and it acts as a serum marker for tumor burden in lymphoid malignancies including MM. B2m is one the most useful prognostic factors in patients with MM, as well in pretreatment and asymptomatic patients [33, 34].

Previous studies reported a correlation between FDG uptake by bone marrow and plasma cell infiltration [12,15,26,27,35–38], while others showed that FDG uptake correlated with b2m [26,27] and CRP [27] and negatively correlated with Hb and Ht [27] as well as Alb [26]. Significant prognostic laboratory parameters, such as b2m, CRP, and LDH, correlated with the number of focal FDG-avid lesions on PET/CT [39]. In newly diagnosed MM patients, the presence of at least 3 focal lesions and $SUV_{max}$>4.2 or extramedullary disease predicted poor progression-free survival [40]. PET/CT may be used to predict the outcomes of patients with new, relapsed, or refractory MM [37,39-44].

Some limitations of the current study should be noted. First, current study is a retrospective study; hence, we lacked data and therefore were not able to assess some

information, for example ISS/R-ISS. Moreover, the date gaps between PET/CT scan and aspiration, and the blood test results were different.

In the current study, a positive correlation was observed between PET/CT FDG uptake and the plasma-cell infiltration rate (r=0.672, P<0.0001), CRP (r=0.339, P=0.008). However, no correlation was observed between FDG uptake and b2m (r=0.198, P=0.148). At this point, the results of current study are different from past reports. B2m is one of the most useful prognostic and staging factors in patients with MM. It reflects the whole aspect of the patients with MM. However, it cannot necessarily reflect the state of the local lesion, which also applies to other laboratory parameters. And the correlation coefficient between FDG uptake and the plasma-cell infiltration rate is strong compared to some papers, because our population size was larger [15, 26, 27]. Based on the results of our study, we can see that the plasma-cell infiltration rate correlates with FDG, CRP, or b2m. Therefore, we can assume that the plasma-cell infiltration rate has the potential to reflect the bone/ bone marrow involvement by FDG, body immunity condition by CRP, and prognostic value of MM by b2m, but this fact should be carefully considered.

On the contrary, FDG-PET/CT reflects the condition of a local lesion in an MM patient. The plasma-cell infiltration rate also comprises local data for pathological data. Therefore, both are similar.

Based on these findings, an increased FDG uptake on PET/CT scan indicates a higher percentage of plasma cells in bone marrow, therefore, in addition to the bone marrow aspiration, PET/CT is a potentially good predictive indicator in the follow-up period because $SUV_{max}$ values in the bone marrow of MM patients with recurrence will be elevated. In brief, FDG-PET/CT is useful in accurately checking the local existence of MM lesions. Furthermore, FDG-PET/CT is useful in judging the curative effect of MM.

On the contrary, b2m levels provide general prognostic information and are useful for staging.

The purposes are often different between FDG-PET/CT and laboratory parameters as stated above. Therefore, we may obtain clinically useful information by properly using both methods.

# Conclusion

An increased uptake of FDG on PET/CT correlated with the percentage of plasma cells in BM. Some biochemical and hematological parameters were statistically different according to the stage and types of paraproteins. Therefore, FDG PET/CT is suitable for evaluating the condition of a patient and the activity of the MM lesion.

# Disclosure Statement:

## Ethics approval and consent to participate

This retrospective study was approved by the Ethics Committee of Dokkyo Medical University, Tochigi, Japan.

## Consent of publication

Not applicable.

## Competing interest

The authors declare that they have no competing interests.


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# Authors' contribution

TG, YN, YK develop the conception and design the study. TG drafted the manuscript. YN supervised the study. TG, KI, YM acquired data. TG, YN, YK, HA, MI, KM analyzed and interpreted the data. KI advised on the plasma cell counting. DK, SH advised on statistical analysis. All authors read and approved the final manuscript.

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# Figure legends

**Figure 1**. 60 y/o male, Durie-Salmon Staging System (DSSS) III

a) Transaxial FDG PET/CT scan image demonstrates active myeloma lesion in the right posterior ilium level with $SUV_{max}$ of 7.76 (white arrow)

b) Plasma cell aspiration sample. (H&E-stained, ×400)
Plasma-cell infiltration rate was 41.5%.

**Figure 2**. 71 y/o female, Durie-Salmon Staging System (DSSS) N/A

a) Transaxial FDG PET/CT scan image shows right posterior ilium level with low FDG uptake, $SUV_{max}$ of 1,34 (white arrow).

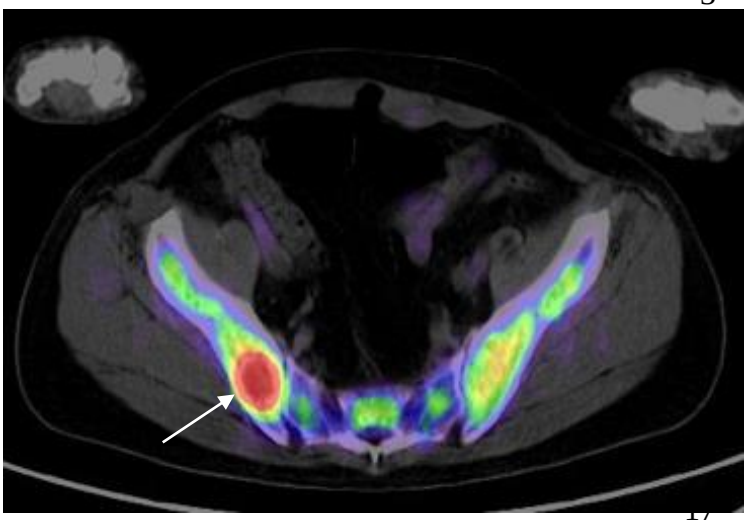
b) Plasma cell aspiration sample. (H&E-stained, ×400)
Plasma-cell infiltration rate was 11.5%.

**Figure 3.** Relationship between FDG uptake and the Plasma-cell infiltration rate
Scatter plot of the relationship between FDG uptake and the Plasma-cell infiltration rate, derived from PET/CT scan and bone marrow aspiration sample (r=0.672, P<0.0001).

**Figure 4.** Relationship between FDG uptake and the b2m
Scatter plot of the relationship between FDG uptake and the b2m, derived from PET/CT scan and hematological test sample (r=0.198, P=0.148).

**Figure 1**

a)



b)

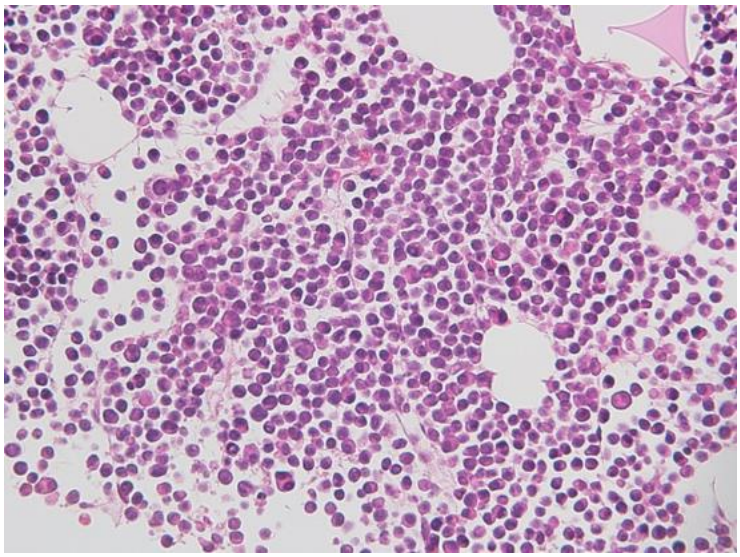
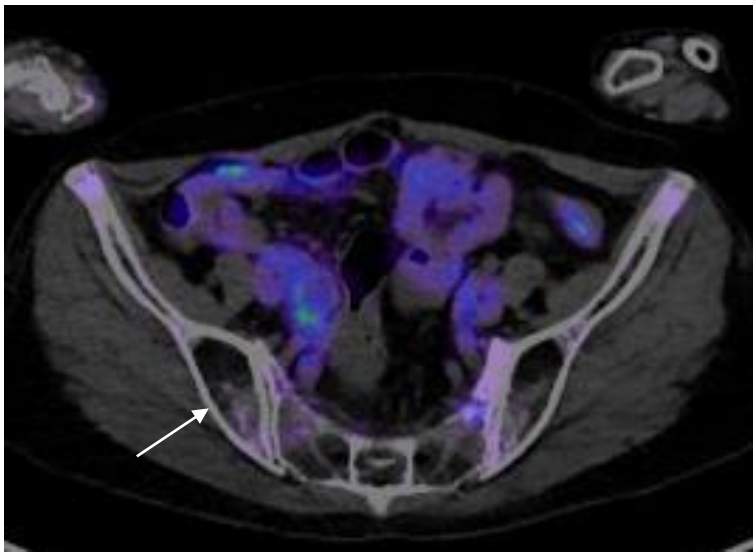


**Figure 2**

a)



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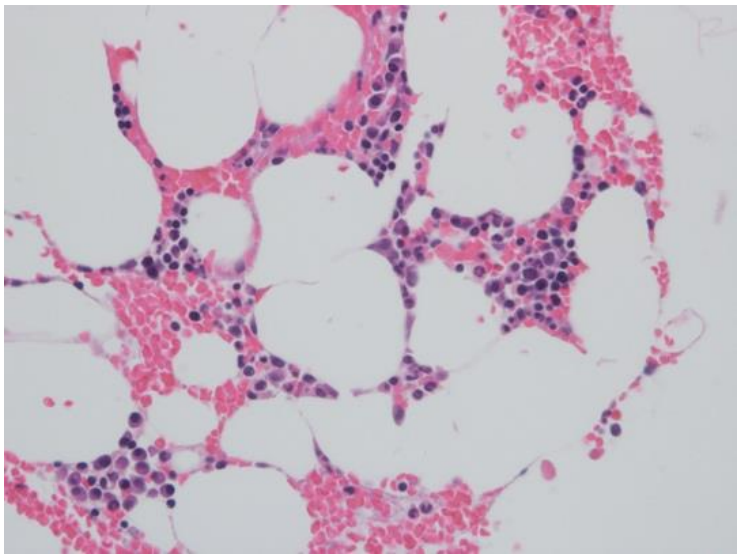

**Figure 3**

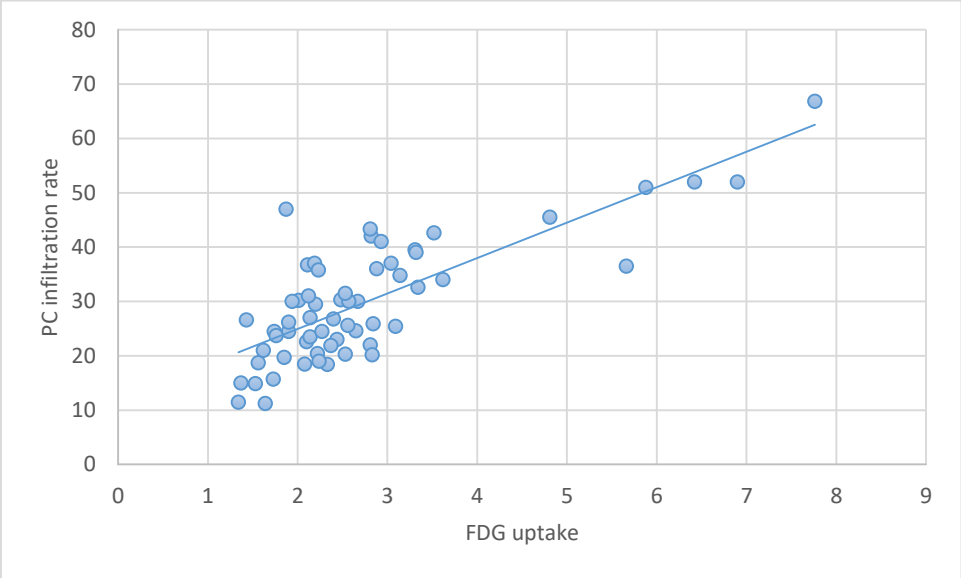


**Figure 4**

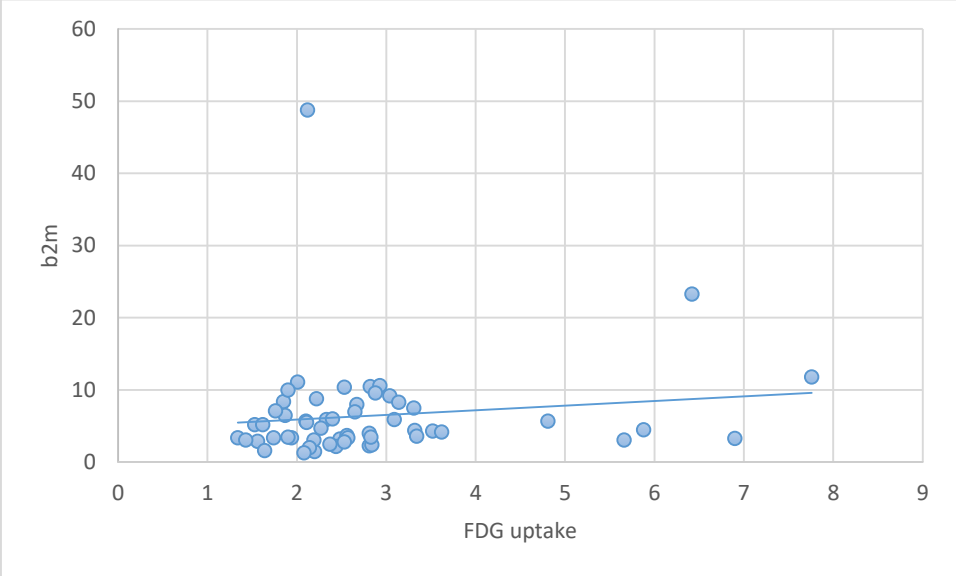

**Table 1** Demographic and clinical properties of patients

| | |
|---|---|
| N | 60 |
| Age (mean ± standard deviation) (years) | 67.3 ± 10.2 |
| Sex (females:males) | 27:33 |
| Types of paraprotein | |
| IgGκ | 31 patients (51.6%) |
| IgGλ | 19 patients (31.6%) |
| IgAλ | 5 patients (8.3%) |
| IgAκ | 2 patients (3.3%) |
| IgDλ | 2 patients (3.3%) |
| IgDκ | 1 patient (1.6%) |
| Durie-Salmon staging system | |
| stage I | 4 (6.6%) |
| stage II | 7 (11.7%) |
| stage III | 34 (56.7%) |
| NA | 15 (25.0%) |

**Table 2. Relationship between Plasma-cell infiltration rate, hematological, biochemical parameters and FDG uptake ratio in MM patients**

| | mean ± standard deviation | r | p-value |
|---|---|---|---|
| PC infiltration rate (%) | 29.8±11.0 | 0.672 | <0.0001* |
| Hb (g/dL) | 9.7±2.8 | -0.165 | 0.208 |
| Ht (%) | 30.4±7.1 | -0.217 | 0.950 |
| CRP (mg/dL) | 0.5±1.0 | 0.339 | 0.008* |
| Cre (mg/dL) | 1.2±0.88 | 0.103 | 0.436 |
| Alb (g/dL) | 3.4±0.7 | -0.029 | 0.828 |
| Ca (mg/dL) | 8.9±0.9 | 0.187 | 0.157 |
| WBC ($10^9$/L) | 5.3±2.2 | -0.065 | 0.621 |
| RBC ($10^{12}$/L) | 3.1±0.8 | -0.213 | 0.102 |
| LDH (U/L) | 204.8±76.9 | 0.009 | 0.946 |
| b2m (mg/L) | 6.4±6.8 | 0.198 | 0.148 |

*statistically significant

PC plasma cell, Hb hemoglobin, Ht hematocrit, CRP C-reactive protein, Cre creatinine, Alb albumin, Ca calcium, WBC white blood cell, RBC red blood cell, LDH lactate dehydrogenase, b2m beta2-microglobulin

**Table 3. P values for the difference of FDG uptake, PC infiltration rate, hematological and biochemical parameters according to types of paraprotein and Durie-Salmon staging system by Kruskal-Wallis test**

| | Types of paraprotein | Stage** |
|---|---|---|
| FDG ($SUV_{max}$) | 0.141 | 0.353 |
| PC infiltration rate (%) | 0.796 | 0.170 |
| Hb (g/dL) | 0.256 | 0.011* |
| Ht (%) | 0.259 | 0.023* |
| CRP (mg/dL) | 0.123 | 0.610 |
| Cre (mg/dL) | 0.028* | 0.297 |
| Alb (g/dL) | 0.102 | 0.372 |
| Ca (mg/dL) | 0.585 | 0.289 |
| WBC ($10^9$/L) | 0.032* | 0.653 |
| RBC ($10^{12}$/L) | 0.181 | 0.009* |
| LDH (U/L) | 0.801 | 0.650 |
| b2m (mg/L) | 0.131 | 0.009* |

*statistically significant

** patients whose stage were NA are excluded.

FDG fluorodeoxyglucose uptake (SUVmax), PC plasma cell, Hb hemoglobin, Ht hematocrit, CRP C-reactive protein, Cre creatinine, Alb albumin, Ca calcium, WBC white blood cell, RBC red blood cell, LDH lactate dehydrogenase, b2m beta2-microglobulin