Table S1: Clinical characteristics comparison between different oxidative stress score in the validation cohort.

Characteristics	**OSS-low (n = 240, %)**	**OSS-high (n = 93, %)**	***P* value**
Sex (%)			0.110
Female	94 (39.2)	27 (29.0)	
Male	146 (60.8)	66 (71.0)	
Age (%)			0.214
Median (IQR)	60 (53-66)	61.0 (56-67)	
< 65	166 (69.2)	57 (61.3)	
≥ 65	74 (30.8)	36 (38.7)	
ECOG (%)			0.127
<2	235 (98.3)	86 (94.5)	
≥2	4 (1.7)	5 (5.5)	
DS (%)			0.057
I	29 (12.1)	5 (5.4)	
II	56 (23.3)	16 (17.2)	
III	155 (64.6)	72 (77.4)	
ISS (%)			< 0.001
I	94 (39.2)	14 (15.1)	
II	73 (30.4)	30 (32.3)	
III	73 (30.4)	49 (52.7)	
RISS (%)			< 0.001
I	44 (27.7)	2 (2.5)	
II	110 (69.2)	55 (68.8)	
III	5 (3.1)	23 (28.7)	
R2ISS (%)			< 0.001
I	41 (33.3)	1 (2.1)	
II	35 (28.5)	4 (8.5)	
III	46 (37.4)	35 (74.5)	
IV	1 (0.8)	7 (14.9)	
Extramedullary (%)			0.765
No	175 (72.9)	70 (75.3)	
Yes	65 (27.1)	23 (24.7)	
Cytogenetic			
Standard Risk	100 (81.3)	30 (63.8)	0.028
High Risk	23 (18.5)	17 (36.2)	
Transplant (%)			0.272
No	201 (83.8)	83 (89.2)	
Yes	39 (16.2)	10 (10.8)	

Characteristics	OSS-low (n = 240, %)	OSS-high (n = 93, %)	*P* value
Treatment (%)			0.092
PIs	71 (29.6)	35 (37.6)	
IMiDs	30 (12.5)	14 (15.1)	
IMiDs_PIs	89 (37.1)	21 (22.6)	
Others	50 (20.8))	23 (24.7)	
β2-MG (%)			< 0.001
Mean (SD)	4.84 (7.5)	8.88 (10.6)	
< 3.5	134 (55.8)	27 (29.0)	
≥ 3.5	106 (44.2)	66 (71.0)	
HGB (%)			< 0.001
Mean (SD)			
< 120	146 (60.8)	81 (87.1)	
≥ 120	94 (39.2)	12 (12.9)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; DS, Durie-Salmon staging system; ISS, international staging system; RISS, revised international staging system; R2ISS, second revision of the international staging system; Pls, proteasome inhibitors; IMiDs, immunomodulatory drugs; β2-MG, β2-microglobulin; HGB, hemoglobin. SD, standard deviation; IQR: interquartile range. All P-values are based on comparisons between categorical variables.

Table S2. The univariate and multivariate Cox regression analyses for OS among the clinical characteristics and OSS in the validation cohort.

Variables	Uni-variate Cox analysis		Multi-variate Cox analysis	
	HR(95%CI)	*P* value	HR(95%CI)	*P* value
Sex				
Female	Reference			
Male	0.819 (0.578-1.162)	0.263		
Age (year)				
< 65	Reference			
≥ 65	1.099 (0.764-1.583)	0.610		
ECOG				
< 2	Reference		Reference	
≥ 2	3.714 (1.728-7.981)	**0.001**	4.633 (2.082-10.309)	< 0.001
DS				
I	Reference			
II	1.062 (0.553-2.040)	0.856		
III	1.197 (1.050-2.371)	0.546		
ISS				
I	Reference		Reference	
II	2.163 (1.377-3.398)	**0.001**	1.142 (0.636-2.051)	0.496
III	2.536 (1.599-4.020)	**< 0.001**	1.600 (0.847-3.022)	0.311

Variables	Uni-variate Cox analysis		Multi-variate Cox analysis	
	HR(95%CI)	***P* value**	**HR(95%CI)**	***P* value**
RISS				
I	Reference		Reference	
II	3.151 (1.519-6.537)	0.002	1.832 (0.739-4.542)	**0.191**
III	8.394 (3.491-20.182)	**< 0.001**	3.018 (1.020-8.928)	**0.046**
R2ISS				
I	Reference			
II	2.090 (0.956-4.572)	0.065		
III	2.492 (1.211-5.126)	**0.013**		
IV	3.501 (0.951-12.886)	0.060		
Extramedullary disease				
No	Reference			
Yes	1.035 (0.688-1.557)	0.869		
Transplant				
No	Reference			
Yes	0.832 (0.500-1.385)	0.479		
Cytogenetic				
Standard Risk	Reference			
High Risk	1.225 (0.672-2.233)	0.507		
β2-MG (mg/L)				
< 3.5	Reference		Reference	
≥ 3.5	1.879 (1.322-2.672)	**< 0.001**	0.976 (0.595-1.600)	0.922
HGB (g/L)				
< 120	Reference		Reference	
≥ 120	0.483 (0.319-0.731)	**0.001**	0.668 (0.414-1.077)	0.098
OSS				
Low	Reference		Reference	
High	2.093 (1.421-3.083)	**< 0.001**	1.584 (1.034-2.427)	**0.035**

Abbreviations: ECOG, Eastern Cooperative Oncology Group; DS, Durie-Salmon staging system; ISS, international staging system; RISS, revised international staging system; R2ISS, second revision of the international staging system; Pls, proteasome inhibitors; IMiDs, immunomodulatory drugs; β2-MG, β2-microglobulin; HGB, hemoglobin. OSS, oxidative stress score.

Table S3. The univariate and multivariate Cox regression analyses for PFS among the clinical characteristics and OSS in the validation cohort.

Variables	Uni-variate Cox analysis		Multi-variate Cox analysis	
	HR (95%CI)	***P* value**	**HR (95%CI)**	***P* value**
Sex				
Male	Reference			
Female	0.919 (0.674-1.255)	0.597		
Age (year)				
< 65	Reference			
≥ 65	1.033 (0.747-1.427)	0.846		
ECOG				
< 2	Reference		Reference	
≥ 2	2.476 (1.157-5.296)	**0.019**	3.430 (1.548-7.600)	**0.002**
DS				
I	Reference			
II	1.258 (0.701-2.261)	0.442		
III	1.461 (0.864-2.470)	0.157		
ISS				
I	Reference		Reference	
II	1.875 (1.279-2.747)	0.001	1.378 (0.838-2.266)	0.207
III	1.651 (1.114-2.449)	**0.013**	1.598 (0.940-2.717)	0.083
RISS				
I	Reference			
II	2.055 (1.208-3.498)	0.008		
III	3.720 (1.865-7.420)	**< 0.001**		
R2ISS				
I	Reference			
II	1.966 (1.056-3.662)	**0.033**		
III	1.423 (0.797-2.540)	0.233		
IV	7.367 (2.794-19.428)	**< 0.001**		
Extramedullary disease				
No	Reference			
Yes	0.965 (0.675-1.382)	0.847		
Transplant				
No	Reference			
Yes	1.013 (0.661-1.552)	0.954		
Cytogenetic				
Standard Risk	Reference		Reference	
High Risk	1.785 (1.094-2.912)	**0.020**	1.878 (1.145-3.081)	**0.013**
β2-MG (mg/L)				
< 3.5	Reference		Reference	
≥ 3.5	1.426 (1.050-1.937)	**0.023**	0.765 (0.488-1.199)	**0.242**

Variables	Uni-variate Cox analysis		Multi-variate Cox analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
HGB (g/L)				
< 120	Reference		Reference	
≥ 120	0.554 (0.391-0.785)	**0.001**	0.628 (0.420-0.940)	**0.024**
OSS				
Low	Reference		Reference	
High	1.601 (1.130-2.268)	**0.008**	1.447 (1.017-2.060)	**0.040**

Abbreviations: ECOG, Eastern Cooperative Oncology Group; DS, Durie-Salmon staging system; ISS, international staging system; RISS, revised international staging system; R2ISS, second revision of the international staging system; Pls, proteasome inhibitors; IMiDs, immunomodulatory drugs; β2-MG, β2-microglobulin; HGB, hemoglobin. OSS, oxidative stress score.

Figure S1. Distribution of Four Cytogenetic High-Risk Subtypes Among Patients
The frequencies of del(17p), t(4;14), t(14;16), and 1q21 gain are shown for patients stratified by oxidative stress score (OSS) into high and low groups.

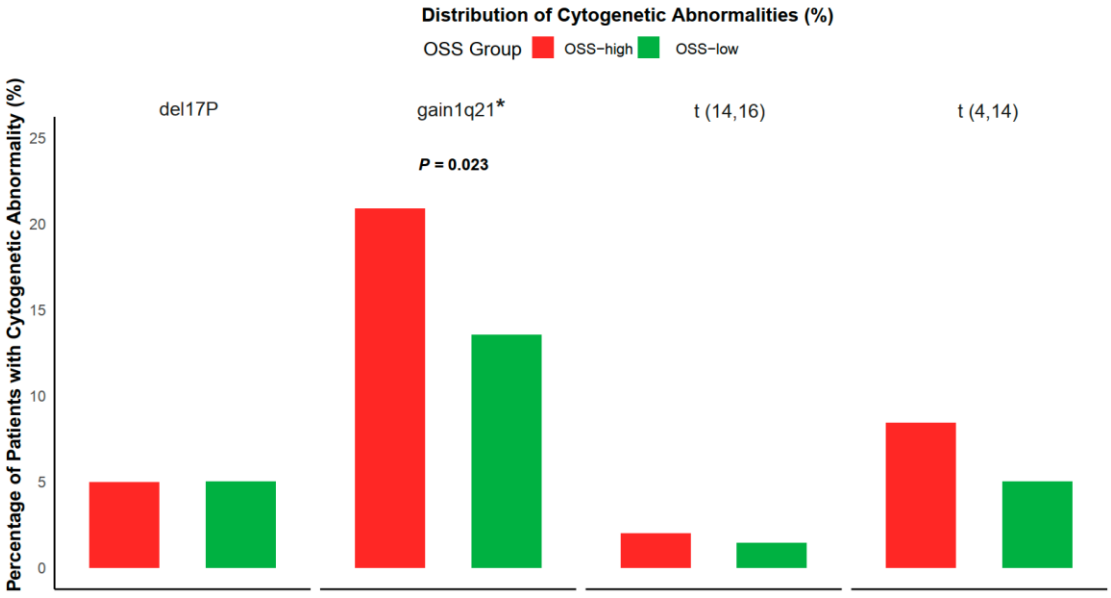


Figure S2. Kaplan–Meier curves for PFS in patients receiving IMiD–PI–based therapy stratified by OSS. Progression-free survival (PFS) comparison between high and low OSS groups among patients treated with combined immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs).

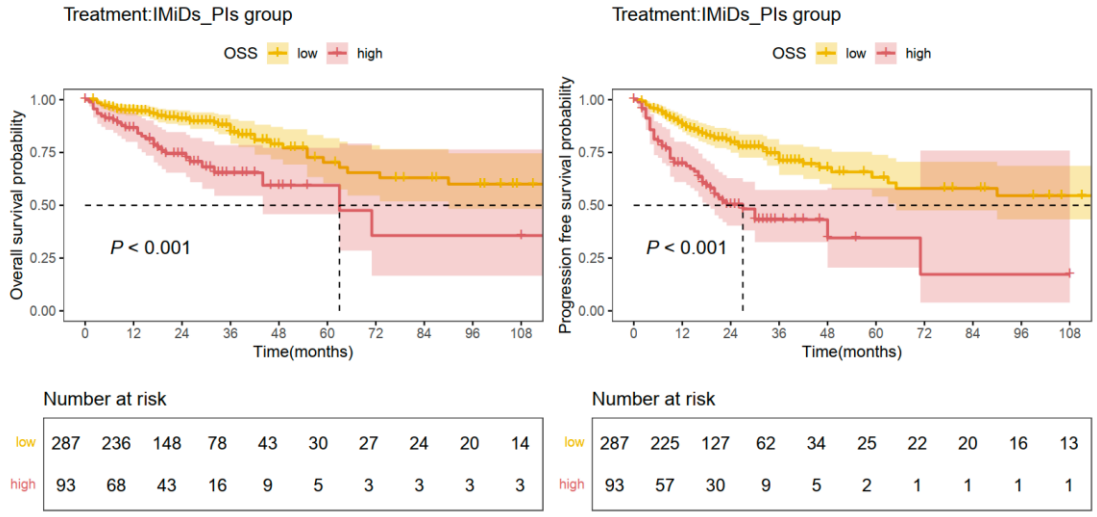


Figure S3. Kaplan–Meier curves for PFS in patients receiving IMiD-based therapy stratified by OSS. Progression-free survival (PFS) comparison between high and low OSS groups among patients treated with immunomodulatory drug (IMiD) monotherapy.

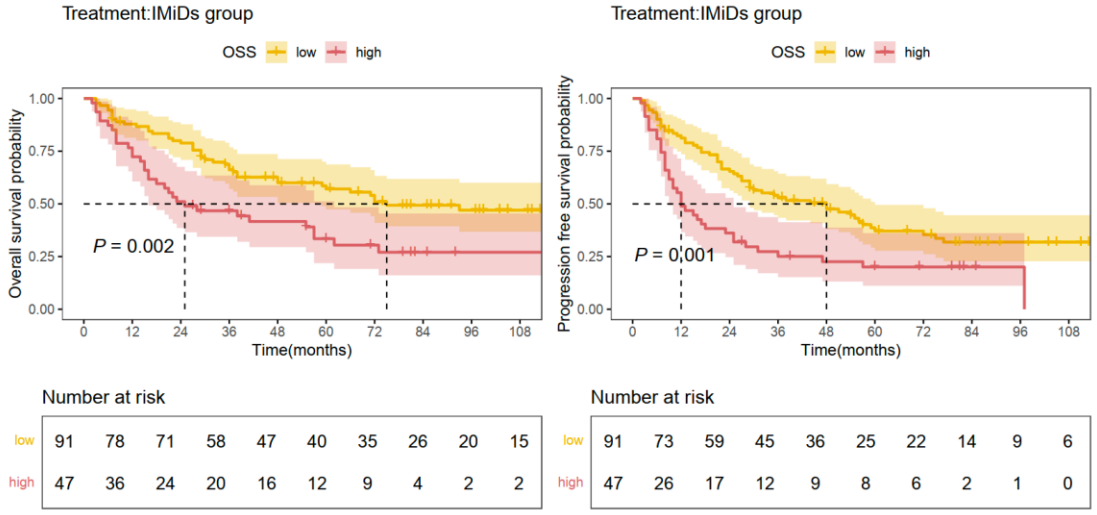


Figure S4. Kaplan–Meier curves for PFS in patients receiving PI-based therapy stratified by OSS. Progression-free survival (PFS) comparison between high and low OSS groups among patients treated with proteasome inhibitor (PI) monotherapy.

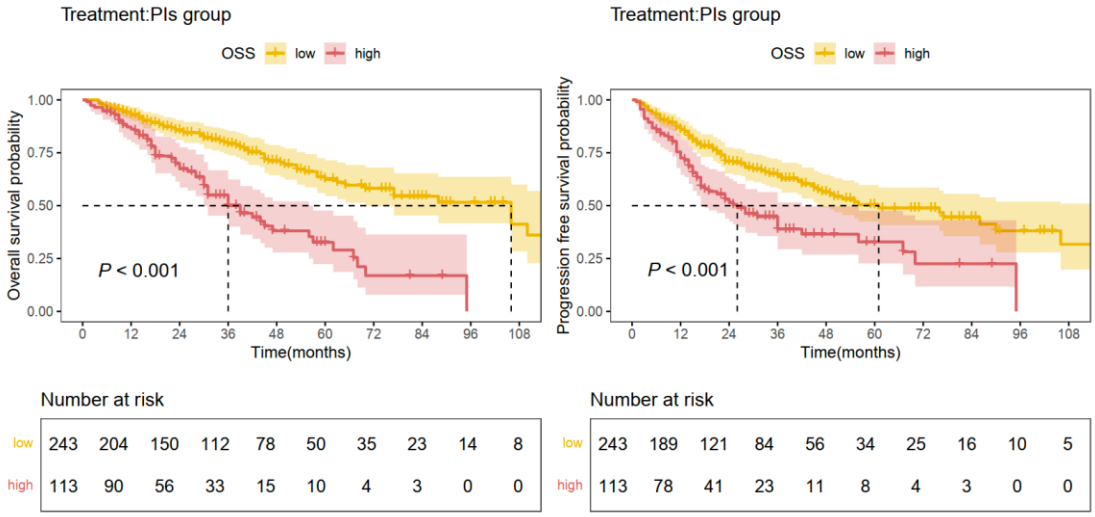


Figure S5. Comparison of prognostic performance between OSS and R2ISS**.** Time-dependent ROC (t-ROC) and decision curve analysis (DCA) were used to compare the 5-year overall survival (OS) predictive value and decision-making utility of the oxidative stress score (OSS) and second revision of the international staging system (R2ISS).

