IJHOSCR

Original Article

International Journal of Hematology-Oncology and Stem Cell Research

# Correlation of Biochemical and FDG PET/CT Responses Following Induction Therapy in Newly Diagnosed Multiple Myeloma: A Prospective Observational Study

**Homdutt Sharma[1], Pradeep Kumar[1], Neelabh Nayan[1], Rakesh Kumar[2], Tulika Seth[1], Rishi Dhawan[1], Jasmita Dass[1], Mukul Aggarwal[1], Ganesh Kumar Viswanathan[1], Richa Chauhan[1], Manoranjan Mahapatra[1]**

[1]Department of Hematology, All India Institute of Medical Sciences, Delhi, India
[2]Department of Nuclear Medicine, All India Institute of Medical Sciences, Delhi, India

**Corresponding Author:** Pradeep Kumar, Department of Hematology, All India Institute of Medical Sciences, Delhi, India
**E-mail**: doctorpkgmu@gmail.com

Received: 04, Jul, 2025
Accepted: 18, Mar, 2026

**ABSTRACT**

**Background:** Multiple myeloma is a heterogeneous malignancy with patchy bone marrow involvement, often leading to discrepancies between biochemical and imaging-based response assessments. Site-specific bone marrow biopsies may miss focal disease, while FDG PET/CT detects metabolically active lesions, and the two approaches offer complementary prognostic value.

**Materials and Methods:** This prospective study included 44 newly diagnosed multiple myeloma patients. The primary aim was to assess the correlation between biochemical and PET/CT responses at six months post-induction. A secondary objective was to evaluate the impact of PET/CT response on 12-month event-free survival (EFS).

**Results:** The median age was 55.5 years. At baseline, more than 3 focal lesions and extramedullary disease (EMD) were observed in 61.4% and 34.1% of patients, respectively. After six months of induction therapy, 86.3% achieved at least a very good partial response (≥VGPR) biochemically, but 52.3% remained PET/CT-positive. Baseline >3 focal lesions and EMD significantly predicted persistent PET/CT positivity ($p = 0.004$). Notably, 50% of patients with ≥VGPR still showed PET/CT-positive findings. At 12 months, 75% of patients who experienced clinical events had been PET/CT-positive at six months, compared with 47.2% of those without events ($p = 0.245$). The 12-month event-free survival was lower in the PET/CT-positive group (73.9% vs. 90.4%, $p = 0.182$), though this difference was not statistically significant.

**Conclusion:** 18-FDG PET/CT can detect residual disease not captured by biochemical markers, highlighting the value of combined assessment in multiple myeloma. Baseline >3 focal lesions and EMD predicted persistent PET/CT positivity. Although PET/CT positivity at six months showed a trend toward worse 12-month EFS, larger studies are needed to confirm its prognostic significance.

**Keywords:** Multiple myeloma; Biochemical response; FDG PET/CT scan; Focal lesion; Extramedullary

## INTRODUCTION

Multiple myeloma (MM) is a malignancy involving terminally differentiated plasma cells, characterized by the infiltration and proliferation of malignant plasma cells, primarily in the bone marrow. Patients with MM present with a constellation of symptoms that have been given the acronym CRAB: Hypercalcemia (C), Renal dysfunction (R), Anemia (A), and Bone lesions (B). Signs and symptoms of MM are related to either marrow infiltration by plasma cells or manifestations of end-organ damage leading to renal dysfunction, bone lesions, and/or

DOI: http://doi.org/10.18502/ijhoscr.v20i2.21781

immunoparesis. About 80–90% of patients with MM develop bone disease[1], hence a thorough workup of skeletal involvement and assessment of structural integrity are required. Diagnosis of MM requires evidence of end-organ damage attributable to a neoplastic clone of plasma cells. With major advances in therapy and the identification of biomarkers, the IMWG revised the diagnostic criteria for MM in 2014[2].

Bone-related complications significantly impact patients' quality of life and are a leading cause of morbidity and mortality. Imaging plays a crucial role in the management of MM, as it is essential for detecting lytic bone lesions, which serve as a marker of disease-related end-organ damage. These lesions are typically used to diagnose MM and assess the need for immediate treatment[3]. Although widely employed, skeletal survey has limitations. Roentgenographically detectable osteolytic lesions require at least 50 to 70 percent loss of bone mass[4], and hence represent advanced bone destruction. Conventional X-rays have limited sensitivity and, consequently, may miss between 10 and 20 percent of early lytic lesions[5]. In addition, reproducibility of skeletal survey results is low and dependent on the expertise of the reviewer[6]. Another limitation of plain X-rays is that they cannot be used to assess response to therapy, as lytic lesions seldom show evidence of healing[7]. MRI is extensively used for both newly diagnosed and relapsed multiple myeloma, as well as in cases where spinal cord compression is suspected. Numerous studies have highlighted the superior sensitivity of MRI compared to skeletal surveys[8,9] and whole-body multidetector computed tomography (MDCT)[10]. MRI is particularly beneficial for visualizing the medullary cavity, allowing for direct evaluation of the extent of myeloma cell infiltration into the bone[11]. In cases of suspected spinal cord compression, MRI is the imaging method of choice, as it provides detailed information on the level and degree of compression, the size of the tumor mass, and its impact on the epidural space[12].

Positron emission tomography (PET/CT) scans using FDG (fluorodeoxyglucose) as a radiotracer are capable of detecting glucose hypermetabolism in medullary and extramedullary lesions, offering both morphological and functional insights. PET, especially when combined with CT, is useful for identifying active myeloma. This imaging modality merges the structural details from CT with the functional metabolic data from PET. The CT component identifies lytic lesions, osteopenia, fractures, and extramedullary disease spread, while the PET component highlights the metabolic activity of each lesion, helping to assess the initial extent of bone marrow involvement and monitor therapy response. Numerous studies show that PET/CT can detect lesions as small as 1 cm in diameter using a standardized uptake value (SUV) cutoff of 2.5 to indicate the presence of disease[13]. Higher sensitivity of modern imaging techniques, such as PET/CT and whole-body MRI, provides the opportunity not only to determine bone destruction in multiple myeloma but also to assess tumor burden and disease activity in a large area—if not the entire bone marrow compartment. Bone marrow infiltration in multiple myeloma is not homogeneous in most patients. Therefore, the ability to identify discrete areas of diffuse versus focal plasma cell infiltration by sensitive imaging techniques provides a novel dimension to the evaluation of disease burden and response assessment.

At present, in most cases at initial diagnosis, genetic testing for risk assessment and definition of complete remission (CR) and minimal residual disease (MRD) assessment in multiple myeloma has relied on plasma cell percentage and bone marrow specimen biology obtained from random biopsies of either the iliac crest or the sternum. However, these sites are not always representative of the true disease burden because the biopsy may either sample or miss a focal lesion and thereby over- or underestimate the plasma cell percentage. Heterogeneity in the biological background and clinical presentation of MM requires a multidimensional approach to disease assessment. There are discrepancies between hematologic and imaging responses. These differences can be explained by the patchy pattern of malignant plasma cell infiltration into the bone marrow. Blind bone marrow biopsies often miss the niche with the highest plasma cell population, leading to falsely reassuring results and inferior outcomes. Thus, MM exhibits variable secretory and biological behavior,

resulting in many patients having suboptimal trajectories despite achieving deep conventionally correlate with PET/CT responses at 6 months and to evaluate the impact of 6-month PET/CT scan response on 12-month event-free survival (EFS). The aim of the study was to assess biochemical response in newly diagnosed multiple myeloma (NDMM) patients, to determine the correlation between hematologic and PET/CT scan response at 6 months post-treatment, and to evaluate the effect of 6-month post-treatment PET/CT response on 12-month EFS.

## MATERIALS AND METHODS

### Study design

Prospective observational study conducted at the Department of Hematology, All India Institute of Medical Sciences, New Delhi.

### Study duration

The study was approved by the AIIMS Institutional Ethics Committee (IECPG–21/31.01.2023), following which it was conducted from February 2023 to December 2024.

### Eligibility criteria

### Inclusion Criteria

All patients with NDMM who were treatment-naïve, willing to undergo therapy at the Department of Hematology, and able to provide informed consent were considered for inclusion in the study. Recruitment commenced upon approval from the Institutional Ethics Committee and continued for one year.

### Exclusion Criteria

Patients not providing consent for inclusion in the study were excluded.

### Sample size

We intended to enroll a minimum of 30 patients of NDMM who were treatment naïve.

### Study procedure

Consent for data collection, storage, analysis, and publication was obtained from all patients at the time of study registration. A detailed clinical history was obtained from each patient, followed by a focused clinical examination. All patients underwent routine investigations, including complete hemogram, liver function tests, renal function tests, and lactate dehydrogenase (LDH). Specific investigations, including PET/CT, were performed at baseline and at 6 months post-treatment. Biochemical response was assessed at 6 months post-treatment (concurrent with the second PET/CT scan) based on the IMWG response criteria.

### Investigation done at baseline and at 6 month

The following investigations were performed: complete hemogram, liver function tests, renal function tests, serum protein electrophoresis, immunofixation analysis, serum free light chain assay, bone marrow aspiration/biopsy, and 18F-FDG PET/CT scan. PET/CT positivity and negativity were reported as per the IMWG guidelines[15]. PET/CT negativity (−) was defined as the disappearance of every area of increased FDG uptake found at baseline, or a decrease in uptake to less than mediastinal blood pool activity, or a decrease in metabolic activity to less than that of surrounding normal tissue.

PET/CT positivity (+) was defined as residual disease at the 6-month mark, with patients considered positive if the PET/CT showed new areas of increased FDG uptake or if existing lesions did not completely resolve.

### Event-free survival (EFS)

The duration of time from the completion of six months of therapy during which the patient remains free of events, such as relapse or a change in therapy aimed at preventing or delaying of disease progression.

### Statistical analysis

Categorical variables, such as gender, clinical profile, high-risk fluorescence in situ hybridization (FISH), and Revised International Staging System (RISS), were expressed as frequencies and percentages. Continuous variables, such as age and test results, were presented as means with standard deviations

or as medians with ranges, depending on the data distribution. Baseline clinical characteristics were (+) versus PET/CT negative (−), were made using Student's t-test for continuous variables and the $\chi^2$ test for categorical variables. One-way ANOVA was used to compare normally distributed continuous variables across categorical groups. For non-normally distributed continuous variables, the Mann–Whitney U test was used. Multivariable analysis was performed using the Cox proportional hazards model, incorporating known unfavorable risk factors, such as the number of focal lesions on PET/CT, high-risk FISH, extramedullary disease (EMD) at diagnosis, and high RISS scores. Survival analysis in the total study cohort, as well as in different subgroups, was performed using the Kaplan–Meier method.

**RESULT**

A total of 91 patients were screened during outpatient visits for suspected plasma cell dyscrasia. collected for the entire cohort, and comparisons between the two subgroups, such as PET/CT positive Of these, 28 patients were excluded from the study: 4 patients underwent whole-body low-dose CT, 14 patients did not meet the diagnostic criteria for MM and had no alternate diagnosis, 5 patients had received partial treatment elsewhere, and 5 patients were lost to follow-up during screening. Of the remaining 63 patients who met the diagnostic criteria for MM, 10 died during follow-up and 4 were lost to follow-up. A total of 49 patients completed 6 months of induction therapy. Of these, 44 patients underwent a second PET/CT scan at 6 months post-therapy, resulting in a final sample size of 44 patients for analysis. The median age of the study population was 55.5 years. As shown in Table 1, approximately two-thirds of patients were between 41 and 70 years of age. Only 4 patients were aged ≥ 71 years, and none were aged ≤ 30 years. Of the 44 patients, 36 were male and 8 were female.

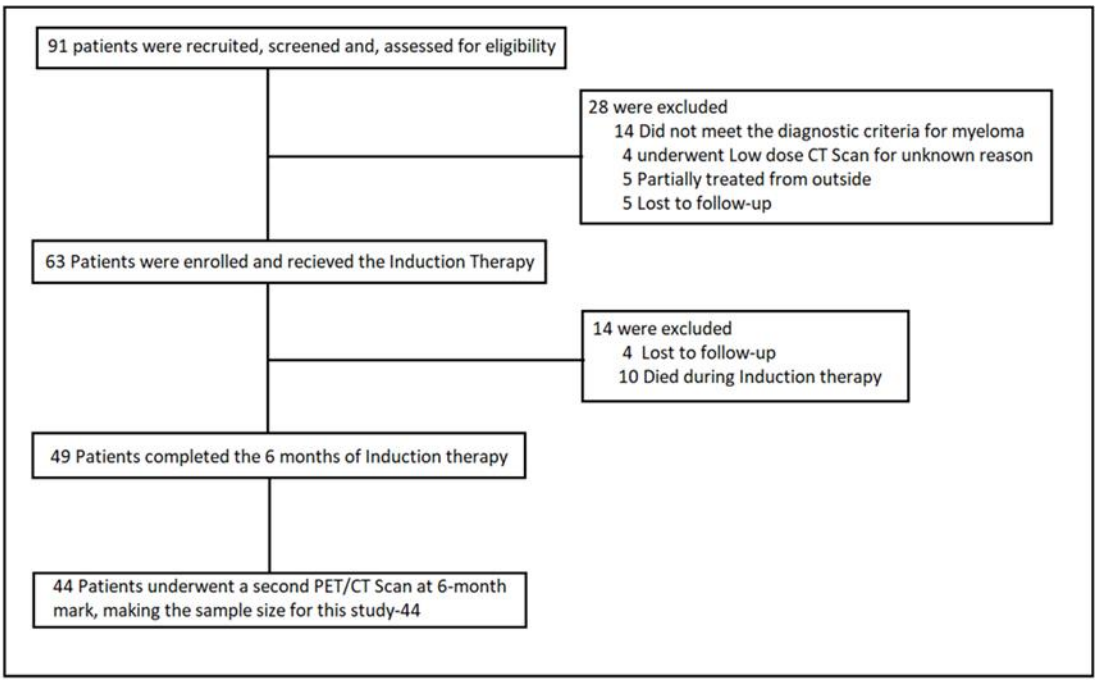



Figure 1. Consort flow diagram

**Table 1:** Demographic characteristics and presenting complaints

| | Mean ± SD \|\| Median (IQR) \|\| Min-Max OR N (%) |
|---|---|
| **Patient Age (Years)** | **56.61 ± 10.49 \|\| 55.50 (49.50-64.50) \|\| 38.00 - 83.00** |
| **Age Group** | |
| 31-40 Years | 2 (4.5%) |
| 41-50 Years | 11 (25.0%) |
| 51-60 Years | 15 (34.1%) |
| 61-70 Years | 12 (27.3%) |
| 71-80 Years | 3 (6.8%) |
| 81-90 Years | 1 (2.3%) |
| **Patient Gender** | |
| Male | 36 (81.8%) |
| Female | 8 (18.2%) |
| **Presenting complaints** | |
| Asymptomatic | 5 (11.4%) |
| Bony pain | 27 (61.4%) |
| Generalised Weakness | 24 (54.5%) |
| Fever | 6 (13.6%) |
| Pedal Oedema | 3 (6.8%) |
| Breathlessness/SOB | 2 (4.5%) |
| Weight Loss | 2 (4.5%) |
| Paraesthesia | 1 (2.3%) |
| Chest Pain | 1 (2.3%) |
| Difficulty In Walking | 1 (2.3%) |
| Constipation | 1 (2.3%) |
| Left Femur Neck Fracture | 1 (2.3%) |
| Epistaxis | 1 (2.3%) |

**Table 2:** The baseline laboratory parameters of the study cohort

| Blood Investigations | Mean ± SD | Median (IQR) | Min – Max |
|---|---|---|---|
| Hemoglobin (g/dL) | 8.56 ± 1.97 | 8.15 (7.10-9.60) | 5.3 - 13.2 |
| TLC (/mm$^3$) | 7058.64 ± 3776.77 | 6270.00 (4745.00-8995.00) | 1500.0 - 23120.0 |
| ANC (/mm$^3$) | 4157.66 ± 3498.68 | 3190.50 (2250.00-4979.00) | 750.0 - 20346.0 |
| Platelet Count (x10$^5$/mm$^3$) | 1.74 ± 1.38 | 1.31 (1.10-2.04) | 0.2 - 7.7 |
| Blood Urea (mg/dL) | 47.30 ± 28.66 | 39.00 (26.50-65.00) | 12.0 - 148.0 |
| S. Creatinine (mg/dL) | 1.60 ± 1.16 | 1.30 (0.85-1.80) | 0.5 - 5.5 |
| eGFR (mL/min/1.73m$^2$) | 74.76 ± 45.71 | 64.88 (42.01-105.60) | 11.4 - 179.0 |
| Uric Acid Level (mg/dL) | 7.07 ± 2.55 | 7.00 (5.80-8.50) | 1.5 - 12.9 |
| S. Calcium Level (mg/dL) | 9.54 ± 1.88 | 9.20 (8.50-9.90) | 5.9 - 15.8 |
| Phosphate Level (mg/dL) | 4.20 ± 1.09 | 4.10 (3.70-4.60) | 1.3 - 7.3 |
| S. Protein (g/dL) | 9.13 ± 2.77 | 8.90 (7.20-10.40) | 5.2 - 17.3 |
| S. Albumin (g/dL) | 3.31 ± 0.78 | 3.40 (2.80-3.77) | 1.7 - 5.4 |
| Globulin (g/dL) | 6.11 ± 3.17 | 5.70 (3.40-7.10) | 2.3 - 15.6 |
| LDH (U/L) | 209.19 ± 95.82 | 189.50 (160.00-238.75) | 104.0 - 691.0 |

**Table 3:** CRAB features as per IMWG Criteria

| CRAB Parameters | N (%) |
|---|---|
| **Hypercalcemia** | **6(13.6%)** |
| **Renal insufficiency** | **14(31.8%)** |
| **Anemia** | **35(79.5%)** |
| **Bony lytic lesions** | **36(81.8%)** |

**Table 4:** Baseline bone marrow findings and genetic markers of study cohort

| | Mean ± SD \|\| Median (IQR) |
|---|---|
| **Bone Marrow Plasmacytosis** | **54.77 ± 27.52 \|\| 60.00 (25.75-70.00)** |
| **Cytogenetic Study** | **N(%)** |
| Failed | 7 (15.9%) |
| 46 XY | 27 (61.4%) |
| 46 XX | 7 (15.9%) |
| Dry Tap | 1 (2.3%) |
| Hyperdiploidy | 2 (4.5%) |
| **FISH Panel for MM** | |
| Negative | 21 (55.3%) |
| 1q Gain | 5 (13.2%) |
| Deletion 17p | 4 (10.5%) |
| Deletion 13q | 10 (26.3%) |
| Translocation (4:14) | 2 (5.3%) |
| Translocation (14:16) | 1 (2.6%) |
| Translocation (11:14) | 1 (2.6%) |
| Trisomy11 | 1 (2.6%) |
| IGH Gene Break Apart | 2 (5.3%) |
| Dry Tap | 1 (2.6%) |
| **Cytogenetic Risk Category** | |
| Standard Risk | 28 (73.7%) |
| High Risk | 10 (26.3%) |

**Table 5:** Baseline paraprotein parameters and staging

| **Parameters** | **Mean ± SD \|\| Median (IQR) \|\| Min-Max OR N (%)** |
|---|---|
| **SPEP-M Band Level (g/dl)** | **3.38 ± 2.46 \|\| 3.60 (0.95-4.75) \|\| 0.00 - 8.20** |
| **Immunofixation Analysis: Immunoglobulin Type** | |
| Light chain only | 6 (14.0%) |
| IgA | 7 (16.3%) |
| IgD | 1 (2.3%) |
| IgG | 29 (67.4%) |
| IgM | 0 (0.0%) |
| **Immunofixation Analysis: Light Chain Type** | |
| Kappa | 21 (48.8%) |
| Lambda | 22 (51.2%) |
| Beta-2 Microglobulin Level (mg/L) | 10.73 ± 6.91 \|\| 8.13 (5.91-14.56) \|\| 1.70 - 30.30 |
| **RISS Stage** | |
| Stage I | 2 (4.5%) |
| Stage II | 24 (54.6%) |
| Stage III | 14 (31.8%) |
| Missing | 4 (9.1%) |

**Table 6:** PET/CT scans findings at Baseline

| **Number of Focal Lesions** | **No. of patients (%)** |
|---|---|
| Absent | 8 (18.2%) |
| ≤3 | 9 (20.4%) |
| >3 | 27 (61.4%) |
| Extramedullary Disease | 15 (34.1%) |

**Table 7: Outcome**

| **IMWG Response at 6 month** | **N(%)** |
|---|---|
| Stringent CR | 5 (11.4%) |
| CR | 14 (31.8%) |
| VGPR | 19 (43.2%) |
| ≥ VGPR | 38 (86.3%) |
| **PR** | 6 (13.6%) |
| **PET/CT Scan Response at 6 month** | |
| Positive | 23 (52.3%) |
| Negative | 21 (47.7%) |

As illustrated in Table 1, the most common presenting complaint among patients with multiple myeloma in our study was bony pain, affecting 61.4% of patients. Generalized weakness was reported in 54.5%, fever in 13.6%, and 11.4% of patients were asymptomatic at presentation.

As summarized in Table 2, the baseline laboratory parameters of the study cohort showed a mean hemoglobin level of 8.56 ± 1.97 g/dL. Anemia, defined as Hb < 10 g/dL, was detected in 35 patients (79.5%). The mean platelet count was 131 × $10^3$/μL, with 10 patients (22.7%) having a platelet count < 100 × $10^3$/μL at baseline, none of whom had severe thrombocytopenia (platelet count < 20,000/μL). Only 1 patient presented with pancytopenia at baseline. The median LDH level was 189.5 U/L, with 13 patients (29.5%) having LDH levels above the upper limit of normal.

As summarized in Table 3, the median creatinine level was 1.30 mg/dL. Renal dysfunction, defined as serum creatinine > 2 mg/dL or creatinine clearance < 40 mL/min, was detected in 14 patients (31.8%). Hypercalcemia, defined as a serum calcium level > 1 mg/dL above the upper limit of normal or a calcium level > 11 mg/dL, was observed in 6 patients (13.6%). At least one bony lytic lesion was detected in 36 patients (81.8%).

The median bone marrow plasma cell infiltration before the commencement of treatment was 60% (IQR: 25.75–70.0%) as shown in Table 4. FISH panel data for myeloma were available for 38 patients in the studied cohort, with high-risk abnormalities detected in 10 patients (26.3%).

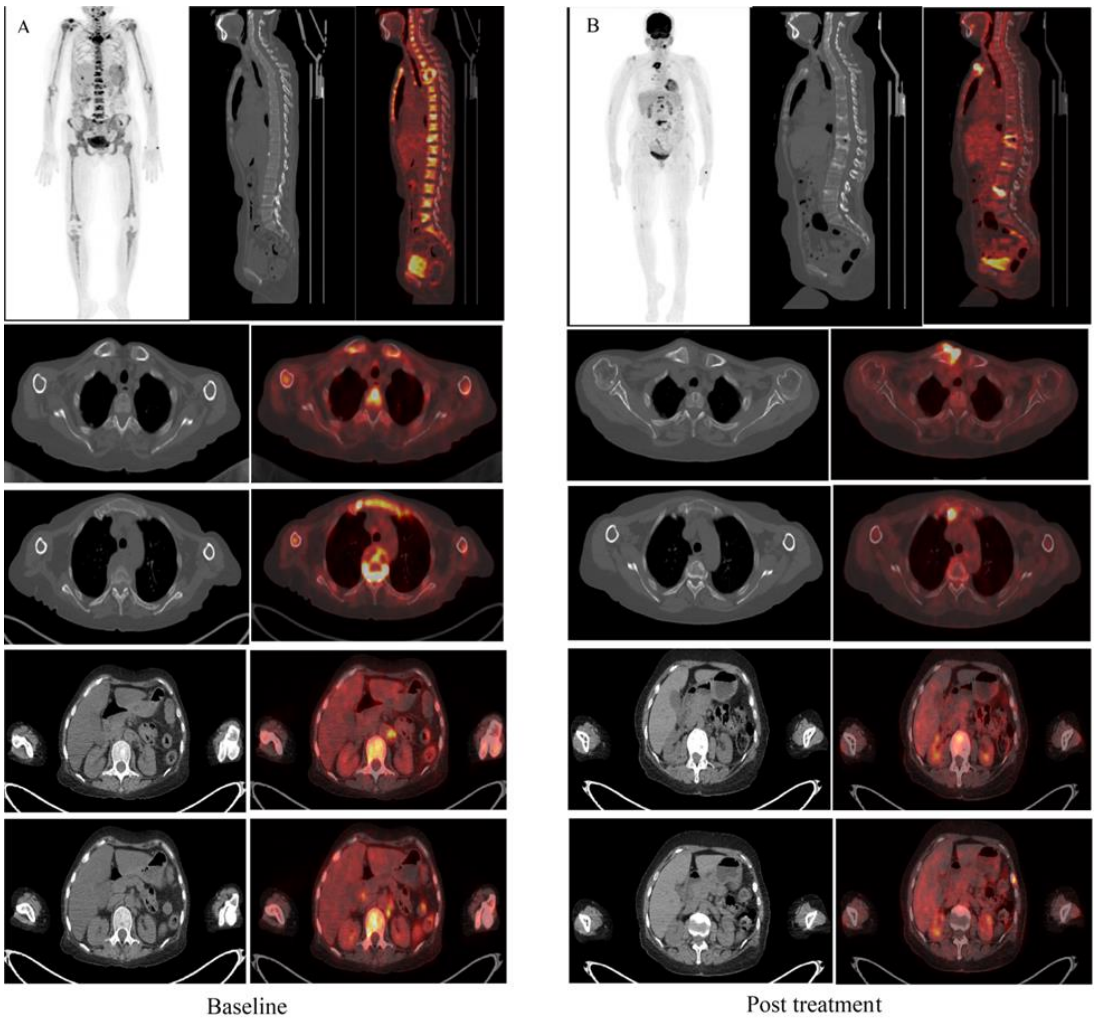
As depicted in Table 5, the median serum protein electrophoresis M-band level was 3.60 g/dL. The most common immunoglobulin detected on immunofixation was IgG (67.4%), followed by IgA (16.3%), and no patients had IgM myeloma. Six patients had light chain myeloma, with no full immunoglobulin detected on immunofixation. The distribution of light chain restriction was nearly equal, with kappa light chain detected in 21 patients (48.8%) and lambda light chain in 22 patients (51.2%). Data were unavailable for 1 patient. The median Beta-2 microglobulin level was 8.13 mg/L. R-ISS Stage II multiple myeloma was diagnosed in 24 patients (54.6%), while 14 patients had R-ISS Stage III myeloma. Data on baseline R-ISS staging were unavailable for 4 patients.

Table 6 shows the baseline PET/CT scan findings of 44 patients. Eight patients (18.2%) had a normal PET/CT scan at baseline, with no focal or bony lytic lesions. More than three focal lesions were observed in 27 patients (61.4%), while 9 patients had three or fewer focal lesions. Additionally, extramedullary disease was detected at baseline in 15 patients (34.1%).

VRd was the most common induction regimen, administered to 68.2% of patients, followed by VCd (13.6%). Only 1 patient received VTd as induction. Six patients initially received VCd induction due to renal dysfunction at baseline; this regimen was later switched to VRd at various time points as serum creatinine improved during follow-up. One patient who was started on VRd therapy sustained bortezomib-induced autonomic dysfunction, and the regimen was changed to D-Rd.

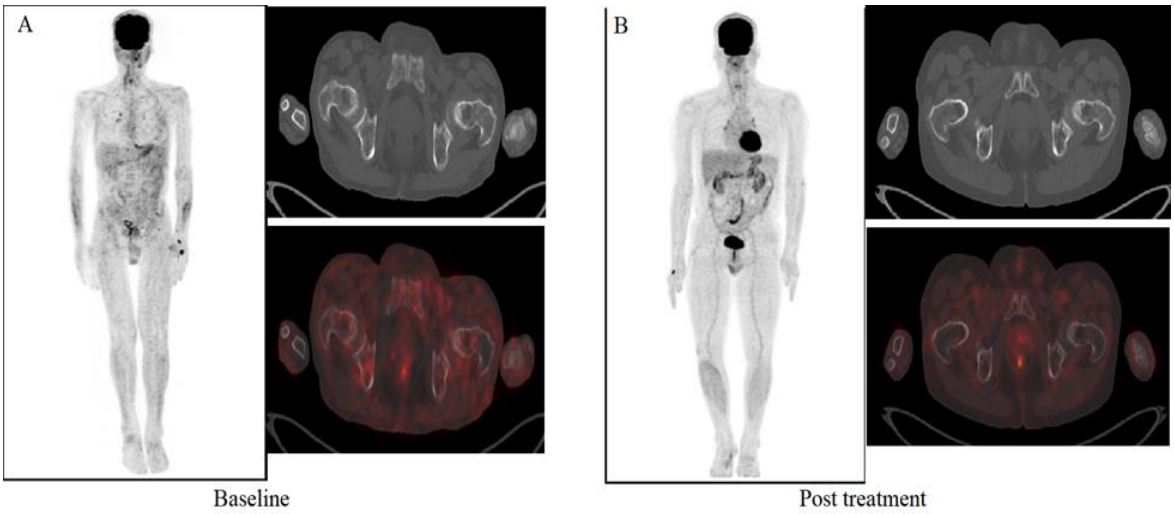
Biochemical and PET/CT scan responses were assessed at 6 months following treatment initiation in all patients. According to the IMWG response criteria, 5 patients (11.4%) achieved stringent CR (sCR), 14 patients (31.8%) achieved complete response (CR), 19 patients (43.2%) achieved very good partial response (VGPR), and 6 patients (13.6%) achieved partial response (PR). Additionally, 23 patients (52.3%) had a positive PET/CT scan at 6 months following induction therapy (Table 7).

Figure 2 and Figure 3 show PET positivity and negativity, respectively, in one of the study participants.




18F-FDG-PET/CT scan performed for one of the study participant at baseline (A) and at 6 month post treatemnt (B) showing PET/CT positivity at 6 month post treatment.

Figure 2. Depiction of PET positivity at 6 months post treatment initiation




18F-FDG PET/CT scan of of the study participant performed at baseline (A) and at 6 month post-treatment (B) showing complete metabolic response with PETCT negativity at 6 month post treatment

Figure 3. Depiction of PET negativity at 6 months post treatment initiation

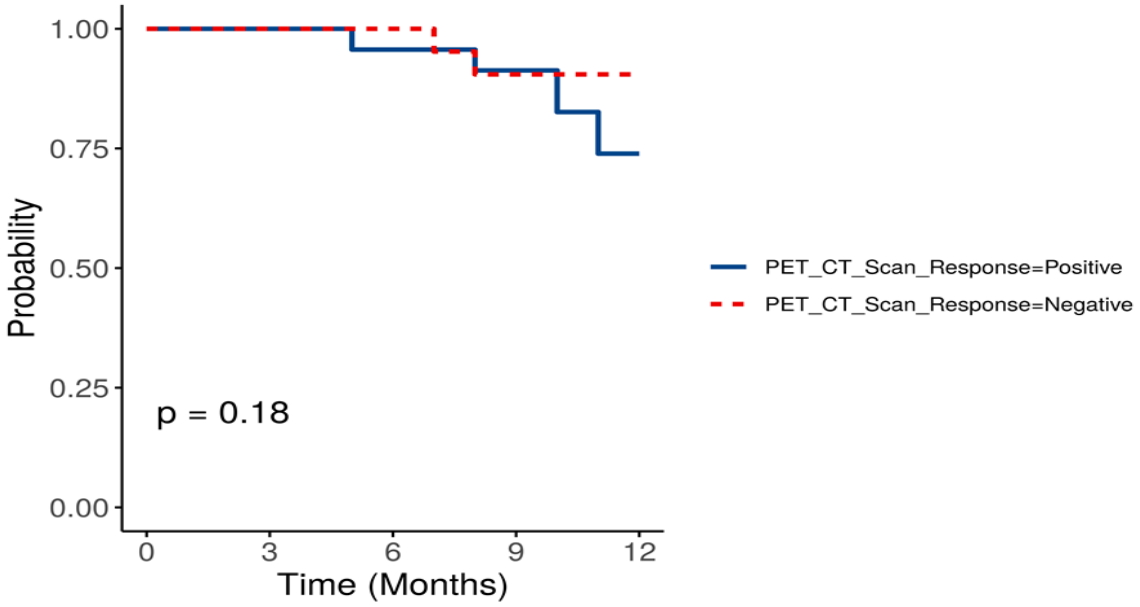
Out of a total of 44 patients, 23 patients (52.3%) had a positive PET/CT scan, while 21 patients (47.7%) had a negative PET/CT scan at completion of 6 months of induction therapy.

Patients who were PET/CT-positive at 6 months were younger (median age: 51 years vs. 58 years), had higher mean LDH levels (212.10 ± 127.01 vs. 206.29 ± 51.72 U/L), and included a greater proportion of R-ISS stage III patients (40% vs. 30%) compared to those who were PET/CT-negative.

A significantly higher proportion of patients with a positive PET/CT response (82.6%, 19 patients) had more than three focal lesions at baseline compared to those with a negative PET/CT response (38.1%, 8 patients; p = 0.002). In the PET/CT-positive group, a nearly equal proportion had EMD (47.8%) compared to those without EMD (52.2%), whereas in the PET/CT-negative group, a larger proportion had no EMD (81.0%) compared to those with EMD (19.0%) (p = 0.044).

A total of 38 patients achieved a very good partial response (VGPR) or better. Among these 38 patients, 50% demonstrated a positive PET/CT response at the six-month mark.

Among 44 patients, 8 events occurred during the 12-month follow-up period: 7 patients experienced relapse, and 1 patient had a poor response to therapy, necessitating a change in therapy. Among participants with events at the 12-month follow-up, 75.0% had a positive PET/CT scan response, while 25.0% had a negative PET/CT scan response. In contrast, among participants without events at the 12-month follow-up, 47.2% had a positive PET/CT scan response, and 52.8% had a negative PET/CT scan response. However, there was no significant difference in the distribution of PET/CT scan responses across the groups ($\chi^2 = 2.024$, p = 0.245). The Kaplan–Meier survival analysis (Figure 4) was performed to assess EFS between patients with PET/CT positivity and negativity. The survival rate at 1 year was 73.9% for the PET/CT-positive group, while the survival rate for the PET/CT-negative group was 90.4%. The median event-free survival was not reached for either group. A non-significant difference in survival between the two groups was observed (p = 0.182).




| PET/CT Scan Response | Total N | Events | No Events | Mean Survival | 95% CI for Mean | Median Survival | 95% CI For Median | P Value |
|---|---|---|---|---|---|---|---|---|
| Positive | 23 | 6 | 17 | 11.26 | 10.58 - 11.94 | | NA – NA | Log Rank Test: p = 0.182 |
| Negative | 21 | 2 | 19 | 11.57 | 10.99 - 12.15 | | NA - NA | |

Figure 4. Kaplan-Meier curve showing event-free survival in patients with PET/CT positive and negative responses at 6 months following initiation of therapy.

## DISCUSSION

A total of 44 patients completed the study, with a median age of 55.5 years, which is consistent with the median age reported in Indian multiple myeloma (MM) patients in previous studies[16]. Some hospital-based studies have noted a slightly lower age of MM onset in Indian patients, with a median age of around 55 years[17-20]. This is approximately a decade earlier than the median ages observed in the USA, where MM onset occurs at a median age of around 67 years among Black patients, 66 years in Hispanic patients, and 71 years in White patients[18,20]. In our study, there was a significant male preponderance, with approximately 82% of the patients being male. The most common presenting symptom among patients in our study was bony pain, which was reported by 61.4% of patients. Generalized weakness was the second most common symptom, affecting 54.5% of patients, followed by fever in 13.6%. Notably, 11.4% of patients were asymptomatic at the time of presentation. These findings align with previous studies, such as the one by Kaur P et al.,[16] where bony pain was the most common presenting complaint (50% of patients), and generalized weakness and fatigue were seen in 46.4% of patients. At least one bony lytic lesion was detected in 36 patients (81.8%).

PET/CT scans were performed at baseline and after 6 months of therapy. Eight patients (18.2%) had a normal PET/CT scan with no focal or bony lytic lesions. More than three focal lesions were observed in 27 patients (61.4%), while nine patients (20.4%) had three or fewer focal lesions. Additionally, EMD was detected at baseline in 15 patients (34.1%), and at least one bony lytic lesion was found in 36 patients (81.8%). In comparison, Zamagni et al.[21] reported that 24% of patients had a negative PET/CT scan at diagnosis, while 32% showed 1 to 3 focal lesions and 44% had either diffuse bone marrow involvement or more than three focal lesions. EMD was observed in 6% of cases. Zamagni et al. also highlighted the prognostic significance of focal lesions at baseline,

with progression-free survival (PFS) values at 4 years projected at 50% for patients with three focal lesions or diffuse bone marrow uptake, compared to 69% (p = 0.006) and 68% (p = 0.02) for those with less severe PET/CT involvement. In our cohort, a higher proportion of patients had more than three focal lesions and a higher incidence of EMD compared to previous studies. Sachpekidis et al.[22] found that 23% of patients had no visible focal lesions, while 77% had at least one focal hypermetabolic lesion. Paramedullary disease (PMD) and EMD were present in 49% and 9% of patients, respectively, with EMD involving nodal sites in 2 patients and extranodal (intramuscular) sites in 2 others.

Biochemical and PET/CT scan responses were assessed at six months for all patients. According to the IMWG response criteria, five patients (11.4%) achieved stringent complete response (sCR), 14 patients (31.8%) achieved CR, 19 patients (43.2%) achieved VGPR, and six patients (13.6%) achieved PR. Overall, 86.3% of patients achieved VGPR or better. This response rate is similar to those reported in previous studies. In comparison, the VRd group patients in the ENDURANCE and PERSEUS studies demonstrated similar or higher response rates. In the ENDURANCE study[23], 85% of patients in the VRd group achieved VGPR or better, while in the PERSEUS study[24], 94% of patients in the VRd group achieved VGPR or better.

Out of a total of 44 patients, 23 patients (52.3%) had a positive PET/CT scan, while 21 patients (47.7%) had a negative PET/CT scan at 6 months following induction therapy. In a study by Charalampos Charalampous et al., at the 6-month mark, 50 patients (25.6%) had a negative PET/CT scan, while 145 patients (74.6%) had detectable disease, including 30 patients (15.3%) showing signs of progression[25]. In another study by Nørgaard et al., out of 159 patients post-autologous stem cell transplant, 53 (33%) were PET-positive[26].

In a study by Faith E. Davies and colleagues, the presence of more than 3 focal lesions detected on PET-CT scan at baseline was associated with worse progression-free survival (PFS; p < 0.0001) and overall survival (OS; p < 0.0001). However, there was no significant difference in either PFS (p = 0.3022) or OS (p = 0.7842) between patient groups with 0 focal lesions and those with 1–3 focal lesions[27]. In our study, a significantly higher proportion of patients with a positive PET/CT response (82.6%, 19 patients) had more than three focal lesions at baseline compared to those with a negative PET/CT response (38.1%, 8 patients; p = 0.002).

Extramedullary disease in myeloma is defined by the presence of plasma cells outside the bone marrow, such as in soft tissue and organs. Extramedullary multiple myeloma (EMM) is an aggressive subtype of MM. It is characterized by the ability of a subclone to thrive and grow independently of the bone marrow microenvironment. This independence results in a high-risk state associated with increased proliferation, evasion of apoptosis, and treatment resistance. EMM can present as either primary or secondary disease. Primary EMD refers to cases where it is present at the initial diagnosis. In contrast, secondary EMD develops later and is diagnosed at the time of relapse. Extramedullary myeloma can be bone-associated, bone-independent, or organ-infiltrative myeloma. In our study, we collected data on EMD and combined all three types into a single analysis. The incidence of EMD observed in 15 patients (34.1%) was significantly higher than previously reported rates in various studies on MM. This variability may be attributed to the lack of a unified definition of EMD across different studies. For instance, a study by Zamagni et al.[21] reported EMD at diagnosis in only 6% of patients. In contrast, Sachpekidis et al.[22] found that paramedullary disease (PMD) and EMD were present in 23 out of 47 patients (49%) and 4 out of 47 patients (9%), respectively. Another study by Charalampos Charalampous et al.[25] reported that 25.1% of patients had EMD, defined as soft tissue masses that did not arise from a known bone lesion or pure EMD (i.e., liver, lymph node, or renal invasion), on their initial evaluation. These differences highlight the heterogeneity in the classification and reporting of EMD. The higher incidence of EMD observed in recent years is likely attributed to the increasing use of more sensitive imaging techniques. Additionally, the prolongation of patient survival due to new treatment strategies and better supportive care may contribute to the observed increase in EMD involvement during follow-up. In our study, among

the patients who had a positive PET/CT scan response, 47.8% had extramedullary disease (EMD), while 52.2% did not have EMD. On the other hand, among the patients with a negative PET/CT scan response, a significantly higher proportion (81.0%) did not have EMD, and only 19.0% had EMD. This difference between the two groups was statistically significant ($p = 0.044$).

The biological diversity and clinical complexity of MM necessitate a multidimensional approach to disease assessment both at diagnosis and during subsequent follow-up. Whole-body PET/CT scans offer a comprehensive evaluation that can address multiple gaps in disease monitoring for MM patients. This underscores why discrepancies sometimes arise between hematologic and imaging responses. Bone marrow biopsies, often blind, can miss areas with the highest plasma cell populations, resulting in falsely reassuring findings and potentially inferior outcomes. In contrast, PET/CT identifies regions with the highest metabolic activity in the bone marrow and can detect extramedullary disease (EMD).

In our study, 50% of patients with VGPR or better responses had PET/CT-positive results. This is in contrast to a study by Nørgaard et al., which reported a 33% PET-positive rate in patients with VGPR or better responses[26]. At the 6-month follow-up, 30.4% of patients with PET/CT positivity achieved responses greater than VGPR (sCR and CR), while 57.1% of patients with PET/CT negativity achieved responses greater than VGPR (sCR and CR). This difference was not statistically significant ($p = 0.248$). A total of 38 patients achieved VGPR or better; of these, 50% had a PET/CT-positive response at 6 months. Our findings suggest that PET/CT may detect metabolically active disease even in patients who show significant clinical response by IMWG criteria, which could affect future outcomes, including progression-free survival, relapse rates, and overall survival.

In our study, among 44 patients, 8 events occurred during the 12-month follow-up period: 7 patients experienced relapse, and 1 patient underwent a therapy change due to a poor response to the initial treatment. Among patients who had events at the 12-month follow-up, 75.0% showed a positive PET/CT scan response, while 25.0% had a negative response. In contrast, among those without events, 47.2% had a positive response, and 52.8% had a negative response (Figure 3). However, there was no significant difference in the PET/CT scan responses between the two groups ($\chi^2 = 2.024$, $p = 0.245$). 18F-FDG PET/CT is a superior imaging modality to evaluate the response to treatment because it can distinguish between active and inactive lesions[28].

The Kaplan–Meier survival analysis (Figure 4) was performed to assess EFS between patients with PET/CT positivity and negativity. The survival rate at 1 year was 73.9% for the PET/CT-positive group, while 90.4% for the PET/CT-negative group. The median EFS was not reached for either group. A non-significant difference in survival between the two groups was observed ($p = 0.182$), probably because of the short duration of follow-up. This is consistent with previously reported survival analyses.

In a 2015 study conducted by Elena Zamagni et al.[29], the median PFS for PET/CT-positive patients was significantly shorter than that of PET/CT-negative patients (44 months vs. 84 months; $p = 0.0009$). OS was also notably worse for PET/CT-positive patients, with a 5-year survival rate of 70% compared to 90% for PET/CT-negative patients ($p = 0.0032$).

In another study by Charalampos Charalampous et al.[25], at the 6-month mark, 50 patients (25.6%) had a negative PET/CT scan, while 145 patients (74.6%) had detectable disease, including 30 patients (15.3%) showing signs of progression. When comparing PET/CT-negative and all PET/CT-positive patients (including those with progression), a significant association was seen for median time to next treatment (55.2 vs. 17.8 months, $p < 0.0001$) and for median overall survival (unreached vs. 60.8 months, $p < 0.0001$), respectively.

Our study highlights that patients with MM showed discordance between imaging and biochemical responses. The IMWG response did not correlate with PET/CT scan response, and patients who were PET/CT-positive at 6 months of therapy faced a higher risk of relapse and poorer EFS. However, due to the smaller sample size in our study, the results were not statistically significant. Therefore, further prospective trials with larger sample sizes are needed to validate these findings.

## CONCLUSION

This study evaluated the clinical, biochemical, and imaging characteristics of MM patients undergoing treatment and the correlation between treatment responses measured by the IMWG criteria and PET/CT. With 44 patients completing the study, the findings provide valuable insights into the demographic, clinical, and therapeutic outcomes of MM patients in an Indian cohort.

Our study highlighted the presence of EMD in 34.1% of patients at diagnosis, a significantly higher rate compared to other reported studies. The increased use of advanced imaging modalities, like PET/CT, has led to a more comprehensive understanding of clinical and biological heterogeneity in MM, including the detection of EMD, which is associated with worse prognosis. Baseline PET/CT revealed that 61.4% of patients had more than three FLs, while 34.1% exhibited EMD, indicating a higher disease burden in this cohort compared to previous reports. The prognostic significance of baseline FLs and EMD in MM is well-established. Our study further demonstrates that the presence of EMD and more than three FLs are associated with increased PET/CT positivity at 6 months. These findings highlight the importance of using PET/CT scans in routine clinical practice to monitor disease burden and adjust treatment strategies accordingly.

One of the most noteworthy findings of this study is the inconsistency between PET/CT and IMWG biochemical responses. Although a significant proportion of patients had a positive PET/CT response, many were classified as achieving CR or VGPR based on biochemical markers. This discordance suggests that PET/CT can detect metabolically active disease that might not be reflected in traditional biochemical markers. This study suggests that PET/CT may not always correlate with the biochemical responses measured by the IMWG criteria, as 50% of patients with VGPR or better responses had PET/CT-positive results.

Heterogeneity in the biological background and clinical presentation of MM dictates a multidimensional approach to disease assessment at diagnosis and during subsequent follow-up. Because of the patchy pattern of malignant plasma cell infiltration into the bone marrow, blind BM biopsies often miss the niche with the highest plasma cell population, leading to falsely reassuring results and inferior outcomes. The discrepancy between PET/CT and IMWG responses is particularly important, as PET/CT can detect residual disease or EMD that may not be apparent on traditional bone marrow aspirates or serum markers. This discrepancy underscores the complex nature of MM, where metabolic activity detected by PET/CT may persist even in the presence of a good biochemical response. This highlights the importance of using both clinical and imaging assessments in evaluating treatment outcomes.

Our study offers valuable insights into the use of PET/CT for monitoring treatment responses in MM patients, but the results are not definitive due to the small sample size and short follow-up period. The findings suggest that while PET/CT positivity at 6 months may indicate a higher risk of relapse, the relationship between PET/CT responses and long-term survival remains unclear.

## LIMITATIONS

**This was a prospective study with real-time** assessment of patients with MM. Our study faced several limitations as well. The study was a single-center study conducted at a tertiary care institute, which gets patients on a referral basis. Hence, the patient population assessed tends to have more complications, which likely influenced the outcome and correlation statistics in our study. The relatively small sample size and limited duration of follow-up hindered our ability to effectively validate EFS data. We could not incorporate other tumor load parameters, such as metabolic tumor volume (MTV), which could have provided a more comprehensive measure of disease burden. Another significant limitation was the variability in treatment regimens received by patients by the 6-month mark. This diversity in therapeutic approaches could have introduced further heterogeneity in the observed outcomes, complicating the interpretation and comparison of results.

### Ethics Statement

This study was conducted after approval from the Institutional Ethics Committee, and informed

consent was obtained from all individual participants included in the study.

**CONFLICTS OF INTEREST**

The authors declare no conflicts of interest.

**Data availability statement**

Due to patient privacy and institutional policies, the data supporting the findings of this study are not publicly available. Requests for access to the data may be directed to the corresponding author.

**REFERENCES**

1. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International myeloma working group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014; 15(12):e538-48.
2. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024; 74(1):12-49.
3. Kyle RA, Rajkumar SV. Multiple myeloma. N Engl J Med. 2004, 351(18):1860-73.
4. Resnick D, Kransdorf MJ. Plasma cell dyscrasias. In: Resnick D, Kransdorf MJ, editors. Bone and Joint Imaging. 3rd ed. Philadelphia: Elsevier Saunders; 2004. pp: 1101-20.
5. Collins CD. Multiple myeloma. Cancer Imaging. 2004, 4 Spec No A(Spec No A):S47-53.
6. Singh J, Fairbairn KJ, Williams C, et al. Expert radiological review of skeletal surveys identifies additional abnormalities in 23% of cases: further evidence for the value of myeloma multi-disciplinary teams in the accurate staging and treatment of myeloma patients. Br J Haematol. 2007, 137(2):172-3.
7. Wahlin A, Holm J, Osterman G, et al. Evaluation of serial bone X-ray examination in multiple myeloma. Acta Med Scand. 1982;12(6): 385-7.
8. Ludwig H, Frühwald F, Tscholakoff D, et al. Magnetic resonance imaging of the spine in multiple myeloma. Lancet. 1987; 2(8555):364-6.
9. Ghanem N, Lohrmann C, Engelhardt M, et al. Whole-body MRI in the detection of bone marrow infiltration in patients with plasma cell neoplasms in comparison to the radiological skeletal survey. Eur Radiol. 2006, 16(5):1005-14.
10. Baur-Melnyk A, Buhmann S, Becker C, et al. Whole-body MRI versus whole-body MDCT for staging of multiple myeloma. AJR Am J Roentgenol. 2008; 190(4):1097-104.
11. Baur-Melnyk A, Buhmann S, Dürr HR, et al. Role of MRI for the diagnosis and prognosis of multiple myeloma. Eur J Radiol. 2005; 55(1):56-63.
12. Joffe J, Williams MP, Cherryman GR, et al. Magnetic resonance imaging in myeloma. Lancet. 1988; 1(8595):1162-3.
13. Nosàs-Garcia S, Moehler T, Wasser K, et al. Dynamic contrast-enhanced MRI for assessing the disease activity of multiple myeloma: a comparative study with histology and clinical markers. J Magn Reson Imaging. 2005, 22(1):154-62.
14. Therneau TM, Kyle RA, Melton LJ III, et al. Incidence of monoclonal gammopathy of undetermined significance and estimation of duration before first clinical recognition. Mayo Clin Proc. 2012, 87(11):1071-1079.
15. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol. 2016; 17(8):e328-e346.
16. Sundaram S, Driscoll J, Fernandez-Ulloa M, et al. FDG PET imaging in multiple myeloma: implications for response assessments in clinical trials. Am J Nucl Med Mol Imaging. 2018; 8(6): 421-7.
17. Kaur P, Shah BS, Baja P. Multiple myeloma: a clinical and pathological profile. Gulf J Oncolog. 2014; 1(16):14-20.
18. Gupta P, Kochupillai V, Singh S, Berry M, Kumar L, Sundaram KR. A twelve year study of multiple myeloma at the All India Institute of Medical Sciences, New Delhi, India. Indian J Med Paediatr Oncol. 1995;16(2):108.
19. Kumar L, Vikram P, Kochupillai V. Recent advances in the mangement of multiple myeloma. Natl Med J India. 2006, 19(2):80-9.
20. Costa LJ, Brill IK, Omel J, et al. Recent trends in multiple myeloma incidence and survival by age, race, and ethnicity in the United States. Blood Adv. 2017;1(4): 282-287.
21. Zamagni E, Patriarca F, Nanni C, et al. Prognostic relevance of 18-F FDG PET/CT in newly diagnosed multiple myeloma patients treated with up-front autologous transplantation. Blood. 2011, 118(23):5989-95.
22. Sachpekidis C, Merz M, Raab MS, et al. The prognostic significance of [18F]FDG PET/CT in multiple myeloma according to novel interpretation criteria (IMPeTUs). EJNMMI Res. 2021; 11(1):100.
23. Kumar SK, Jacobus SJ, Cohen AD, et al. Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE): a multicentre, open-label, phase 3, randomised, controlled trial. Lancet Oncol. 2020; 21(10):1317-1330.
24. Sonneveld P, Dimopoulos MA, Boccadoro M, et al. Daratumumab, bortezomib, lenalidomide, and

dexamethasone for multiple myeloma. N Engl J Med. 2024; 390(4):301-13.
25. Charalampous C, Goel U, Broski SM, et al. Utility of PET/CT in assessing early treatment response in patients with newly diagnosed multiple myeloma. Blood Adv. 2022; 6(9):2763-72.
26. Nørgaard JN, Abildgaard N, Lysén A, et al. Intensifying treatment in PET-positive multiple myeloma patients after upfront autologous stem cell transplantation. Leukemia. 2023; 37(10):2107-14.
27. Davies FE, Rosenthal A, Rasche L, et al. Treatment to suppression of focal lesions on positron emission tomography-computed tomography is a therapeutic goal in newly diagnosed multiple myeloma. Haematologica. 2018; 103(6):1047-53.
28. Zamagni E, Tacchetti P, Cavo M. Imaging in multiple myeloma: How? When?. Blood. 2019; 133(7): 644-651.
29. Zamagni E, Nanni C, Mancuso K, et al. PET/CT improves the definition of complete response and allows to detect otherwise unidentifiable skeletal progression in multiple myeloma. Clin Cancer Res. 2015; 21(19):4384-90.