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Prognostic importance of PET score obtained from IMPeTUs criteria in multiple myeloma

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ABSTRACT

Aims: Multiple myeloma (MM) is a clonal plasma cell malignancy that infiltrates the bone marrow, bone, and sometimes extramedullary sites. Reliable staging and prognostic factors are essential for patient management. Imaging modalities, especially 18F-FDG PET/CT, are essential for the assessment of disease extent. This study evaluates a scoring system based on the IMPeTUs criteria for predicting progression-free survival (PFS) in MM.

Methods: This study included 35 newly diagnosed, treatment-naive MM patients (13 females, 22 males). Baseline ^{18}F-FDG PET/CT scans were obtained within one month of diagnosis. Five different assessments were performed. The PET score is a scoring system adapted from the previously established IMPeTUs to provide a more nuanced assessment of PET scan results in newly diagnosed patients. This system incorporates the DS (Deauville score), a standardised measure of treatment response in lymphoma, together with an assessment of the number of lesions seen on the PET scan.

Results: The mean age of the cohort was 65 years. Ig G kappa was the most common MM type (37.1%). Diffuse bone marrow uptake and focal lesions were observed in 37.2% and 57.2% of patients, respectively, DS ≥4. The PET score cut-off of 6.5 predicted PFS with 61.5% sensitivity and 72.7% specificity (AUC 0.715). Median PFS was significantly different between patients with PET score <6.5 and ≥6.5 (35±4.1 months vs. 23.6±4.03 months, p=0.027).

Conclusion: The PET score cut-off value of 6.5 serves as a potential prognostic tool for MM, aiding in patient stratification and treatment decisions.

Keywords: Multiple myeloma, positron-emission tomography, neoplasm staging

INTRODUCTION

MM is a clonal plasma cell malignancy that infiltrates the bone marrow, bone and sometimes extramedullary sites. This disease may vary over time depending on factors such as genetics and stage; survival and clinical features may vary from a few months to more than ten years. Therefore, reliable staging and identification of prognostic factors are important. In fact, many clinical-laboratory parameters, imaging modalities and cytogenetics have been proposed to improve staging and prognosis of the disease.[1] Currently used staging systems for myeloma patients are Durie and Salmon, International Staging System (ISS) and Revised International Staging System.[2] One of the most important factors in assessing the prognosis of MM patients is the extent of the disease, and imaging modalities are of critical importance. Bone survival, traditionally used in the Durie and Salmon system, has been replaced by more advanced imaging modalities such as CT, 18F-2-fluoro-2-deoxyglucose ^{18}F-FDG positron emission tomography/computed tomography (PET/CT) and magnetic resonance imaging (MRI). Recent studies have shown that ^{18}F-FDG PET/CT and MRI are useful for prognostic staging of MM patients based on the presence and number of focal lesions and diffuse bone marrow infiltration.[3,4] In addition to its role in staging, ^{18}F-FDG PET/CT has a role in evaluating treatment response and monitoring minimal residual disease in MM. The metabolic activity of myeloma lesions visualised by PET/CT can provide early information on the efficacy of treatment. This makes PET/CT an important tool not only in initial staging but also in the ongoing management of myeloma.[5] Whole-body ^{18}F-FDG PET/CT has the advantage of assessing both medullary and extramedullary disease and identifying metabolically active lesions before and after treatment.[3] However, due to the variable pattern of bone marrow involvement in MM, standardisation of ^{18}F-FDG PET/CT reports can be difficult.[6] Most standardisation studies are based on the assessment of ^{18}F-FDG uptake by SUVmax values, while others are based on visual assessment or a combination of both method.[7,8] The Italian Myeloma PET Usage (IMPeTUs) have recently been developed to standardise

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the interpretation of ^{18}F-FDG PET/CT images.[9-11] These criteria allow visual assessment of ^{18}F-FDG uptake using the Deauville 5-point scoring (5-PS), widely used in lymphoma patients, and identification of the metabolic status of the bone marrow and target lesion.[12] The location and number of focal bone lesions, the number of lytic lesions and the presence of possible paramedullary lesions, extramedullary lesions and fractures are also reported. PET/CT has also been effective in identifying high-risk myeloma patients. Patients with high SUVmax values or persistent PET-positive lesions after initial treatment have been shown to have a worse prognosis.[13] In this study, we present the scoring system we developed to easily calculate IMPeTUs criteria in clinical practice and its adequacy in predicting progression-free survival according to these criteria.

METHODS

The study was carried out with the permission of the Gazi Yaşargil Training and Research Hospital Clinical Researches Ethics Committee (Date: 03.03.2023, Decision No: 339/2023). We obtained an informed consent form from all patients for procedure. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. This study was conducted at Gazi Yaşargil Training and Research Hospital and was designed as a retrospective study covering the period between March 2019 and June 2023. A total of 35 patients (13 women and 22 men) diagnosed with multiple myeloma were included in the study. Inclusion criteria were as follows: presence of previously untreated newly diagnosed active myeloma requiring induction therapy and eligible for transplantation; age ≤70 years; baseline ^{18}F-FDG PET/CT available within maximum 1 month after diagnosis of MM requiring treatment. All patients participating in the study received three or four cycle bortezomib-cyclophosphamide-dexamethasone treatment followed by autologous stem cell transplantation. Multiple myeloma type, ISS stage, date of diagnosis, chemotherapy regimens, number of lines of treatment, date of autologous stem cell transplantation, date of relapse if any, follow-up period and date of excitus if any were recorded. Bone marrow Deauville 5-PS, number of bones with focal bone involvement, Deauville 5-PS in focal bone involvement, number of lytic bones, number of paramedullary and extramedullary involvement, and Deauville 5-PS in these areas were recorded at diagnosis on ^{18}F-FDG PETCT. In this study, we developed and established a novel PET scoring system specifically designed to provide a more refined assessment of PET scan results in newly diagnosed MM patients. Our scoring system, referred to as the IMPeTUs-derived PET score, is an adaptation of the previously validated IMPeTUs criteria, incorporating both the DS and the number of lesions observed on PET scans.

Image Acquisition Protocol

All patients were asked to fast and discontinue intravenous (IV) glucose for at least 6 hours prior to scanning. Patients' blood glucose levels were confirmed to be ≤140 mg/dl using the finger-stick method, and 3.5-5.5 MBq/kg of ^{18}F-FDG was administered intravenously. One hour after injection, CT images (120 kV, 80 mAs/slice, 700 mm transaxial field of view (FOV), no gap, 64x0.625 mm collimation, pitch 1.4, 0.5s rotation time, 3.3 mm slice thickness, 512x512 matrix) were acquired from the vertex to mid-thigh in the supine position using the Discovery IQ 4 ring 20 cm axial FOV PET/CT unit (GE Healthcare, Milwaukee, WI, USA). PET images were then acquired over 2.5 min per bed position [3D FOV 20 cm, ordered subset expectation-maximisation algorithm (OSEM) 5 iterations/12 subset, full width at half maximum (FWHM) 3 mm]. Intravenous non-ionic contrast was administered at a dose of 1.5 ml/kg to all patients with no contraindications. All ^{18}F-FDG PET/CT images were reviewed on an AW 4.7 workstation (Advantage Workstation software version 4.7; GE Healthcare, Milwaukee, WI, USA). PET/CT scans acquired from whole body and evaluated by two experts with at least 10 years of FDG-PET/CT experience. The IMPeTUs are largely based on visual assessment to minimise interpretation variability. However, in addition to visual assessment, lesion-background SUVmax measurements at interval thickness times were used. Five different assessments were performed. The PET score is a scoring system adapted from the previously established IMPeTUs to provide a more nuanced assessment of PET scan results in newly diagnosed patients. This system incorporates the DS, a standardised measure of treatment response in lymphoma, together with an assessment of the number of lesions seen on the PET scan.

PET scoring according to DS:

- DS 1: Scored as 0 point.
- DS 2-3: Scored as 1 point.
- DS 4-5: Assigned as 3 points.

PET scoring according to number of lesions:

- 0 lesions: Assigned 0 point.
- 1-3 lesions: Scored as 1 point.
- More than 3 lesions: Assigned 2 points (**Figure 1, Table 1**).

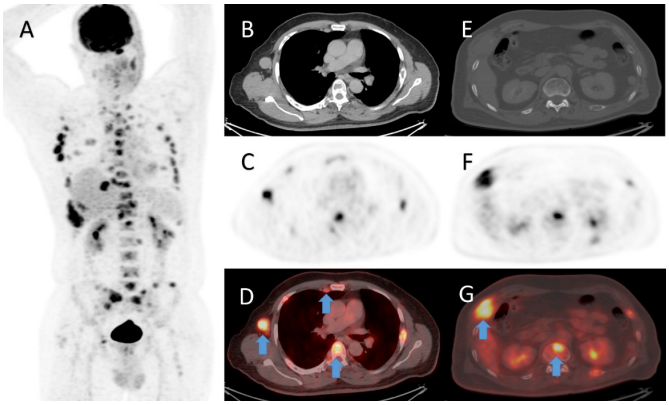

Figure 1. A 65-year-old male patient's imaging

A 65-year-old male patient with multiple myeloma underwent FDG PET/CT imaging before treatment. According to the impetus; diffuse BM DS 2, focal lesion score 4, focal lesion DS 5, lytic lesion score 4, EM present, EM DS 5, PM present. However, it was found as 11 according to the PET score we developed. The PFS of the patient was 15.7 months.

A; MIP B; CT, C; PET and D; Fusion images: right axilla and parasternal lymph node involvement (PM, blue arrow) and lytic bone lesions (blue arrow), E; CT, F; PET and G; Fusion images; bone lesion destructing the right 6th costa (EM, blue arrow) and lytic bone lesions (blue arrow).

FDG: Fluorodeoxyglucose, PET: Positron emission tomography, CT: Computed tomography, BM: BM: Bone marrow, DS: Deauville score, PFS: Progression-free survival, MIP: Maximal inspiratory pressure

Table 1. IMPeTUs criteria vs PET score	
IMPeTUs criteria	**PET score**
DS of diffuse BM uptake	
No uptake at all	0
≤ mediastinal blood pool uptake	1
> mediastinal blood pool uptake, ≤ liver uptake	
> liver uptake +10%	2
>> liver uptake (twice or more)	
Number of focal lesion	
No lesion	0
1 to 3 lesions	1
4 to 10 lesions	2
>10 lesions were scored	
DS of focal lesions	
No uptake	0
≤ mediastinal blood pool uptake	1
> mediastinal blood pool uptake, ≤ liver uptake	
> liver uptake +10%	2
>> liver uptake (twice or more)	
No of lytic lesions	
No lesion	0
1 to 3 lesions	1
4 to 10 lesions	2
>10 lesions were scored	
DS of extramedullary lesions	
No uptake	0
≤ mediastinal blood pool uptake	1
> mediastinal blood pool uptake, ≤ liver uptake	
> liver uptake +10%	2
>> liver uptake (twice or more)	
Extramedullary	
0	0
1	1
Paramedullary	
0	0
1	1

IMPeTUs: Italian myeloma criteria for PET use, PET: Positron emission tomography, DS: Deauville score, BM: Bone marrow

Statistical Analysis

SPSS 26.0 (IBM Corporation, Armonk, NY, United States of America) was used to analyse the variables. The Kolmogorov-Smirnov test was used to determine whether univariate data were normally distributed. Kaplan-Meier (product-limit method) log-rank analysis was used to examine the effect of factors on death and survival. The PFS cut-off value to differentiate MM patients was performed by ROC curve analysis. Quantitative variables were expressed as mean±SD (standard deviation) and median (interquartile range), while categorical variables were expressed as n (%). Variables were analysed with 95% confidence interval and $p<0.05$ was considered significant.

RESULTS

Thirty-five MM patients, 13 (37%) females and 22 (63%) males, were included in our study. The mean age of the patients was 65 years, with a minimum of 46 and a maximum of 70 years. Regarding the types of multiple myeloma, 8 (22.9%) of the patients had Ig G lambda, 13 (37.1%) had Ig G kappa, 4 (11.4%) had Ig A lambda, 4 (11.4%) had Ig A kappa, 3 (8.6%) had lambda light chain and 3 (8.6%) had kappa light chain. ISS stage 1 disease was present in 28.6%, ISS stage 2 disease in 37.1% and ISS stage 3 disease in 34.3% of the patients. 2 patients were excitus. Only one patient had t (4;14) and 13q del mutation, the others had no mutation about myeloma. The number and percentages of patients in terms of metabolic state of the bone marrow according to Deauville 5-PS, number of focal PET-positive lesions, presence of extramedullary and paramedullary disease, number of lytic lesions are given in the Table 2. The presence of extramedullary disease (EMD) was observed in 29 patients (82.9%), while it was absent in 6 patients (17.1%). Similarly, paramedullary disease (PMD) was present in 20 patients (57.1%) and absent in 15 patients (42.9%). Diffuse bone marrow uptake was observed in 37.2% of patients, while focal lesions were present in 57.2%, both with a Deauville score (DS) of 4 or higher. ROC curve analysis identified a PET score cutoff value of 6.5, which showed a sensitivity of 61.5% and a specificity of 72.7% for detecting progression-free survival (PFS) in multiple myeloma (MM), with statistical significance (area under the curve (AUC): 0.715±0.091, p=0.036) (Figure 2). The median PFS was 35±4.1 months (95% CI, 26.9-43.1) for patients with PET score <6.5 and 23.6±4.03 months (95% CI, 15.7-31.5) for patients with PET score ≥6.5 (Table 3). The 1-year rate of PFS was 100% for patients with PET score <6.5 and 68.1% for patients with PET score ≥6.5. The 3-year rate of PFS was 57.8% for patients with PET score <6.5 and 37.2% for patients with PET score ≥6.5 (Figure 3).

Table 2. Number and percentages of patients according to the IMPeTUs criteria										
	Diffuse BM DS		**F**		**FS**		**L**		**EM DS**	
Valid*	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
1	1	2.9	16	45.7	9	25.7	8	22.9	32	91.4
2	9	25.7	11	31.4	1	2.9	4	11.4	1	2.9
3	12	34.3	-	-	5	14.3	2	5.7	-	-
4	11	31.4	8	22.9	12	34.3	21	60	1	5.7
5	2	5.7	-	-	8	22.9	-	-	-	-

*Valid numbers are Deauville scores, IMPeTUs: Italian myeloma criteria for PET use, PET: Positron emission tomography, BM: Bone marrow, DS: Deauville 5-point Scale, F: Focal bone lesions, FS: Hotest focal bone lesion Deauville 5-PS, L: Lytic lesions, EM: Extramedullary

Table 3. Relapse frequency according to PET score			
PET score	**Total number**	**Number of relapse**	**Percentage**
<6.5	21	5	76.2%
≥6.5	14	8	42.9%
Overall	35	13	62.9%

PET: Positron emission tomography

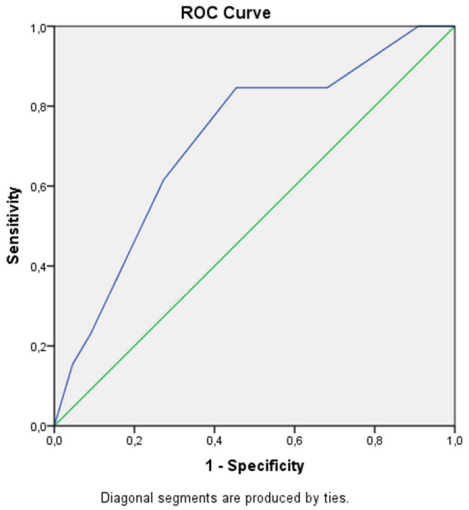

Figure 2. ROC curve

The PET score cut-off value of 6.5 had a sensitivity of 61.5% and a specificity of 72.7% for the detection of PFS in MM and was statistically significant (AUC 0.715)

ROC: Receiver operating characteristic, PET: Positron emission tomography, PFS: Progression-free survival, MM: Multiple myeloma, AUC: Area under the curve

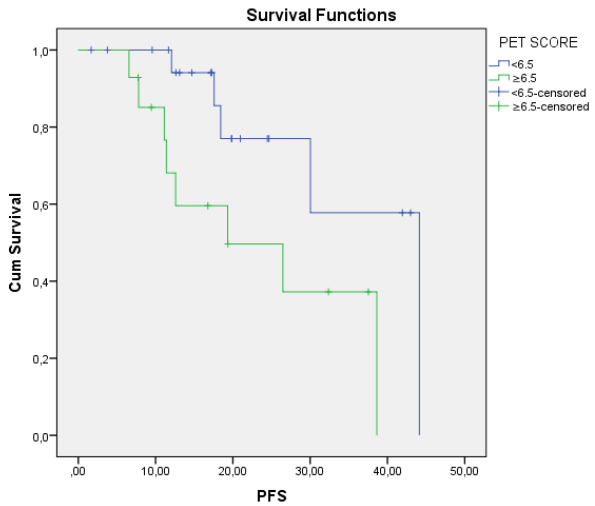

Figure 3. Kaplan meier test for patients with PET score <6.5 and ≥6.5

PET: Positron emission tomography

DISCUSSION

^{18}F-FDG PET/CT is a highly valuable diagnostic tool for patients with both newly diagnosed and relapsed or refractory MM. It offers high sensitivity and specificity in assessing bone damage, detects extramedullary proliferative sites of clonal plasma cells, and provides crucial prognostic information. However, ^{18}F-FDG PET/CT may be difficult to interpret in some patients. In MM-associated anemia, there is a significant increase in BM tracer uptake, resulting in a hot background in the bone. Since FDG uptake varies, a baseline study is essential for reference. New fractures may appear as false positives and metallic bone implants can cause significant artefacts in the images.[3] Most importantly, response criteria have not been defined. Due to the need for standardised interpretation criteria for the evaluation of ^{18}F-FDG PET/CT scans in MM, IMPeTUs criteria were developed.[9] It should be noted that in order to apply the IMPeTUs criteria to the clinical management of MM patients, it is necessary to determine the limits of positivity for each defined parameter and to reduce the number of non-prognostic parameters. Our study included 35 patients with newly diagnosed MM who received first-line treatment with bortezomib-cyclophosphamide-dexamethasone followed by autologous stem cell transplantation. 13 (37%) were women and 22 (63%) were men, aged between 46 and 85 years, with a mean age of 65 years. The cohort represented a diverse spectrum of MM types and stages, with Ig G kappa being the most prevalent type (37.1%) and ISS stage 2 being the most common stage (37.1%). A significant finding of our study was the presence of diffuse bone marrow uptake in 37.2% of patients and focal lesions in 57.2%, with a DS greater than or equal to 4 in both cases. This indicates a high level of metabolic activity in a substantial proportion of the cohort, which is consistent with the aggressive nature of MM. Also, the demographic characteristics, MM type distribution and imaging findings of our study are consistent with those previously reported in the literature.[7,12] The presence of diffuse and focal bone marrow involvement with high SUVmax values is an important finding that is consistent with published data and demonstrates that our results are within the expected range for MM patients. Analysis of the PET score by ROC curve analysis revealed a cut-off value of 6.5, which had a sensitivity of 61.5% and a specificity of 72.7% for predicting PFS in MM patients. This was statistically significant with an area under the curve (AUC) of 0.715. Median PFS was significantly different between patients with PET score below and above 6.5. Patients with a PET score of less than 6.5 had a median PFS of 35±4.1 months, compared to 23.6±4.03 months for patients with a PET score of 6.5 or higher (p=0,027). This significant difference highlights the potential utility of PET score as a prognostic marker in MM. In the study by Fonti et al.,[6] there were no statistically significant differences in visual parameter values between patients with or without progression, except for the number of lytic lesions that was significantly different in patients with progressive disease as compared to those without progression (p=0.022). Additionally, the SUVmax value was significantly different between patients with or without progression (p=0.04). The study by Zamagni et al.[8] demonstrated that PET/CT parameters, including the number of focal lesions (FLs), SUV, and extramedullary disease (EMD), were strong prognostic indicators in multiple myeloma. Specifically, the presence of at least three FLs (≥3 FLs), an SUV >4.2, and EMD at baseline were associated with poorer 4-year progression-free survival (PFS) rates (50%, 43%, and 28%, respectively). Furthermore, SUV >4.2 and EMD were linked to reduced overall survival (OS) rates (77% and 66%, respectively). In the study by Deng et al.,[14] DS plus stage III (p=0.021) and Deauville bone marrow score equal to or above 4 (p=0.031) were found to be reliable prognostic factors in newly diagnosed MM patients. Individual parameters may not be predictive in IMPeTUs. Combined PET scoring system may provide a more comprehensive assessment of disease prognosis. The statistically significant result obtained at the PET score cut-off value of 6.5 reinforces the importance of a comprehensive approach in the interpretation of PET scan in MM. In Deng's study they found that Durie-Salmon Plus staging system based on IMPeTUs stage III and the Deauville score of bone marrow ≥4 were independent prognostic

factors associated with OS.[14] Similar to that study, our results showed a significant relationship between the PET score, which we developed based on IMPeTUs scoring, and survival prediction. However, the lack of a significant correlation between individual IMPeTUs criteria and PFS in our study suggests that further refinement of these criteria may be necessary. Furthermore, the discordance with the study by Sachpekidis,[15] who found no significant association between the presence of PMD and PFS, suggests that further research is needed to confirm these findings in different patient cohorts.

Limitations

The limitation of our retrospective design and evaluation in a selected group of patients is the following; the clinical utility of our scoring system should be evaluated in studies with a larger number of patients grouped according to ISS stage. The strength of our study is that we evaluated in a homogenous patient group.

CONCLUSION

The PET score, derived from IMPeTUs criteria, cut-off value of 6.5 could serve as a valuable prognostic tool in clinical practice, aiding in the stratification of patients. Future studies with larger cohorts and longer follow-up periods are warranted to further validate these findings and refine the prognostic criteria for MM.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Gazi Yaşargil Training and Research Hospital Clinical Researches Ethics Committee (Date: 03.03.2023, Decision No: 339/2023).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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