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# IMPeTUs parameters correlate with clinical features in newly diagnosed multiple myeloma

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ABSTRACT

*Objectives:* To investigate the correlations between IMPeTUs-based 18 F-FDG PET/CT parameters and clinical features in patients with newly diagnosed multiple myeloma (MM).

*Materials and methods:* PET/CT were analysed according to the IMPeTUs criteria. We correlated these PET/CT parameters with known clinically relevant features, bone marrow plasma cell (BMPC) infiltration rate and the presence of cytogenetic abnormalities.

*Results:* A total of 149 patients (86 males, 63 females; mean age, 59.9 ± 9.7 years) were included. Bone marrow metabolic state correlated with the most clinical features including hemoglobin (rho=-0.23, p=0.004), FLC ratio (rho=0.24, p=0.005), β2 M (rho=0.28, p=0.001), CRP (rho=0.25, p=0.003), serum calcium (rho=0.22, p=0.02), serum creatinine (rho=0.24, p=0.004) and BMPC (rho=0.21, p=0.003). Besides, the level of hemoglobin was significant lower (0.043), and the levels of FLC ratio (0.037), β2 M (p=0.024), CRP (p=0.05), and BMPC (p=0.043) were significant higher in patients having hypermetabolism in limbs and ribs. Hottest bone lesion Deauville criteria had a moderate correlation with CRP (rho=0.27, p=0.001) and serum calcium (rho=0.25, p=0.01).

*Conclusion:* Several IMPeTUs-based PET/CT parameters showed significant correlations with clinical features reflecting disease burden and biology, suggesting that these new criteria can be used in the risk stratification in MM patients.

## 1. Introduction

Multiple myeloma (MM) is a hematologic malignancy characterized by abnormal clonal plasma cells in the bone marrow [1]. The diagnostic methods had significantly progressed with contemporary laboratory, molecular, and imaging modalities and call for an update on the specific diagnostic criteria and prognostic indices [2]. In clinical practice, various biological characteristics such as age, renal function, cytogenetic abnormalities, lactate dehydrogenase (LDH), and β2-microglobulin (β2 M) are widely used for prognostics prediction in MM [3]. Besides, risk-stratification systems including Durie-Salmon system (DS) [4], International Staging System (ISS) [5] and Revised ISS (R-ISS) [6] have been applied. Some serological parameters, such as calcium, hemoglobin, C-reactive protein (CRP), free light chain (FLC) levels are also closely related with patient Progression-Free Survival (PFS) and Overall Survival (OS) [7].

For thoroughly evaluating the disease burden and biology of patients with MM, the International Myeloma Working Group included PET/CT within the diagnostic flow-chart for both initial evaluation and therapy response assessment [8]. However, MM is a heterogeneous disease from an imaging point of view, raising challenges in the interpretation of PET/CT [9]. To standardize PET/CT reading in MM patients, the novel Italian Myeloma criteria for Pet Use (IMPeTUs) was proposed, which had been validated as reproducible [10]. To the best of our knowledge, the correlations between IMPeTUs-based 18 F-FDG PET/CT parameters and prognostic clinical features have not been thoroughly investigated.

Thus, the aim of this study was to investigate the correlations between IMPeTUs-based 18 F-FDG PET/CT parameters and clinical features reflecting disease burden and biology in patients with newly diagnosed MM.

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## 2. Materials and methods

This retrospective study had received the institutional review board approval and was performed with waiver of informed consent.

### 2.1. Patient population

Consecutive patients with newly diagnosed MM treated at our hospital who had undergone 18 F-FDG PET/CT between January 1, 2018 to June 1, 2023 were included according to the following criteria: (1) underwent PET/CT and bone marrow biopsies or aspirates from the iliac crest and other serological examinations within a period 4 weeks; (2) underwent PET/CT before start of any therapy; (3) had both quality-satisfactory image data and integrated clinical data for further analyses. Exclusion criteria: (1) patients with severe diabetes, active infection, or concomitant skeletal-rheumatoid disease at the time of PET/CT examination; (2) had received growth factors or steroids within 15 days around PET/CT examination. Patient information was anonymized and de-identified prior to analysis.

### 2.2. Clinical features

Demographics, clinical, and laboratory data including gender, age, subtype of MM, involved to uninvolved FLC ratio, hemoglobin, β2 M, albumin, CRP, serum calcium, serum creatinine, and LDH were collected at the time of PET/CT examination. Bone marrow biopsies or aspirates from the iliac crest and fluorescence in situ hybridization (FISH) were performed within 4 weeks around the PET/CT examination and before start of any therapy in all patients. The infiltration rate of malignant plasma cell (BMPC) represents the number of plasma cell in comparison to all nucleated, hematopoietic cells in the bone marrow. FISH was performed on CD138-purified plasma cells for testing high-risk cytogenetic abnormalities: del17p13, amp1q21, and t (11;14), t (4;14), t (14,16). Patients were staged according to the MM DS and ISS. Besides, R-ISS score was documented for the definition of high-risk disease.

### 2.3. PET/CT acquisition and analysis

FDG PET/CT procedure met the European Association of Nuclear Medicine PET procedures guidelines for FDG studies [11]. Briefly, preparation prior to image acquisition included fasting for at least 4 h and proper hydration. The blood glucose level required prior to FDG administration was set to ≤ 200 mg/dL. Sixty minutes after injection of 18 F-FDG (dose of 0.15 mCi/kg), patients were scanned using a dedicated PET/CT system (Biograph mCT, S64, Siemens Co., Erlangen, Germany) from the vertex to the lower third of the femur, operated in a 3-dimensional mode, 2–3 min per bed position. Attenuation correction was performed with a low-dose CT (120 kV, 80 mA), and iterative image reconstruction was based on the ordered-subset expectation maximization algorithm (21 subsets, 2 iterations, and Gaussian filtering of 5 mm FWHM).

Whole-body PET images and low-dose CT part of the studies were visually evaluated by two experienced nuclear medicine physicians, blindly to clinical results to avoid any bias. When disagreement existed, a third investigator was advised to make the final decision. Image analysis was based on IMPeTUs, taking into consideration the following parameters (Figs. 1–3).

- Bone marrow (BM) metabolic state in lower lumbar vertebra according to Deauville criteria: score 1, no uptake at all; score 2, ≤ mediastinal blood pool uptake; score 3, > mediastinal blood pool uptake, ≤ liver uptake; score 4, > liver uptake +10 %; score 5, >> liver uptake (twice); whether there is hypermetabolism (> liver uptake +10 %) in limbs and ribs (LR).
- Number of focal PET-positive lesions: F1, no lesion; F2, 1–3 lesions; F3, 4–10 lesions; F4, > 10 lesions.

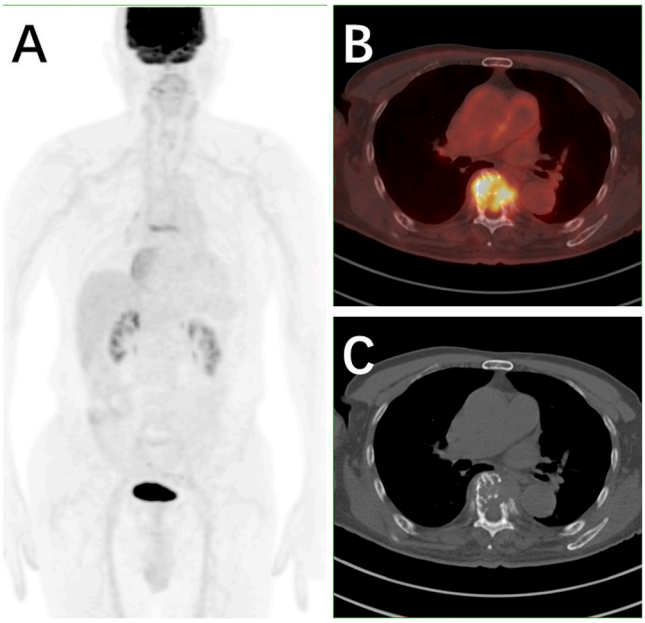


**Fig. 1.** A 76-year-old male patient showed normal metabolic state in the bone marrow, and one focal PET-positive lesion with underlying lytic lesion in thorax spine. PM was also observed. IMPeTUs results were: BM3, F2, L2, PM.

- Hottest bone lesion Deauville criteria (the hottest focal lesion, or the hottest area in patients without focal lesion).
- Number of lytic lesions at CT associated to PET: L1, no lesion; L2, 1–3 lesions; L3, 4–10 lesions; L4, > 10 lesions.
- Presence of at least one fracture at CT.
- Presence of para-medullary disease (PM): a bone lesion involving surrounding soft tissues with bone cortical interruption.
- Presence of extra-medullary disease (EM), and hottest EM lesion Deauville criteria.

### 2.4. Statistical analysis

Shapiro-Wilk test was used to determine whether the continuous variables accord with normal distribution. Continuous variables were presented as means and SD (normal distribution), or as medians and quartiles (non-normal distribution). Depending on the variables tested, different approaches were applied for correlation analyses. For the correlation between continuous variables, Pearson correlation test (normal distribution with equal variance) or Spearman rank correlation test (non-normal distribution) was used, interpreted as follows: 0–0.2, weak agreement; 0.2–0.5, moderate agreement; 0.5–0.7, substantial agreement; 0.7–1.0, almost perfect agreement. For the correlation between continuous variables and ordered categorical variables with more than two levels, one way ANOVA or Kruskal-Wallis test and Spearman rank correlation test were used. For the correlation between continuous variables and categorical variables with only two levels, student t test or Wilcoxon rank-sum test was used. For the correlation between ordered categorical variables with more than two levels, Kruskal-Wallis test and Spearman rank correlation test were used. For the correlation between categorical variables with only two levels (four-fold table), including the presence or absence of hypermetabolism in limbs and ribs, lytic lesion, PM, EM, and fracture, Chi-squared test or Fisher's exact test was used. All reported p values were two-sided. A p value of $< 0.05$ was considered statistically significant. All statistical analyses were performed using R-4.2.3 (https://www.r-project.org).

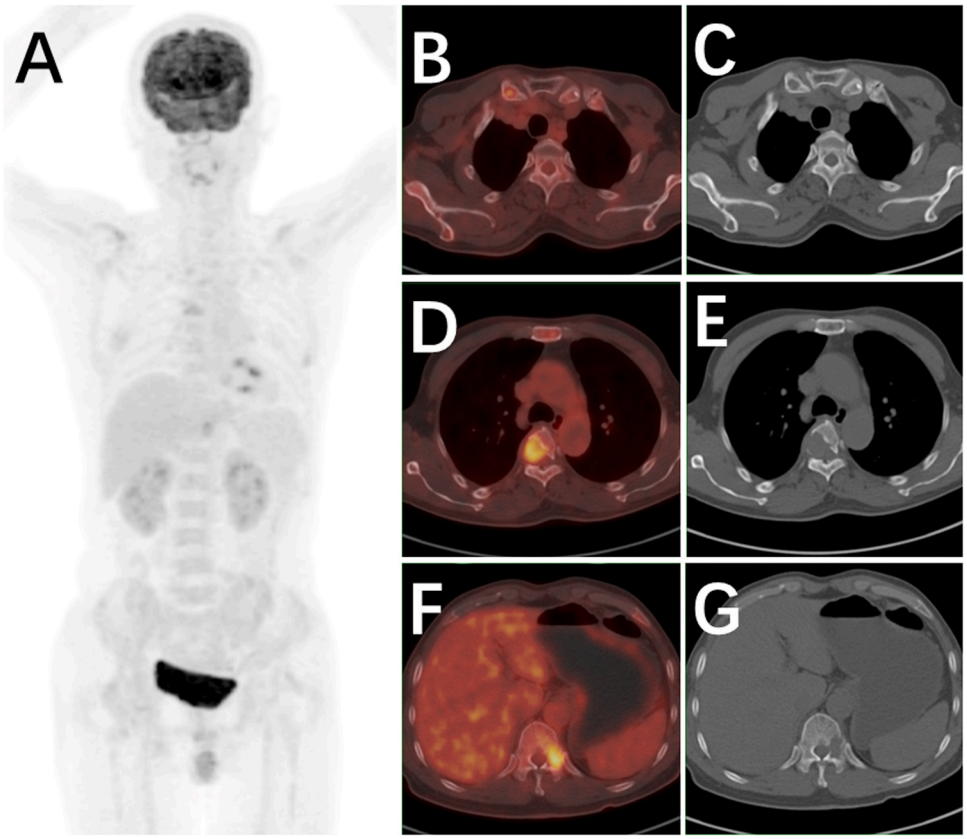


**Fig. 2.** A 56-year-old male patient showed normal metabolic state in the bone marrow, and at least four PET-positive lesions with underlying lytic lesion in right collarbone and spine. No PM or EM was observed. IMPeTUs results were: BM3, F3, L3.

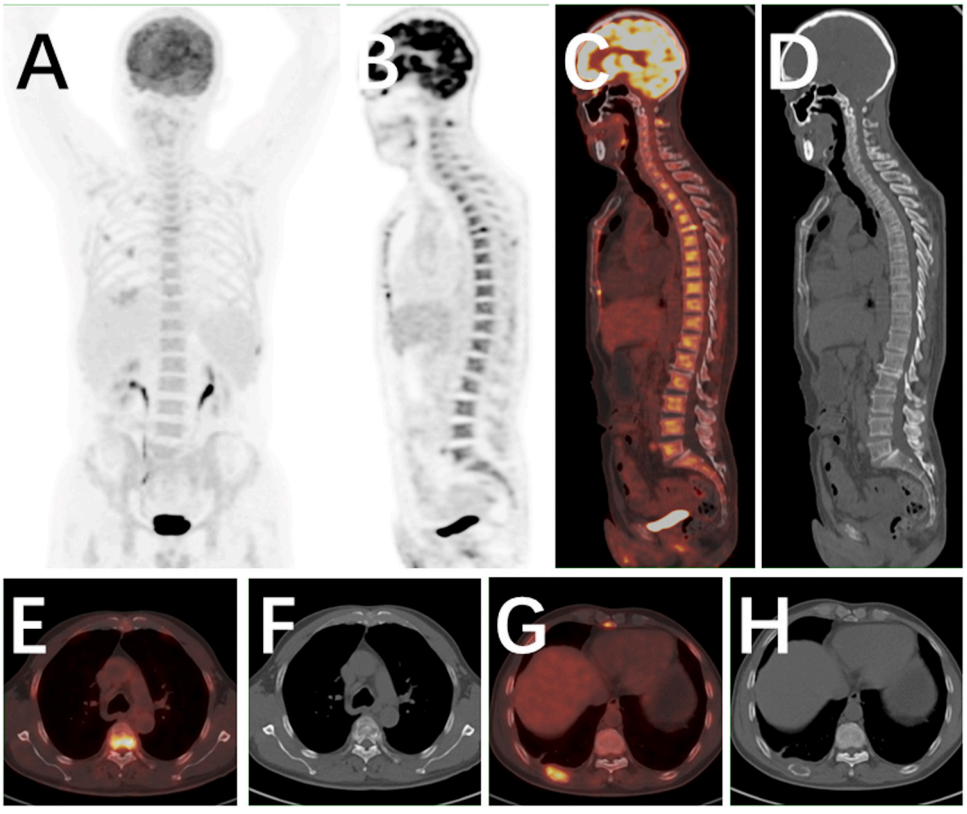


**Fig. 3.** A 60-year-old male patient showed diffused highly metabolic state in the bone marrow involving ribs and limbs, and at least four PET-positive lesions with underlying lytic lesion. A compression fracture in T5 was also observed. No PM or EM was observed. IMPeTUs results were: BM4, LR (+), F3, L3, fracture (+).

## 3. Results

### 3.1. Patient clinical features

A total of 149 patients (86 males, 63 females; mean age, 59.9 ± 9.7 years; range, 34–83 years) with newly diagnosed MM who had undergone 18 F-FDG PET/CT at our hospital were included in this study. According to R-ISS, 33 (22.15 %) patients were classified in stage I, 83 (55.7 %) patients in stage II, and 33 (22.15 %) patients in stage III. The clinical features of the patients were summarized in Table 1.

### 3.2. PET/CT parameters

The median SUV values derived from liver and mediastinum blood pool were measured as 2.9 (range, 2.5–3.5) and 1.5 (range, 1.2–3.1), respectively. The application of IMPeTUs revealed the following results: the median five-point Deauville scale of bone marrow metabolic state was 3 (range, 2–5). Sixty-three (42.3 %) patients showed no focal PET-positive lesion, while 86 (57.7 %) patients showed at least one hypermetabolic focal lesion. The median Deauville scale of the hottest bone lesion was 4 (range, 2–5). Para-medullary and extra-medullary disease was present in 30 (20.1 %) and 17 (11.4 %) patients, respectively. Seventy (46.9 %) patients showed no lytic lesion, while 79 (53.1 %) patients showed at least one lytic lesion. Fracture was detected in 52 (34.9 %) patients. The PET/CT parameters of the patients were summarized in Table 2.

**Table 1**
Patient clinical features.

| Characteristics | Number (%) | Median (IQR) | Normal Range |
|---|---|---|---|
| Gender (male/female) | 86 (57.7)/63 (42.3) | / | / |
| Age (mean, range) | / | 59.9 (34, 83) | / |
| Subtype of MM | | | / |
| IgG/IgA/IgD/LC | 68 (45.6)/26 (17.5)/1 (0.7)/54 (36.2) | / | / |
| Kappa/Lambda | 86 (57.7)/63 (42.3) | / | / |
| FLCratio, ≥ 100 | 51 (34.2) | 54.6 (8.3, 173.1) | 0.31–1.56 |
| HGB, < 90 g/L | 63 (42.3) | 97 (77, 121) | 130–175(male)/115–150(female) |
| β2 M, > 3.0 mg/L | 110 (73.8) | 4.48 (2.98, 9.82) | 1.0–3.0 |
| Albumin, < 40 g/L | 104 (69.8) | 35 (31.7, 40.9) | 40–55 |
| CRP, >10 mg/L | 28/140 (18.8) | 2.25 (0.75, 6.52) | 0–8 |
| Calcium, > 2.7 mmol/L | 17 (11.4) | 2.35 (2.24, 2.48) | 2.2–2.7 |
| CREA, > 135 umol/L | 36 (24.2) | 74.4 (60.7, 128.4) | 57–111 |
| LDH, > 250 U/L | 25/143 (16.8) | 175.2 (136.5, 230.2) | 120–250 |
| BMPC | / | 0.4 (0.2, 0.7) | 0.01–0.015 |
| FISH | 52 (34.9) | / | / |
| Durie-Salmon I/II/III | 16 (10.7)/ 16 (10.7)/117 (78.6) | / | / |
| ISS I/II/III | 42 (28.2)/ 42 (28.2)/65 (43.6) | / | / |
| R-ISS I/II/III | 33 (22.15)/83 (55.7)/ 33 (22.15) | / | / |

FLCratio, ratio of involved to uninvolved free light chains; HGB, hemoglobin; β2 M, β2-microglobulin; CRP, C-reactive protein; CREA, creatinine; LDH, lactate dehydrogenase; BMPC, infiltration rate of malignant plasma cell in bone marrow; FISH, fluorescence in situ hybridization; ISS, International Staging System; R-ISS, Revised ISS; IQR, interquartile range

**Table 2**
IMPeTUs-based PET/CT parameters.

| Parameter | Number (%) |
|---|---|
| Bone marrow Deauville criteria 1/2/3/4/5 | 0/13(8.7)/96(64.4)/35(23.5)/5(3.4) |
| Hypermetabolism in limbs and ribs No/Yes | 72(48.3)/77(51.7) |
| Number of focal lesions 1(0)/2(1−3)/3(4−10)/4(>10) | 63(42.3)/22(14.8)/27(18.1)/37(24.8) |
| Hottest bone lesion Deauville criteria 1/2/3/4/5 | 0/3(2)/33(22.1)/62(41.6)/51(34.3) |
| Presence of para-medullary disease No/Yes | 119(79.9)/30(20.1) |
| Presence of extra-medullary disease No/Yes | 132(88.6)/17(11.4) |
| Number of lytic lesions 1(0)/2(1−3)/3(4−10)/4(>10) | 70(46.9)/22 (14.8)/22(14.8)/35(23.5) |
| Presence of fracture No/Yes | 97(65.1)/52(34.9) |

IMPeTUs, Italian Myeloma criteria for Pet Use

### 3.3. Correlation between PET/CT parameters and clinical features

Exploratory correlation analyses revealed that BM metabolic state correlated with the most clinical features (Table 3). BM Deauville criteria had a moderate correlation with lower level of hemoglobin (rho=-0.23, p=0.004), and higher levels of FLC ratio (rho=0.24, p=0.005), β2 M (rho=0.28, p=0.001), CRP (rho=0.25, p=0.003), serum calcium (rho=0.22, p=0.02), serum creatinine (rho=0.24, p=0.004) and BMPC (rho=0.21, p=0.003) (Fig. 4). Hottest bone lesion Deauville criteria had a moderate correlation with higher levels of CRP (rho=0.27, p=0.001) and serum calcium (rho=0.25, p=0.01) (Fig. 5). Both numbers of focal PET-positive lesions (p>0.05) and lytic lesions (p>0.05) had no significant correlation with clinical features.

In the analyses of categorical PET/CT parameters with only two levels, lower level of hemoglobin was significant lower (0.043), and the levels of FLC ratio (0.037), β2 M (p=0.024), CRP (p=0.05), and BMPC (p=0.043) were significant higher in patients having hypermetabolism in limbs and ribs. The levels of CRP (p=0.012) and serum calcium (p=0.038) were higher in patients having lytic lesion. The level of CRP (p=0.012) was also higher in patients having fracture (Table 4).

## 4. Discussion

The development of the IMPeTUs criteria aimed to improve the reproducibility of PET/CT interpretation in a standardized and simple fashion, but the positivity cut-off value of five-point Deauville scale had not been defined. Mainly based on reviewers' experience and concordance, a cut-off value of score 4 was clarified for BM and focal lesion [10,12]. Recently, Zamagni et al. confirmed the prognostic value of BM metabolic state with a positivity cut-off value of score 4 [13]. Consistent with previous studies, we quantified BM metabolic state according to the five-point Deauville scale with a positivity cut-off value of score 4, while the hottest lesion with a cut-off value of score 5.

In this study, we investigated the correlations between IMPeTUs-based PET/CT parameters and clinical features reflecting disease burden and biology in patients with newly diagnosed MM. The major finding from our analyses was that BM metabolic state correlated with the most clinical features including the levels of FLC ratio, hemoglobin, β2 M, CRP, serum calcium, serum creatinine, and BMPC. Previous studies categorized the BM tracer uptake pattern into four types, including normal, focal, diffuse and mixed pattern, and found that diffuse/mixed pattern was correlated with clinical and imaging parameters indicating high tumor burden or poor prognosis [14–16]. The same as BM metabolic state ≥ 4, diffuse/mixed pattern of BM tracer uptake also indicates high metabolic activity in bone marrow. These results suggested that BM metabolic state can be used as a surrogate of

**Table 3**
Correlation between clinical features and bone marrow Deauville criteria.

| | BM 2 | BM 3 | BM 4 | BM 5 | p value | rho (p value) |
|---|---|---|---|---|---|---|
| FLCratio | 6.9 (3.8, 53.3) | 52 (9, 163) | 74.1 (17.2, 307) | 484 (360, 1039) | 0.011 | 0.24 (0.005) |
| HGB | 116 (87, 125) | 101.5 (79, 119.5) | 88 (71.5, 106) | 83 (64, 91) | 0.044 | −0.23 (0.004) |
| β2 M | 3.43 (2.56, 7.37) | 3.87 (2.81, 8.21) | 7.12 (4.28, 12.97) | 9.82 (7.44, 18.41) | 0.004 | 0.28 (0.001) |
| Albumin | 37.5 (34.3, 40.7) | 35.1 (30.9, 41.5) | 34.4 (32.2, 38.7) | 34.3 (31.8, 38.4) | 0.906 | −0.05 (0.536) |
| CRP | 1.2 (0.86, 1.8) | 2.08 (0.59, 5.1) | 4 (1.8, 11.54) | 10.78 (4, 30.3) | 0.022 | 0.25 (0.003) |
| Calcium | 2.3 (2.2, 2.4) | 2.34 (2.24, 2.46) | 2.39 (2.3, 2.78) | 3.2 (2.7, 3.37) | 0.08 | 0.22 (0.02) |
| CREA | 69.9 (65.4, 230) | 68.4 (55.4, 85.5) | 99.2 (74.3, 188) | 123 (76.4, 214.3) | 0.002 | 0.24 (0.004) |
| LDH | 186 (141, 212) | 172 (134, 219) | 209 (151, 242) | 113 (99, 289) | 0.245 | 0.1 (0.244) |
| BMPC | 0.3 (0.1, 0.5) | 0.4 (0.2, 0.63) | 0.49 (0.25, 0.73) | 0.8 (0.5, 0.83) | 0.1 | 0.21 (0.03) |

FLCratio, ratio of involved to uninvolved free light chains; HGB, hemoglobin; β2 M, β2-microglobulin; CRP, C-reactive protein; CREA, creatinine; LDH, lactate dehydrogenase; BMPC, infiltration rate of malignant plasma cell in bone marrow; BM, bone marrow Deauville criteria

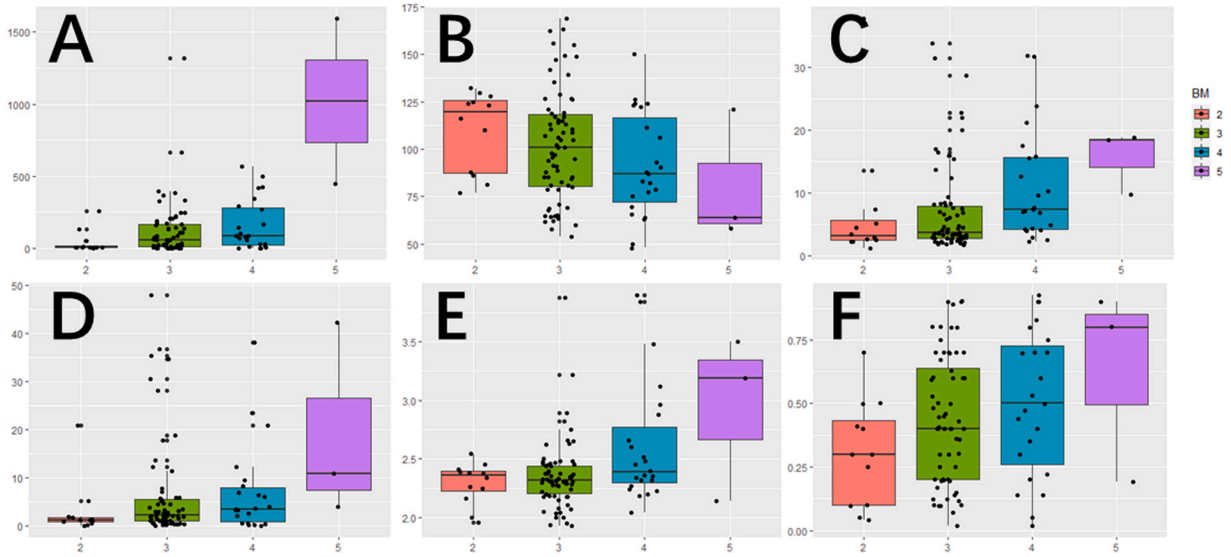


**Fig. 4.** Bone marrow Deauville criteria had a moderate correlation with FLC ratio (A), hemoglobin (B), β2 M (C), CRP (D), serum calcium (E), and BMPC (F).

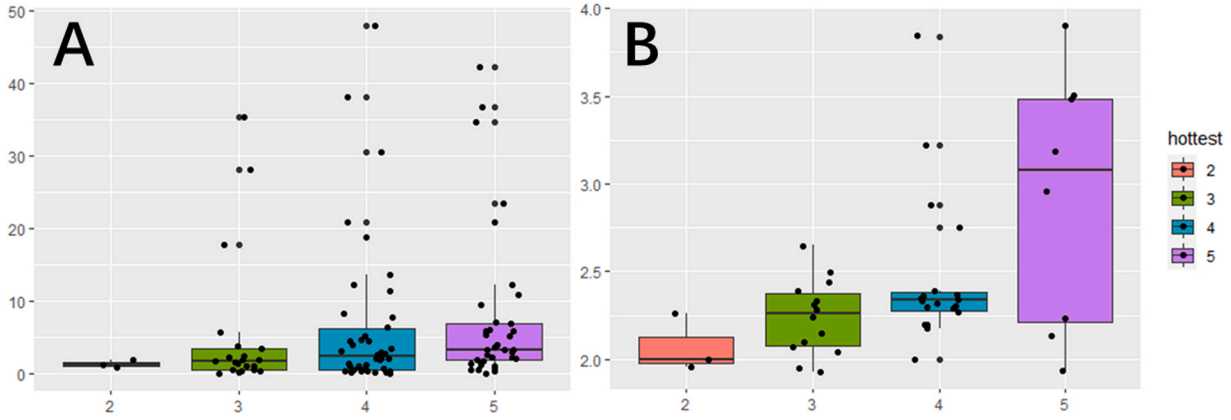


**Fig. 5.** Hottest bone lesion Deauville criteria had a moderate correlation with CRP (A) and serum calcium (B).

tumor burden in MM patients.

However, no significant difference was observed in the levels of hemoglobin between patients with BM $\geq$ 4 and those with BM $<$ 4. A possible explanation may be that MM-related anemia can cause a significant and diffuse increase in BM tracer uptake. This can give rise to a hot background in the BM and be easily confused with a similarly hypermetabolic diffuse BM myeloma infiltration.

Similar to previous studies investigating the correlation between diffuse 18 F-FDG uptake in appendicular skeleton and poor MM prognostic factors [15,17], we evaluated the presence of hypermetabolism in limbs and ribs according to IMPeTUs criteria [10]. Appendicular involvement was found to be correlated with adverse prognostic factors including higher levels of β2 M and LDH, and advanced R-ISS [15]. In this study, hypermetabolism in limbs and ribs confirmed a positive correlation with the levels of β2 M, serum calcium, and BMPC, which is substantially in agreement with previous report [15]. These results indicated that hypermetabolism in limbs and ribs may be an adversely prognostic factor for MM patients. However, the same as

**Table 4**
Correlations between clinical features and categorical PET/CT parameters with only two levels.

| | LR (No/Yes) | PM (No/Yes) | EM (No/Yes) | Lytic (No/Yes) | Fracture (No/Yes) |
|---|---|---|---|---|---|
| FLC ratio | 21.4 (6137.7)/ 73.4 (15.8275.6) | 55.4(9.1, 199)/ 47.9(4.9, 93.2) | 54.6(9, 183)/ 45.2(7.6, 84.4) | 74.1 (14.3, 171)/ 54(6.6, 174) | 58(9.2207)/ 53(5.5134) |
| p value | 0.037 | 0.262 | 0.365 | 0.727 | 0.389 |
| HGB | 105 (81,125)/ 91(74,113) | 95(75.5, 118)/ 110 (84.3, 125.3) | 100.5(79, 122.3)/ 85(65, 101) | 90(68.5, 107.5)/ 99.5(79, 124) | 101 (77,122)/ 92 (78.5111) |
| p value | 0.043 | 0.085 | 0.073 | 0.073 | 0.519 |
| β2 M | 3.7(2.7, 8.8)/ 6.4 (3.5, 9.8) | 4.7(3, 10.5)/ 4 (2.7, 7.4) | 4.4(2.9, 9.8)/ 6.1(3.8, 9.8) | 5.9(3.7, 8.5)/ 4.2(2.9, 11.7) | 4.6(3, 9.6)/ 4.4(3, 13.2) |
| p value | 0.024 | 0.3 | 0.466 | 0.346 | 0.774 |
| Albumin | 35.8 (31.6,41.3)/ 34.3 (31.8,40.4) | 34.9 (31.8, 40.6)/ 38.4 (31.5, 42) | 35.5(32, 41.1)/ 33.3 (29.9, 38.7) | 33.7 (27.8, 42)/ 35.6 (32.1, 40.8) | 35 (31.8,40.7)/ 35.1 (31.7,41.1) |
| p value | 0.624 | 0.289 | 0.238 | 0.45 | 0.861 |
| CRP | 1.8 (0.55,4.61)/ 3.24 (1.24,10.15) | 2.1(0.6, 7.9)/ 2.8(1.2, 5.3) | 2.14 (0.75, 6.04)/ 4(0.9, 17.1) | 1(0.4, 3.9)/ 2.8(1.1, 7) | 1.86 (0.55,5.27)/ 3.9(1.65,8.3) |
| p value | 0.05 | 0.798 | 0.304 | 0.012 | 0.012 |
| Calcium | 2.33 (2.25,2.45)/ 2.37 (2.22,2.59) | 2.34 (2.21, 2.49)/ 2.38 (2.29, 2.48) | 2.35 (2.24, 2.49)/ 2.32 (2.24, 2.44) | 2.3(2.14, 2.41)/ 2.37 (2.26, 2.49) | 2.33 (2.24,2.46)/ 2.38 (2.26,2.54) |
| p value | 0.124 | 0.534 | 0.587 | 0.038 | 0.155 |
| CREA | 71.9 (55.4113.6)/ 76.4 (61.7149.8) | 74(60, 143)/ 77.7(66, 98.2) | 73.8 (60.7, 137)/ 78 (69, 105) | 77(59.7, 135.6)/ 73.8 (61.3, 113.8) | 76.3 (60.7136.4)/ 71.9 (60.7109) |
| p value | 0.362 | 0.852 | 0.781 | 0.797 | 0.561 |
| LDH | 172 (138,226)/ 177 (134,236) | 176(136, 234)/ 167(139, 211) | 175(140, 230)/ 175(114, 239) | 212(150, 238)/ 170(135, 226) | 172 (136,229)/ 186 (139,237) |
| p value | 0.377 | 0.538 | 0.633 | 0.182 | 0.401 |
| BMPC | 0.4 (0.16,0.52)/ 0.49 (0.23,0.7) | 0.4(0.2, 0.69)/ 0.4(0.19, 0.65) | 0.4(0.2, 0.63)/ 0.55 (0.33, 0.8) | 0.5(0.14, 0.7)/ 0.4(0.2, 0.63) | 0.31 (0.14,0.6)/ 0.49 (0.35,0.7) |
| p value | 0.043 | 0.624 | 0.159 | 0.466 | 0.003 |
| FISH | (20/72)/ (32/77) | (46/ 119)/ (6/30) | (46/ 132)/ (6/ 17) | (10/31)/ (42/118) | (33/97)/ (19/52) |
| p value | 0.078 | 0.055 | 0.971 | 0.729 | 0.759 |

FLCratio, ratio of involved to uninvolved free light chains; HGB, hemoglobin; β2 M, β2-microglobulin; CRP, C-reactive protein; CREA, creatinine; LDH, lactate dehydrogenase; BMPC, infiltration rate of malignant plasma cell in bone marrow; LR, hypermetabolism in limbs and ribs; PM, presence of para-medullary Disease; EM, presence of extra-medullary disease; Lytic, presence of lytic lesion

higher BM metabolic activity that is not specific for myeloma infiltration, higher FDG uptake in limbs and ribs can also be resulted from increased red marrow reconversion, either related to severe anemia or to treatment-induced changes [15].

Previous study demonstrated a significant correlation between BM SUVmax and the percentage of BM plasma count, CRP and ISS [18], whereas we found that metabolic activity of the hottest bone lesion significantly correlated with the levels of CRP and serum calcium, but showed no correlation with BMPC. As mentioned above, the heterogeneity of the distribution of myeloma infiltration across the BM system may be a possible explanation. Interestingly, the numbers of both focal PET-positive lesions and lytic lesions had no correlation with the levels of hemoglobin, serum calcium, serum creatinine, and other clinical features.

This study was a retrospective review and is thus subject to the limitations associated. The confused finding that the presence of paramedullary or extra-medullary disease was associated with lower level of FLC ratio indicated the relatively small sample size of this study. Further studies with larger patient population are warranted to validate these findings. Besides, the vast majority of the PET/CT-positive myeloma lesions had not been histologically confirmed, which remains impractical in the clinical routine. Due to the short follow-up time for the patients included in this study, we could not evaluate their survival outcomes. Our study is ongoing and more clinical and survival data will be available. There are publications evaluating other PET radiotracers in MM, such as FluoroCholine (FCH). The combination of FDG and FCH could provide metabolic information useful for the management of these patients [19]. In further research, the use of more than one radiotracer can be of interest to detect different metabolic characteristics of the tumor with potential therapeutic implications [20].

## 5. Conclusion

Several IMPeTUs-based PET/CT parameters showed significant correlations with clinical features reflecting disease burden and biology, suggesting that these new criteria can be used in the risk stratification in MM patients.

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## Ethical statement

Institutional Review Board approval from Shandong Provincial Hospital Affiliated to Shandong First Medical University was obtained.

## CRediT authorship contribution statement

**Shuaishuai Xu:** Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Shengxiu Jiao:** Software, Resources, Methodology, Formal analysis, Data curation. **Huimin Guo:** Software, Methodology, Formal analysis. **Wenkun Chen:** Methodology, Investigation, Formal analysis, Data curation. **Shuzhan Yao:** Writing – review & editing, Validation, Resources, Conceptualization.

## Declaration of Competing Interest

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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