



# A prognostication system based on clinical parameters and [<sup>18</sup>F]-FDG PET/CT in patients with newly diagnosed multiple myeloma

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## Abstract

**Purpose** This study aimed to assess prognosis of patients with newly diagnosed multiple myeloma (NDMM) by combining [<sup>18</sup>F]-FDG positron emission tomography (PET)/CT parameters and clinical indices.

**Methods** Clinical data and PET/CT parameters of 133 NDMM patients were retrospectively analyzed for associations between clinical indices and PET/CT parameters. Independent predictors of progression-free survival (PFS) and overall survival (OS) were determined. A new prognostic prediction system (NPPS) was constructed based on our findings. Prediction effectiveness was compared among the NPPS, International Staging System (ISS), Revised ISS (R-ISS), and R2-ISS.

**Results** Prevalence of elevated  $\beta$ 2-microglobulin, serum creatinine (sCr), serum calcium (sCa), and C-reactive protein concentrations was higher in patients with higher SUVmax ( $\geq 5.3$ ). Prevalence of elevated sCa, sCr, and extramedullary disease (EMD) was higher in patients with a higher number of focal lesions ( $\geq 10$ ). SUVmax, serum free-light chain (sFLC) ratio, and EMD were independent predictors of PFS and OS. The NPPS used SUVmax, sFLC ratio, and EMD could effectively predict OS and was more effective at prognostication than the ISS, R-ISS, and R2-ISS.

**Conclusions** [<sup>18</sup>F]-FDG PET/CT parameters play a significant role in predicting prognosis in NDMM patients. The NPPS based on SUVmax, sFLC ratio, and EMD outperformed the ISS, R-ISS, and R2-ISS in prognostication.

**Keywords** Multiple myeloma · PET/CT · Prognosis · Clinical parameters · Staging

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Multiple myeloma (MM) is a bone marrow malignancy characterized by proliferation of plasma cells. Prognosis varies by individual and treatment. Identification of early prognostic factors has significant management implications as prompt and accurate diagnosis and staging are paramount to reduce mortality. According to National Comprehensive Care Network (NCCN) guidelines [1], MM prognosis is determined using the International Staging System (ISS) and Revised ISS (R-ISS) guidelines.  $\beta$ 2-microglobulin, lactate dehydrogenase (LDH), albumin, and fluorescence in situ hybridization (FISH) have been identified as predictive factors of overall survival (OS) and are included in both the ISS, R-ISS, and newly R2-ISS [2–4]. However, some serological parameters, such as  $\beta$ 2-microglobulin, are also closely associated with renal function, which limits their predictive accuracy [5].

[<sup>18</sup>F]-FDG PET/CT can be utilized to detect skeletal disease with high sensitivity, localize extramedullary disease (EMD), and evaluate prognosis and therapeutic efficacy in patients with MM [6]. In this population, significant PET

parameters include SUVmax, focal lesions, and EMD [7–9]. However, non-specific [ $^{18}\text{F}$ ]-FDG uptake in bone may be a confounding factor when assessing MM [10]. Although two previous studies have examined the prognostic value of [ $^{18}\text{F}$ ]-FDG PET/CT combined with clinical parameters in NDMM patients, they were limited by small sample size and incomplete laboratory data [2, 9]. In this study, we aimed to identify independent prognostic factors and construct a new prognostic prediction system (NPPS). Furthermore, we compared prognostic efficacy of the NPPS with those of the ISS, R-ISS, and R2-ISS.

We conducted a retrospective review of MM patients scanned in our PET center between August 1, 2014, and August 1, 2020. Inclusion criteria were as follows: (1) new diagnosis of MM according to NCCN guidelines and International Myeloma Working Group [5]; (2) PET/CT was performed before treatment; (3) no other malignancy; and (4) complete clinical and follow-up data (including myeloma type, serum free-light chain [sFLC] ratio, BMPC%, FISH, and concentrations of  $\beta$ 2-microglobulin, serum calcium [sCa], hemoglobin, LDH, C-reactive protein [CRP], and serum creatinine [sCr]).

Clinical staging was determined using the ISS, R-ISS, Durie–Salmon stage, and Mayo Clinic Stratification for Myeloma and Risk-Adapted Therapy (m-SMART). For the ISS, stage I was defined as albumin  $\geq 35$  g/L and  $\beta$ 2-microglobulin  $< 3.5$  mg/L; stage III was defined as  $\beta$ 2-microglobulin  $\geq 5.5$  mg/L. Patients who did not meet criteria for ISS stages I and III were classified as stage II. For the R-ISS, stage I was defined as ISS I and non-high-risk cytogenetics with normal LDH concentration; stage III was defined as high-risk cytogenetics or elevated LDH concentration. Patients who did not meet criteria for R-ISS stages I and III were classified as stage II. R2-ISS was stratified into four risk groups on the basis of the total additive scores.

Criteria for diagnosis on [ $^{18}\text{F}$ ]-FDG PET/CT were as follows [7]: Focal lesions were defined as lesions with high [ $^{18}\text{F}$ ]-FDG uptake on more than two consecutive PET levels, regardless of detection on CT. High [ $^{18}\text{F}$ ]-FDG uptake was defined as uptake visually higher than the surrounding background (except for osteoarthritis, spinal degeneration, or trauma) or areas with SUVmax  $> 2.5$  and diameter  $> 1$  cm. Areas in the bone marrow that had higher [ $^{18}\text{F}$ ]-FDG uptake than the liver and spleen were defined as diffuse intramedullary infiltration. EMD was defined by high uptake of [ $^{18}\text{F}$ ]-FDG in extramedullary tissue (usually soft tissue). Diagnosis of EMD lesions was either pathologically confirmed by tissue biopsy or clinically confirmed by follow-up observation. The number of focal lesions in each patient was recorded.

Finally, one hundred thirty-three patients were included for analysis. Mean age was  $59.0 \pm 9.6$  years (range, 53.0–67.0) and 77 were men (57.9%). Patient characteristics are shown in Table 1. The most common MM type was

IgG (57.9%). Elevated  $\beta$ 2-microglobulin was present in 110 patients (82.7%). Anemia (hemoglobin  $\geq 100$  g/L) was present in 84 (63.1%). Renal impairment (sCr  $\geq 144$   $\mu\text{mol/L}$ ) was present in 28 patients (21.1%). Elevated sCa ( $\geq 2.65$  mmol/L) was present in 18 (13.5%). EMD was present in 18 patients (13.5%). Sites affected by EMD included the thyroid, anterior mediastinum, pleura, liver, spleen, ileocecum, ascending colon, groin, psoas major, soft tissue adjacent to the posterior superior iliac spine, and soft tissue anterior to the sacrum. The relationship between PET characteristics (SUVmax and focal lesions) and clinical parameters is shown in Table S1. Prevalence rates of elevated  $\beta$ 2-microglobulin, sCr, sCa, and CRP significantly differed between patients with SUVmax  $\geq 5.3$  (median SUVmax of this set of patients) and those with SUVmax  $< 5.3$ . Prevalence of R-ISS stage I, R2-ISS I, and II was significantly lower in patients with SUVmax  $> 5.3$ . Prevalence rates of elevated sCr and sCa and patients with EMD significantly differed between patients with  $\geq 10$  focal lesions and those with  $< 10$ .

In the follow-up, one hundred thirteen patients underwent first-line chemotherapy alone and one patient underwent chemotherapy combined with lumbar radiation therapy. One patient was treated with chemotherapy combined with surgery. Four patients received chimeric antigen receptor T-cell immunotherapy, two received targeted drug therapy, and 12 underwent autologous stem cell transplantation in addition to chemotherapy.

The mean clinical follow-up of the patients was  $22.0 \pm 13.9$  months (range, 2.0–68.0). Fifty-three patients died and 26 relapsed or progressed. Median progression-free survival (PFS) and OS in the entire cohort were  $22.0 \pm 8.1$  months, respectively. PFS ( $25.0 \pm 4.4$  vs  $54.0 \pm 3.2$  months) and OS ( $32.5 \pm 6.5$  vs  $54.0 \pm 8.1$  months) were significantly worse in the [ $^{18}\text{F}$ ]-FDG PET/CT-positive patients (Fig. S1). Univariate Cox proportional hazards regression showed that hemoglobin, sCa, sCr, sFLC ratio, EMD, ISS, SUVmax  $\geq 5.3$ , and  $\geq 10$  focal lesions were significant predictors of PFS (Table 2). LDH, sCa, sCr, sFLC ratio, EMD, ISS, R-ISS, R2-ISS, m-SMART stage,  $\geq 10$  focal lesions, and SUVmax  $\geq 5.3$  were predictors of OS. In multivariate analysis, SUVmax  $\geq 5.3$ , EMD, and elevated sFLC ratio were independent predictors of PFS and OS.

The factors (SUVmax, sFLC ratio, and EMD) found significant above were further used in the NPPS. Staging was as follows: stage I, no risk factors; stage II, one or two risk factors; and stage III, three risk factors. PFS and OS significantly differed between the three NPPS stages (Fig. 1). Median OS according to stage using the NPPS, ISS, and R-ISS is shown in Table 3. Effectiveness of the NPPS, ISS, R-ISS, and R2-ISS in predicting OS is compared in Table 4, which shows that the NPPS is most effective, while the ISS, R-ISS, and R2-ISS were restricted in different ways. The

**Table 1** The clinical features of the enrolled patients

Characteristics	N (%)	Median, IQR
Gender (Male)	77 (57.9)	/
Type of myeloma		
IgG/IgD/IgA	77/6/24 (57.9/4.5/80.4)	/
Only kappa/only lappa	13/13 (19.5/19.5)	/
SUVmax, $\geq 2.5/\geq 5.3$	103/66 (77.4/49.6)	5.3 (2.7–7.8)
Focal lesions (Fls), 0–3/ $\geq 10$	76/51 (57.1/38.3)	/
With extramedullary disease	18 (13.5)	/
$\beta 2$ -microglobulin*, $\geq 3.0$ mg/L	110 (82.7)	4.4 (3.5–8.2)
Serum creatinine*, $\geq 144$ $\mu$ mol/L	28 (21.1)	87.8 (66–145)
Serum calcium*, $\geq 2.65$ mol/L	18 (13.5)	2.27 (2.10–2.49)
Hemoglobin*, $\geq 100$ g/L	84 (63.1)	93 (73–107)
Lactate dehydrogenase*, $\geq 245$ U/L	31 (23.3)	180 (139–235)
Albumin*, $< 3.5$ g/L	64 (48.1)	35.2 (29.2–40.3)
C-reactive protein*, $\geq 8.0$ mg/L	32 (24.1)	3.14 (3.03–7.60)
FISH (high risk)	16 (12.0)	
sFLC ratio, $\geq 100$	47 (35.3)	40 (5.2–150.0)
BMPC%, $\geq 30\%$	36 (27.1)	15 (8.5–32.7)
International Staging System (ISS)		
I/II/III	20/63/50 (15.0/47.4/37.6)	/
Revised-ISS		
I/II/III	21/93/19 (15.8/69.9/14.3)	/
Revised 2-ISS		
I/II/III/IV	11/43/69/10 (8.3/32.3/51.9/7.5)	
Durie–Salmon		
I/II/III	23/32/78 (17.3/24.1/58.6)	/
m-SMART 3.0		
High/standard risk	62/71 (46.6/53.4)	/

*IQR*, interquartile range; *FISH*, fluorescence in situ hybridization; *sFLC*, serum free-light chain; *BMPC*, bone marrow plasma cell infiltration; *m-SMART*, Mayo myeloma classification and risk management stratification system. \*Normal ranges:  $\beta 2$ -microglobulin, 0.8–2.4 mg/L; serum creatinin, 88.4–176.8  $\mu$ mol/L; calcium, 2.25–2.65 mol/L; hemoglobin, 120–160 g/L; lactate dehydrogenase (LDH), 109–245 U/L; albumin, 35–50 g/L; C-reactive protein, 0–8.0 mg/L; sFLC ratio, 0.26–1.65; BMPC%, 0–2.1%

representative patients (Fig. 2) with NPPS III (ISS II, R-ISS II, and R2-ISS III) and NPPS I (ISS II, R-ISS II, and R2-ISS III) are shown to have a poor prognosis and a favorable outcome, respectively.

## Discussion

In this study, [ $^{18}\text{F}$ ]-FDG PET/CT had profound significance in prognosticating patients with NDMM. Several independent risk factors for survival were found, namely SUVmax, EMD, and sFLC ratio. We also constructed a novel grading system that combined these parameters and predicted OS more effectively than the ISS and R-ISS, which should improve patient management. Moreover, higher SUVmax and greater number of focal lesions were associated with worse clinical parameters and advanced clinical stage.

ISS and R-ISS are the most widely used staging systems to predict MM prognosis [2–4]. However, several serological factors inherent to these systems are influenced by renal function, which may weaken their utility. In our study, the ISS performed poorly in differentiating the prognosis between ISS stages I and II; similarly, the R-ISS performed poorly in differentiating R-ISS stages II and III. Even the newly R2-ISS system had a poor performance in prognostic prediction. Therefore, new systems should be explored. By adding significant [ $^{18}\text{F}$ ]-FDG PET/CT parameters, the NPPS used in this study optimized OS prediction. Compared to those in previous studies [5, 6], our grading system included more clinical indicators and was based on data from a larger sample size, which may explain its greater accuracy.

[ $^{18}\text{F}$ ]-FDG PET/CT has exhibited value in MM staging and prognostication [10–12]. Our study showed that SUVmax, sFLC ratio, and EMD were independent

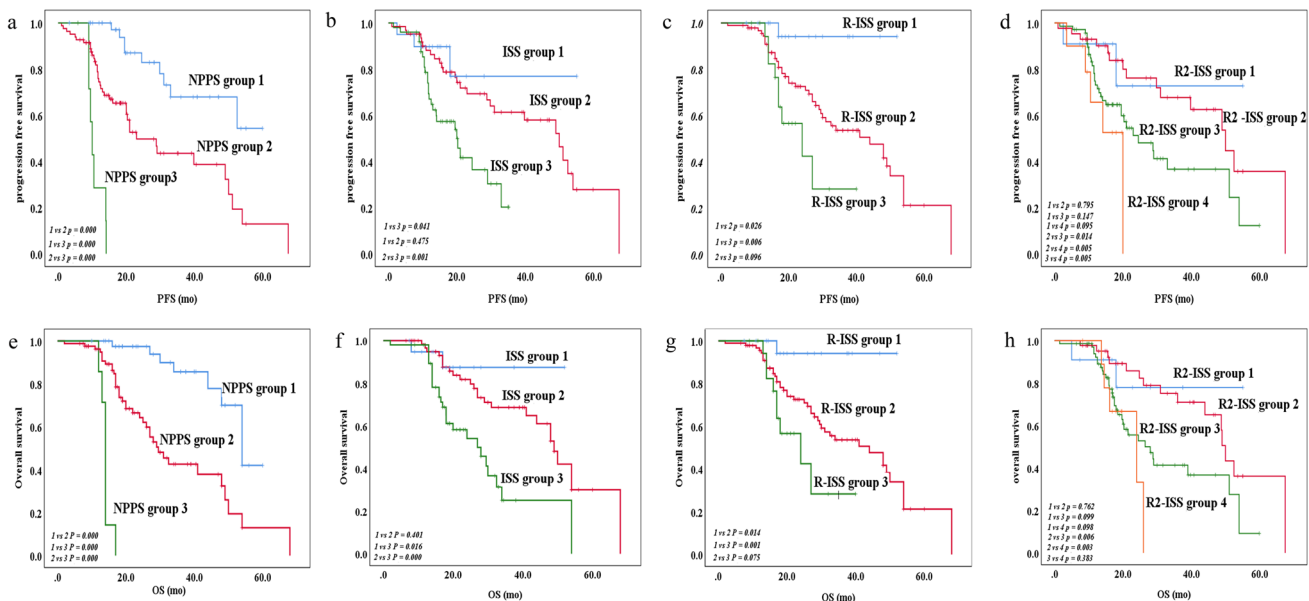
**Table 2** Univariate and multivariate Cox proportional risk regression of predicting PFS and OS

Variables (PFS)	PFS				OS			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age	1.036 (0.632–1.670)	0.888	NA		0.751 (0.431–1.310)	0.314	NA	
Gender	1.586 (0.946–2.661)	0.080	NA		1.281 (0.726–2.258)	0.393	NA	
Hemoglobin	2.581 (1.522–4.374)	<b>0.000*</b>	NA		2.970 (1.678–5.256)	0.393	NA	
β2-microglobulin	1.098 (0.541–2.231)	0.795	NA		1.257 (0.566–2.792)	0.575	NA	
Albumin	1.009 (0.616–1.652)	0.972	NA		1.169 (0.679–2.015)	0.574	NA	
LDH	1.427 (0.805–2.530)	0.223	NA		1.956 (1.076–.553)	<b>0.028*</b>	NA	
C-reactive protein	1.388 (0.794–2.428)	0.250	NA		1.581 (0.875–2.856)	0.129	NA	
Serum calcium	2.978 (1.653–5.364)	<b>0.000*</b>	NA		2.618 (1.318–5.198)	<b>0.006*</b>	NA	
Serum creatinin	2.704 (1.596–4.580)	<b>0.000*</b>	NA		3.034 (1.715–5.369)	<b>0.000*</b>	NA	
sFLC ratio	2.327 (1.406–3.850)	<b>0.001*</b>	2.617 (1.467–4.669)	<b>0.001*</b>	3.190 (1.825–5.578)	<b>0.000*</b>	3.451 (1.919–6.206)	<b>0.000*</b>
ISS	2.581 (1.522–4.374)	<b>0.000*</b>	NA		2.970 (1.678–5.256)	<b>0.000*</b>	NA	
R-ISS	1.899 (0.952–3.785)	0.069	NA		2.308 (1.092–4.877)	<b>0.028*</b>	NA	
R2-ISS	2.414 (1.342–4.435)	0.069	NA		0.380 (0.211–0.683)	<b>0.001*</b>	NA	
FIs (≥ 10)	1.741 (1.066–2.844)	<b>0.027*</b>	NA		2.152 (1.246–3.715)	<b>0.006*</b>	NA	
SUVmax (≥ 5.3)	2.495 (1.498–4.156)	<b>0.000*</b>	2.300 (1.289–4.104)	<b>0.005*</b>	3.348 (1.860–6.026)	<b>0.000*</b>	2.488 (1.387–4.462)	<b>0.000*</b>
EMD (yes)	5.216 (2.794–9.738)	<b>0.000*</b>	6.657 (3.233–13.706)	<b>0.000*</b>	9.005 (4.598–17.634)	<b>0.000*</b>	8.098 (3.962–16.550)	<b>0.000*</b>
m-SMART3.0	1.635 (0.984–2.717)	0.058	NA		2.313 (1.295–4.129)	<b>0.005*</b>	NA	
FISH	1.380 (0.654–2.908)	0.398	NA		1.768 (0.791–3.951)	0.165	NA	

\*and/or values in bold indicate statistically significant; NA, non-significance; FISH, fluorescence in situ hybridization; sFLC, serum free-light chain; BMPC, bone marrow plasma cell infiltration; m-SMART, Mayo myeloma classification and risk management stratification system

predictors of PFS and OS. Similar to our study, Zamagni et al. also reported that patients with higher SUVmax (> 4.2) at baseline or after induction chemotherapy had

shorter OS and PFS [7]. Number of focal lesions is not institution-specific and has been widely used in MM studies. Tu et al. reported that ≥ 10 focal lesions was an



**Fig. 1** Kaplan–Meier curves of progression-free survival (a–d) and overall survival (e–h) according to new prognostic prediction system (NPPS) stage, International Staging System (ISS) stage, Revised International Staging System (R-ISS) stage, and R2-ISS. Mo refers to month

**Table 3** Survival outcomes following the four systems

Systems		ISS	R-ISS	R2-ISS	NPPS
Median OS (95% CI)	I	52.0 (40.8–53.4)	52.0 (46.0–53.8)	45.7 (34.1–57.3)	54.0 (46.9–61.1)
	II	49.0 (43.4–54.6)	44.0 (29.1–58.9)	50.0 (48.0–52.0)	29.6 (23.5–35.5)
	III	27.0 (17.7–36.3)	24.0 (11.2–36.8)	28.0 (18.5–37.5)	14.0 (13.5–14.5)
	IV	/	/	24.0 (12.5–35.5)	/

ISS, International Staging System; R-ISS, Revised International Staging System; NPPS, new prognostic prediction system; / refers to no comparisons

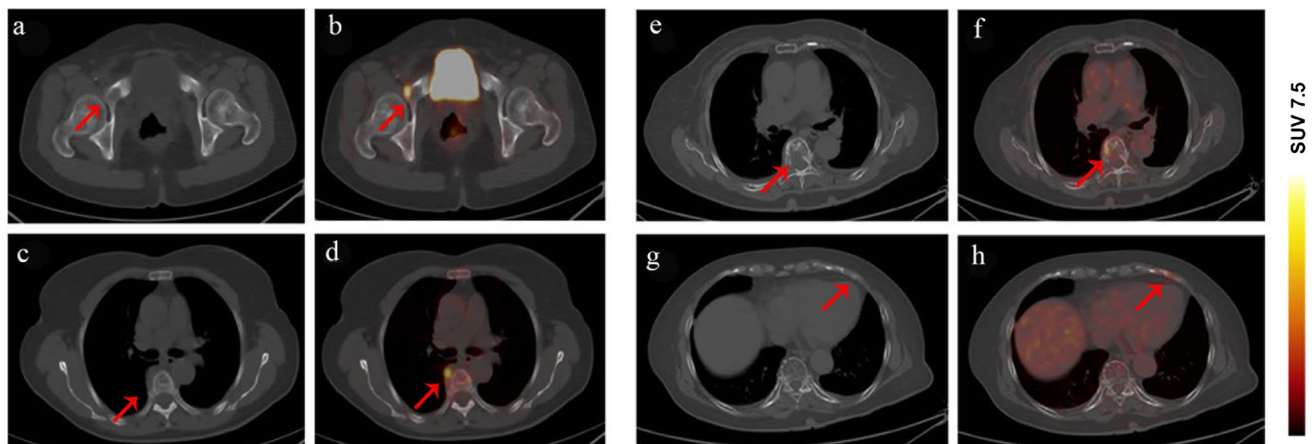
**Table 4** Comparative analysis of OS differences among four systems

Groups (P)	ISS	R-ISS	R2-ISS	NPPS
I vs II	0.401	0.014*	0.762	0.000*
I vs III	0.016*	0.001*	0.099	0.000*
I vs IV	/	/	0.098	/
II vs III	0.000*	0.074	0.006*	0.000*
II vs IV	/	/	0.003*	/
III vs IV	/	/	0.383	/

\* statistically significant; / refers to no comparisons

independent predictor of OS [2]. However, we found no association between number of focal lesions and patient survival. This may be because the patients with fewer focal lesions also had a high proportion of myelomas with abnormal genetics, which worsens prognosis. Nonetheless, we concluded that [<sup>18</sup>F]-FDG PET/CT positivity predicts worse PFS and OS, which is consistent with previous studies [11, 12].

EMD is commonly divided by location into soft tissue and bone-associated extramedullary infiltration, as prognosis differs between the two. In this study, the presence of soft tissue EMD was a strong predictor of PFS (hazard ratio, 4.534) and OS (hazard ratio, 8.433). Pour et al. demonstrated that OS was significantly lower in patients with soft tissue EMD than those with bone-related extramedullary recurrence and without EMD; they suggested that soft tissue infiltration is a significant predictor of poor prognosis [13]. We also found that presence of baseline EMD significantly reduced survival. Abnormal sFLC ratio reflects abnormal amplification of clonal plasma cells and disease progression and plays a role in diagnosis and prognostication. In our study, sFLC ratio was an independent predictor of PFS and OS, which has also been reported in other study [14]. This study had several limitations. Its retrospective design may have introduced bias. The NPPS proposed here should be verified in prospective studies using standardized treatment regimens.



**Fig. 2** A 68-year-old woman was diagnosed with multiple myeloma at stage III using NPPS. The disease was stage II using ISS and R-ISS and stage III using R2-ISS. CT showed osteolytic destruction of the right pubis (a) as well as paravertebral soft tissue and sternal abnormalities (c). [<sup>18</sup>F]-FDG PET showed increased uptake in the pubis and paravertebral soft tissue (b and d, SUVmax: 10.8 and 5.3, respectively). Progression-free and overall survival times were 10.5 months

and 12.0 months, respectively. A 69-year-old woman was diagnosed with multiple myeloma at stage I using NPPS. The disease was stage II using ISS and R-ISS and stage III using R2-ISS. CT showed a pathological vertebral fracture (e) and bony destruction of a rib (g). [<sup>18</sup>F]-FDG PET showed increased uptake at the fracture site and rib (f and h, SUVmax: 5.1 and 3.1, respectively). At last follow-up, the patient was in good condition without disease progression



## Conclusions

This study proposed a new prognostication system for patients with NDMM that includes PET (SUVmax and EMD) and clinical (sFLC ratio) parameters. This system appears to be more effective at prognostication than the ISS, R-ISS, and R2-ISS. Prospective large-scale studies are needed to validate this new system.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s00259-022-06088-x>.

**Author contribution** X. L. conceived and designed the study devised and supervised the project. X. Z. and J. L. finished the clinical experiments and wrote the manuscript. C. S. and Y. H. provided clinical data. Y. G. synthesized the probe and completed the examination. C. Q. and X. S. analyzed the image data. J. L., X. Z., G. C., and X. X. contributed to patient clinical data analysis.

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**Data availability** Not applicable.

## Declarations

**Ethical approval** All procedures involving human participants were carried out in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Consent to participate and publication** The requirement for informed consent was waived.

**Conflict of interest** The authors declare no competing interests.

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