

Prognostic Value of Baseline ^{18}F -FDG PET/CT Metabolic Tumor Burden in Multiple Myeloma

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Abstract

Purpose

To evaluate prognostic value of baseline ^{18}F -FDG PET/CT Metabolic tumor burden in multiple myeloma.

Methods

This retrospective, single-center study included 148 patients with newly diagnosed MM who underwent baseline ^{18}F -FDG PET/CT before systemic therapy. Total metabolic tumor volume (tMTV), total lesion glycolysis (TLG), SUVmax, and morphologic findings were evaluated. Overall survival was analyzed using Kaplan–Meier methods and Cox regression; receiver operating characteristic analyses (ROC) assessed discrimination for mortality.

Results

Median tMTV, TLG, and SUVmax were 92.55, 272, and 5.2, respectively. Paramedullary and extramedullary disease were present in 37.8% and 11.5% of patients. During a median follow-up of 319 days, 41 patients (27.7%) died. TLG had the highest discrimination for mortality (area under the curve, 0.674), whereas tMTV was the only independent imaging predictor of overall survival among imaging variables (hazard ratio, 1.07 per 100-unit increase; $P = .01$). The exploratory optimal tMTV threshold was > 288 .

Conclusion

Baseline ^{18}F -FDG PET/CT-derived volumetric measures provide prognostic information in newly diagnosed MM. tMTV may complement conventional risk assessment, but the proposed threshold requires external validation.

Introduction

Multiple myeloma (MM) is a malignant plasma cell disorder characterized by clonal proliferation of plasma cells within the bone marrow and marked biological and clinical heterogeneity. The disease course is frequently complicated by osteolytic bone lesions, anemia, renal impairment, hypercalcemia, and recurrent infections.[1] Despite major therapeutic advances including proteasome inhibitors, immunomodulatory agents, monoclonal antibodies, and cellular therapies, substantial variability in prognosis and treatment response remains among patients.[2] Therefore, reliable prognostic biomarkers that better reflect tumor burden and disease biology are still needed.

Risk stratification in MM has evolved from the Durie–Salmon staging system to the International Staging System (ISS) and subsequently the Revised ISS (R-ISS), which incorporates serum $\beta 2$ -microglobulin, albumin, lactate dehydrogenase (LDH), and high-risk cytogenetic abnormalities.[3] However, these staging systems do not adequately assess disease dissemination, focal lesion burden, or metabolic activity. Since diffuse marrow infiltration and extramedullary involvement are associated with poor prognosis, functional imaging has become increasingly important in MM evaluation.[4]

¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG PET/CT) provides integrated metabolic and anatomical information and demonstrates superior sensitivity compared with conventional imaging modalities in detecting active bone marrow involvement, focal lesions, and extramedullary disease. Current International Myeloma Working Group (IMWG) and European Association of Nuclear Medicine (EANM) guidelines recommend PET/CT for baseline staging, treatment response assessment, and evaluation of residual disease in MM.[5]

Beyond visual interpretation, quantitative PET-derived metabolic parameters have emerged as promising prognostic biomarkers. While SUVmax reflects the metabolic activity of the single most active lesion, it does not represent total disease burden. In contrast, volumetric parameters such as total metabolic tumor volume (tMTV) and total lesion glycolysis (TLG) provide more comprehensive assessment by integrating lesion volume and metabolic activity.[6] Several studies have demonstrated associations between elevated tMTV or TLG and inferior survival outcomes in MM patients.[6–9] More recently, studies evaluating artificial intelligence-based PET segmentation and whole-body metabolic assessment have further highlighted the growing role of volumetric imaging biomarkers in MM prognostication.[10]

Our study aimed to evaluate the prognostic significance of baseline PET/CT-derived metabolic and morphologic parameters in patients with newly diagnosed multiple myeloma and trying to determine clinically relevant prognostic cut-off values for imaging biomarkers associated with mortality.

Materials and Methods

This retrospective single-center study included patients with newly diagnosed multiple myeloma who underwent baseline ¹⁸F-FDG PET/CT imaging before initiation of systemic therapy between January 2020 and December 2024. Clinical characteristics, laboratory findings, treatment information, and survival outcomes were obtained from electronic medical records. Disease staging was performed according to the Revised International Staging System (R-ISS).

All whole-body ¹⁸F-FDG PET/CT examinations were performed according to standardized institutional imaging protocols. Patients fasted for at least 6 hours before imaging, and blood glucose levels were confirmed to be within acceptable limits before tracer injection. PET/CT images were acquired from the skull base to the mid-thigh approximately 60 minutes after intravenous administration of ¹⁸F-FDG.

Lesions were segmented using a semi-automated approach. Metabolic tumor volume (MTV) was calculated for each lesion individually. Total metabolic tumor volume (tMTV) was defined as the sum of all MTV values. Total lesion glycolysis (TLG) was calculated using the formula:

$$\text{TLG} = \sum (\text{MTV} \times \text{SUVmean})$$

Morphological parameters including osteolytic lesions, paramedullary disease (PMD), and extramedullary disease (EMD) were evaluated on the CT component of PET/CT.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation or median (interquartile range), as appropriate. Correlation analyses were performed to assess associations between PET-derived parameters and

laboratory findings. Overall survival (OS) was defined as the time from diagnosis to death from any cause or last follow-up.

Survival analyses were performed using Kaplan–Meier estimates and Cox proportional hazards regression models. Variables significant in univariate analysis were included in multivariate models. Receiver operating characteristic (ROC) curve analyses were performed to evaluate the prognostic performance of PET/CT-derived parameters and determine optimal cut-off values for mortality prediction. A p-value < 0.05 was considered statistically significant. Kaplan–Meier curves were compared with the log-rank test. The ROC-derived tMTV threshold (> 288) was used for the exploratory survival-group comparison. Patients without a valid diagnosis-to-last-follow-up interval were excluded from this complete-case Kaplan–Meier analysis.

Results

A total of 148 patients with newly diagnosed multiple myeloma were included. The mean age at diagnosis was 66.1 ± 10.8 years, and 49.3% of patients were female. According to R-ISS classification, 53.6% of patients had stage III disease. Baseline demographic, laboratory, and treatment characteristics are summarized in Table 1.

Table 1 Evaluation of 18F-FDG PET/CT Parameters According to the Characteristics of Patients Diagnosed with Multiple Myeloma (n=148)

Characteristics	Metabolic tumor volume (MTV)	Total lesion glycolysis (TLG)	Maximum standardized uptake value (SUVmax)	PET focal lesion Deauville score	Number of CT lytic lesions	Bone marrow Deauville score
Sex, Median						
Female	90(12.7-320)	251.39(34.25-107.89)	5.3(3.7-11.1)	4(1-5)	3.5(2-4)	3(2-3)
Male	89.5(12.4-412.3)	287.86(30.50-1850.93)	4.9(3.8-9)	4(1-4)	3(1.5-4)	3(2-4)
p-value*	0.93	0.64	0.84	0.20	0.64	0.20
R-ISS						
I	59.65(16.83-268.7)	168.96(50.52-1066.52)	5.4(3.83-9.78)	4(3-5)	4(2.25-4)	2.5(2-4)
II	60.5(13.6-237)	181.64(20.46-1590.8)	4.5(3.5-8.2)	4(1-5)	3(2-4)	3(2-4)
III	258(21.8-782)	807.36(48.66-2572)	6.4(4.2-9.4)	4(3-5)	4(2-4)	3(2-4)
p-value†	0.15	0.36	0.07	0.21	0.31	0.83
Localization of Focal Lesions						
Skull						
Absent	68.3(11.1-320.5)	191.34(25.84-1253.93)	4.80(3.6-9.4)	4(1-5)	2(1-4)	3(2-4)
Present	136.4(28.75-755.35)	555.85(82.48-2589.62)	6.05(4.48-10.02)	5(4-5)	4(4-4)	3(2-4)
p-value*	0.12	0.09	0.06	0.01	<0.001	0.47
Vertebrae						
Absent	11.5(5.2-89.5)	40.2(12.38-238.36)	3.7(3.1-4.9)	1(1-3)	1(1-2)	2(2-3)
Present	212.8(55.85-557.75)	711.86(153.6-2017.69)	6.55(4.5-10.7)	5(4-5)	4(3-4)	3(2-3)
p-value*	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Other sites						
Absent	14.55(5.2-84.2)	41.82(12.74-224.18)	3.65(3.1-5.37)	1(1-1.75)	1(1-2)	
Present	207.3(33.7-570.5)	683.82(85.21-2048.78)	6.3(4.4-10.42)	5(4-5)	4(3-4)	

p-value*	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Fracture						
Absent	60.5(10.6-276.15)	191.34(24.52-1192)	4.8(3.4-8.15)	4(1-5)	3(1-4)	3(2-4)
Present	152.75(29.05-513)	637.85(61.98-2431.85)	6.2(4.62-11.12)	5(4-5)	4(3-4)	3(2-4)
p-value*	0.06	0.04	0.004	<0.001	<0.001	0.009
PMD						
Absent	24.2(6.88-241.3)	59.84(17.91-712.03)	4.1(3.22-5.9)	3(1-4)	2(1-4)	2.5(2-4)
Present	237(103.7-570.1)	825.9(332.98-2353.13)	7.4(4.95-13.05)	5(4-5)	4(3-4)	3(2-4)
p-value*	<0.001	<0.001	<0.001	<0.001	<0.001	0.001
EMD						
Absent	82.3(10.15-357.6)	246.5(28.5-1417.16)	4.9(3.6-8.1)	4(1-5)	3(1.5-4)	3(2-4)
Present	160.95(43.88-681.9)	745.58(79.04-2354.25)	10.1(5.7-13.02)	5(4-5)	3(2-4)	2(2-4)
p-value*	0.18	0.21	0.001	0.001	0.23	0.18
Transplantation						
No	121.8(18-644.2)	645.68(56.54-2595.31)	5.5(3.9-10.1)	4(1-5)	3(2-4)	3(2-4)
Yes	70.6(15.5-285.5)	191.34(23.4-914.53)	5(3.7-8.1)	4(2-5)	4(2-4)	3(2-4)
p-value*	0.21	0.04	0.61	0.49	0.06	0.35
Paraprotein Type						
IgG	60.8(12.88-334.15)	221.7(28.61-1151.23)	5.25(3.98-8.67)	4(1-5)	3.5(2-4)	3(2-4)
IgA	258(17.5-856)	730.07(48.51-2702.94)	5.3(3.7-11)	4(2-5)	4(1-4)	3(2-4)
LC	125.35(21.4-581.7)	652.67(72.86-4485.98)	5.05(3.57-11.51)	4.5(3-5)	4(2-4)	3(2.75-4)
Other	94.9(4.6-794.95)	434.63(12.46-272.75)	6.3(2.9-13.23)	3(1-5)	1.5(1-3.5)	2.5(5-3.75)
p-value†	0.29	0.25	0.89	0.84	0.44	0.61
Paraprotein Light-Chain Type						

Kappa	87.35(24.2-293.5)	257.03(47.01-1140.73)	5.2(3.9-8.5)	4(1.75-5)	3(2-4)	3(2-4)
Lambda	173.8(7.3-782.8)	730.07(20.75-2595.31)	5.5(4-11.5)	4(3-5)	4(2-4)	3(2-4)
p-value*	0.67	0.50	0.96	0.27	0.35	0.88

Data are presented as median (25th–75th percentiles). *Mann–Whitney U test; †Kruskal–Wallis H test. $p < 0.05$ was considered statistically significant.

On baseline ^{18}F -FDG PET/CT, measurable tMTV and TLG were identified in 82.4% of patients, while SUVmax was measurable in 84.5%. Median tMTV, TLG, and SUVmax values were 92.55, 272, and 5.2, respectively.

Focal skeletal lesions were present in 60.8% of patients, most commonly involving the vertebral column. PMD was detected in 37.8% of patients, whereas EMD was observed in 11.5%.

Baseline PET/CT parameters according to first-line treatment, treatment response, progression status, and survival status are summarized in Table 2. Patients who died during follow-up had significantly higher tMTV, TLG, SUVmax, PET focal lesion Deauville scores, and CT lytic lesion counts than surviving patients.

Table 2 Baseline ^{18}F -FDG PET/CT parameters according to first-line treatment, treatment response, progression, and survival status

Characteristic	tMTV	TLG	SUVmax	PET focal lesion Deauville score	CT lytic lesions	Bone marrow Deauville score
First Line Treatment						
VCD	71.5(17-608)	317.96(38.24-2657.71)	4.95(3.83-8.8)	4(1-5)	3.5(2-4)	3(2-4)
VRD	207.3(16.6-373.1)	659.66(42.5-1262.4)	5.4(4-9.4)	4(2-5)	4(2-4)	3(2-4)
Other	71.4(19.75-405.5)	445.24(53.26-1394.94)	7.55(3.33-15.07)	4(1.5-5)	3(1.25-4)	2.5(2-3.75)
p-value†	0.94	0.95	0.80	0.16	0.10	0.14
First-Line Treatment Response						
CR	134.95(12.85-318)	555.85(39.26-1125.64)	5.35(3.93-10.95)	4(1-5)	3.5(1.75-4)	3(2-4)
VGPR	149(21.8-595.14)	659.66(43.31-1986.61)	5.3(4-9.4)	4(2-5)	4(2-4)	3(2-4)
PR-SD-PD	56.15(14.35-117.42)	199(42.27-1547.18)	5.4(3.8-10.27)	4.5(2.5-5)	4(3-4)	3(2-4)
p-value†	0.42	0.62	0.81	0.83	0.76	0.25
Progression Status						
No	89.5(11.5-383.7)	287.86(29.53-1500.7)	5.2(3.7-9.4)	4(1-5)	3(1-4)	3(2-4)
Yes	88.95(56.35-171.27)	257.03(188.92-1005.5)	5.45(3.98-13.51)	4.5(3.5-5)	4(3-4)	4(2.75-4)
p-value*	0.90	0.68	0.32	0.92	0.49	0.98
Final Status						
Alive	61.1(11.5-266.8)	171.59(28.29-849.19)	4.9(3.6-7.4)	4(1-5)	3(1-4)	3(2-4)
Deceased	254.95(40.95-717.7)	1276.83(160.1-5039.9)	6.9(4.07-11.75)	5(3.25-5)	4(2-4)	3(2-4)
p-value*	0.01	0.003	0.009	0.01	0.03	0.29

Data are presented as median (interquartile range). *Mann-Whitney U test; †Kruskal-Wallis test. Abbreviations: CR, complete response; CT, computed tomography; PET, positron emission tomography; SUVmax, maximum standardized uptake value; TLG, total lesion glycolysis; tMTV, total metabolic tumor volume; VCD, bortezomib-cyclophosphamide-dexamethasone; VGPR, very good partial response; VRD, bortezomib-lenalidomide-dexamethasone.

β 2-microglobulin levels demonstrated weak but statistically significant positive correlations with both tMTV ($r = 0.22$, $p < 0.05$) and TLG ($r = 0.30$, $p < 0.05$). No significant correlations were identified between PET-derived parameters and hemoglobin, albumin, or LDH levels.

During a median follow-up period of 319 days, 41 patients (27.7%) died. Patients who died during follow-up demonstrated significantly higher tMTV, TLG, SUVmax, and PET focal lesion Deauville scores compared with surviving patients (all $p < 0.05$).

In univariate Cox regression analysis, tMTV, SUVmax, and the number of osteolytic lesions on CT were significantly associated with overall survival (Table 3). In multivariate Cox regression analysis, only tMTV remained independently associated with overall survival (hazard ratio [HR] = 1.07 per 100-unit increase in tMTV, 95% CI 1.02–1.11; $P = .01$), whereas SUVmax and osteolytic lesion number lost statistical significance (Table 3).

Table 3 Univariable and multivariable Cox proportional hazards regression analyses for overall survival

Analysis	Parameter	Hazard ratio	95% confidence interval	P value
Univariable	tMTV	1.08 per 100 units	1.04–1.11	0.0003
	TLG	1.000	0.999-1.000	0.40
	SUVmax	1.07	1.01-1.13	0.02
	PET Focal Lesion Deauville Score	1.19	0.99-1.43	0.07
	Number of osteolytic lesions on CT	1.32	1.01-1.71	0.04
	Bone Marrow Deauville Score	1.12	0.86-1.44	0.40
Multivariable	tMTV	1.07 per 100 units	1.02–1.11	0.01
	SUVmax	1.03	0.97-1.11	0.33
	Number of osteolytic lesions on CT	1.14	0.83-1.58	0.42

Abbreviations: CI, confidence interval; CT, computed tomography; SUVmax, maximum standardized uptake value; TLG, total lesion glycolysis; tMTV, total metabolic tumor volume.

ROC curve analyses were performed to evaluate the prognostic performance of PET/CT-derived metabolic and morphologic parameters for mortality prediction (Table 4).

TLG demonstrated the highest discriminative performance with an AUC of 0.674 (95% CI: 0.583–0.756) and an optimal cut-off value of >914.53 . This threshold yielded a sensitivity of 57.14%, specificity of 78.16%, positive predictive value (PPV) of 51.3%, and negative predictive value (NPV) of 81.9% ($p = 0.002$).

SUVmax showed an AUC of 0.651 (95% CI: 0.56–0.734) with an optimal cut-off value of >6.3 . Sensitivity and specificity were 62.86% and 70%, respectively ($p = 0.007$).

Importantly, tMTV demonstrated statistically significant prognostic performance with an AUC of 0.642 (95% CI: 0.55–0.727) and an optimal cut-off value of >288. At this threshold, sensitivity was 45.71%, specificity was 79.31%, PPV was 47.1%, and NPV was 78.4% (p = 0.01).

PET focal lesion Deauville score >4 and osteolytic lesion number >2 also demonstrated significant but moderate discriminative ability. In contrast, bone marrow Deauville score did not demonstrate statistically significant prognostic performance.

Overall, although all significant parameters demonstrated moderate discriminative ability, the identified cut-off values may provide clinically useful thresholds for imaging-based risk stratification.

Table 4 Receiver operating characteristic analysis of PET/CT- and CT-derived parameters for mortality

Parameter	AUC (95% CI)	Cut-off	Sensitivity (%)	Specificity (%)	P value	PPV (%)	NPV (%)
tMTV	0.642(0.55-0.727)	>288	45.71	79.31	0.01	47.1	78.4
TLG	0.674(0.583-0.756)	>914.53	57.14	78.16	0.002	51.3	81.9
SUVmax	0.651(0.56-0.734)	>6.3	62.86	70	0.007	44.9	82.9
PET Focal Lesion Deauville Score	0.625(0.542-0.703)	>4	56.10	75.70	0.02	46.9	81.8
Number of osteolytic lesions on CT	0.612(0.529-0.691)	>2	68.29	51.40	0.02	35	80.9
Bone Marrow Deauville Score	0.555(0.471-0.637)	>4	15	94.39	0.31	50	74.8

Abbreviations: AUC, area under the curve; CI, confidence interval; CT, computed tomography; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value; SUVmax, maximum standardized uptake value; TLG, total lesion glycolysis; tMTV, total metabolic tumor volume.

In the complete-case Kaplan–Meier analysis (n = 136), patients with tMTV >288 had significantly inferior overall survival compared with those with tMTV ≤288 (log-rank P = .002; Fig. 1).

Discussion

Our study demonstrates that baseline ¹⁸F-FDG PET/CT-derived volumetric parameters provide prognostically relevant information in patients with multiple myeloma. Among the evaluated imaging biomarkers, total metabolic tumor volume (tMTV) was the only PET/CT parameter independently associated with overall survival in multivariable analysis. This finding suggests that quantification of whole-body metabolically active tumor burden may capture aspects of disease extent and biological aggressiveness that are not fully represented by conventional staging systems or single-lesion measurements.

Our findings are consistent with previous studies supporting the prognostic value of baseline ^{18}F -FDG PET/CT in multiple myeloma. Bartel et al. demonstrated that the number of focal lesions, high FDG uptake, and extramedullary disease predicted progression-free and overall survival independently of conventional clinical variables.[8] Zamagni et al. subsequently confirmed the prognostic relevance of PET/CT findings in newly diagnosed patients treated with upfront autologous transplantation.[9] Later studies extended these observations by showing that volumetric parameters can quantify whole-body disease burden more comprehensively than conventional visual or single-lesion indices. Fonti et al. reported that baseline metabolic tumor volume predicted clinical outcome,[11] whereas McDonald et al. showed that TLG added prognostic information to gene-expression profiling and the ISS.[12] Sachpekidis et al. also demonstrated associations between volumetric PET parameters and survival outcomes,[6] and Aki et al. reported significant relationships between whole-body MTV, TLG, and adverse clinical or laboratory characteristics in newly diagnosed disease.[7]

More recent comparisons of conventional and volumetric PET parameters further support this concept. Terao et al. found that pretreatment MTV and TLG were superior to conventional PET/CT variables for outcome prediction in routine clinical practice.[13] In a direct comparison, Fonti et al. showed that volumetric measurements provided relevant prognostic information beyond visual PET findings.[14] In addition, Marchiori et al. demonstrated that both IMPeTUs-based visual findings and quantitative metabolic tumor burden contributed prognostic information in newly diagnosed, transplant-eligible multiple myeloma.[15] Collectively, these studies support the complementary use of standardized visual interpretation and volumetric tumor-burden assessment.

In our study, TLG showed the highest discrimination for mortality in ROC analysis, with an AUC of 0.674 and an optimal threshold of >914.53 . SUVmax also demonstrated moderate discrimination at a threshold of >6.3 , while tMTV showed significant discriminatory capacity at a threshold of >288 . However, only tMTV remained independently associated with overall survival after multivariable adjustment. This apparent difference is not necessarily contradictory: ROC analysis evaluates discrimination for a binary outcome at a selected threshold, whereas Cox regression incorporates follow-up time and adjusts for other prognostic variables. Therefore, the higher AUC of TLG does not establish it as the strongest independent survival predictor.

The independent prognostic value of tMTV is biologically plausible. SUVmax represents the metabolic intensity of only the single most FDG-avid lesion and may not adequately reflect the spatial heterogeneity or total extent of multifocal disease. In contrast, tMTV integrates the volume of all metabolically active lesions throughout the body. TLG combines metabolic volume with SUVmean and may capture both disease extent and glycolytic activity; however, its dependence on uptake measurements may also increase its sensitivity to acquisition conditions, reconstruction methods, uptake time, partial-volume effects, and the segmentation technique used to delineate lesions.[16] Such methodological variability may partly explain why TLG showed the highest unadjusted discrimination but did not retain independent significance in the multivariable model.

The tMTV threshold of >288 identified patients with inferior overall survival. Nevertheless, this value should be considered an exploratory and cohort-specific threshold. Published MTV and TLG cut-offs vary across studies because of differences in patient populations, treatments, scanners, reconstruction algorithms, lesion-inclusion rules, and segmentation methods.[6,11,13–16] The threshold identified in our cohort therefore requires independent validation, ideally in prospective multicenter studies, before it can be incorporated into routine risk stratification or therapeutic decision-making.

Standardized interpretation is essential for improving the reproducibility and clinical translation of PET biomarkers. The International Myeloma Working Group has emphasized the role of ^{18}F -FDG PET/CT in prognostic assessment and treatment-response evaluation in multiple myeloma.[5] The IMPeTUs framework provides structured evaluation of bone marrow uptake, focal lesions, fractures, paramedullary disease, and extramedullary disease.[17] Furthermore, Zamagni et al. established Deauville-based criteria for defining metabolic complete response and demonstrated the prognostic importance of residual uptake relative to reference tissues.[18] Although these systems primarily standardize visual response assessment, their integration with reproducible volumetric measurements could provide a more comprehensive imaging-based risk model.

The associations between PET parameters and anatomical patterns of involvement further support the biological relevance of metabolic tumor burden. In our cohort, vertebral and other skeletal-site involvement was associated with higher tMTV, TLG, SUVmax, focal-lesion Deauville scores, and numbers of CT-detected lytic lesions. Patients with paramedullary disease also had significantly higher values for all evaluated PET/CT parameters. By contrast, extramedullary disease was associated with higher SUVmax and focal-lesion Deauville scores, but not with significantly higher tMTV or TLG. These findings indicate that paramedullary and extramedullary disease should not be considered interchangeable imaging phenotypes. Paramedullary disease represents direct soft-tissue extension from a bone lesion, whereas extramedullary disease reflects hematogenous dissemination independent of bone and is associated with adverse biological features and inferior outcomes.[4,5] Previous PET/CT studies have likewise identified extramedullary disease as an adverse prognostic finding.[8,9]

The molecular basis of PET-defined high-risk disease is increasingly being investigated. A genome-wide transcriptomic analysis from the CASSIOPET study demonstrated associations between PET imaging biomarkers and gene-expression profiles related to myeloma biology.[19] These findings suggest that imaging-defined tumor burden may reflect underlying molecular characteristics rather than merely anatomical disease volume and provide a rationale for integrating quantitative imaging with cytogenetic, genomic, and laboratory risk factors.

In our study, $\beta 2$ -microglobulin showed weak but significant positive correlations with volumetric PET parameters, consistent with the relationship between metabolic burden and adverse laboratory characteristics reported previously.[7] These associations indicate partial concordance between biochemical and imaging-based estimates of disease burden. However, their modest magnitude suggests that PET/CT may provide complementary information concerning spatial disease distribution, focal-lesion burden, and tumor activity outside the sampled bone marrow compartment. Moreover, PET parameters did not differ significantly across R-ISS stages in our cohort. Because the R-ISS combines $\beta 2$ -microglobulin, albumin, LDH, and high-risk cytogenetics,[3] whereas tMTV directly quantifies whole-body metabolically active disease, these approaches may characterize partly distinct dimensions of disease biology.

The relatively high negative predictive values of TLG, SUVmax, and focal-lesion Deauville score suggest that low values may be more useful for identifying patients with a lower probability of death than high values are for definitively identifying high-risk patients. Conversely, the modest positive predictive values indicate that PET/CT biomarkers should not be interpreted in isolation. Their greatest clinical value may lie in combination with established prognostic factors, including age, performance status, $\beta 2$ -microglobulin, LDH, renal function,

cytogenetic abnormalities, and treatment response. Multimodal prognostic models may therefore be more informative than any single imaging threshold.

Automated segmentation and artificial intelligence may facilitate the clinical implementation of volumetric PET analysis by reducing analysis time and interobserver variability. Sachpekidis et al. demonstrated that artificial intelligence-based volumetric assessment of bone marrow metabolic activity predicted survival in multiple myeloma.[10] Lee et al. similarly showed that clustering of autoencoder-extracted PET/CT features could identify patients with poor prognosis.[20] These approaches are promising, but external validation across scanners, reconstruction protocols, segmentation platforms, and patient populations remains necessary before widespread clinical adoption.

Several limitations should be acknowledged. First, this was a retrospective, single-center study and was therefore susceptible to selection bias and unmeasured confounding. Second, the follow-up duration was relatively limited, and the ROC analysis of mortality did not fully account for differences in follow-up time. Third, the number of deaths was limited relative to the number of candidate predictors, which may affect the stability of the multivariable model. Fourth, cytogenetic risk and minimal residual disease results were not available for all patients, preventing a complete assessment of whether tMTV adds prognostic information beyond contemporary biological risk markers. Fifth, the PET-derived thresholds were identified and evaluated in the same cohort, creating a risk of optimism and overfitting. Finally, volumetric measurements may vary according to segmentation method and imaging protocol, limiting direct transferability of the identified thresholds to other centers.

Despite these limitations, the study has several strengths, including the evaluation of baseline whole-body PET/CT in a clinically relevant cohort, uniform image analysis using dedicated software, comparison of conventional and volumetric imaging biomarkers, and survival analyses incorporating ROC-derived thresholds and multivariable Cox regression. Overall, our findings support tMTV as a promising imaging biomarker that warrants external validation and prospective evaluation alongside cytogenetic, molecular, and MRD-based prognostic factors.

Conclusion

Baseline ^{18}F -FDG PET/CT-derived volumetric parameters provide prognostically relevant information in patients with multiple myeloma. Although TLG showed the highest discrimination for mortality in ROC analysis, tMTV was the only PET/CT parameter independently associated with overall survival in multivariable analysis.

These findings suggest that whole-body metabolic tumor volume may provide a more comprehensive representation of disease burden than single-lesion metabolic intensity. The exploratory tMTV threshold of >288 identified patients with inferior overall survival; however, this cohort-derived threshold requires independent validation before clinical implementation.

The integration of standardized visual criteria, reproducible volumetric measurements, and established clinical, cytogenetic, molecular, and MRD-related prognostic factors may improve individualized risk assessment in multiple myeloma.

Declarations

Ethics approval: The study was approved by the institutional ethics committee. The requirement for informed consent was waived because of the retrospective design. The study was conducted in accordance with the Declaration of Helsinki and its later amendments.

Consent to participate: The requirement for informed consent was waived by the institutional ethics committee because of the retrospective design.

Consent for publication: Not applicable.

Competing interests: The authors declare no competing interests.

Data availability: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author contributions: All authors contributed to the study conception and design, data acquisition or analysis, and interpretation of the results. All authors contributed to drafting or critically revising the manuscript and approved the final version.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Figures

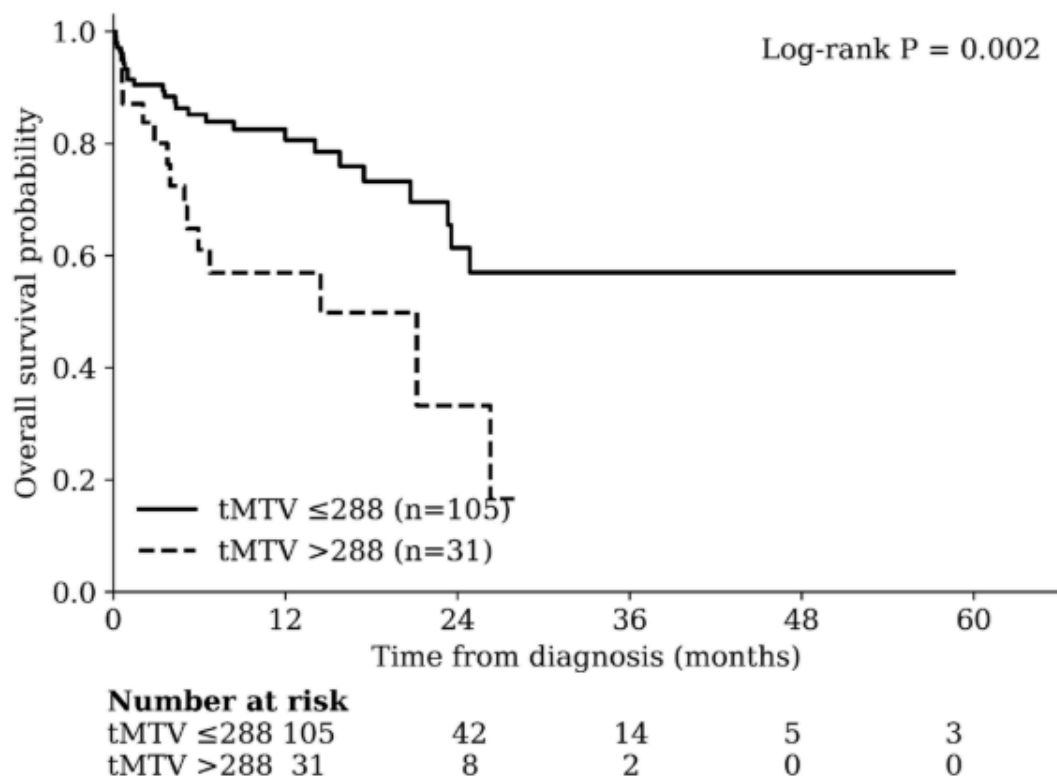


Figure 1

Kaplan–Meier estimates of overall survival according to the exploratory ROC-derived tMTV threshold (>288 versus ≤288). The analysis included 136 patients with available baseline tMTV and valid diagnosis-to-last-follow-up intervals. P value was calculated using the log-rank test