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Comprehensive analysis and establishment of a prognostic model based on non-genetic predictors in multiple myeloma[1]

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Abstract.
BACKGROUND: Multiple myeloma (MM) is a systemic hematological malignancy usually incurable. The value of some important prognostic factors may gradually decrease.
OBJECTIVE: We aimed to explore the non-genetic indexes, prognostic models, and significance of clinical staging systems of MM.
METHODS: A retrospective analysis was conducted on clinical data from 110 patients with MM who first visit the First Affiliated Hospital of Guangzhou Medical University between September 2005 to December 2018.
RESULTS: Bone marrow plasma cell percentage (BMPC%), cystatin C (CysC), and β2 microglobulin (β2-MG) were positively correlated with Durie-Salmon (D-S) and international staging system (ISS) stages, while red blood cell count (RBC) and hemoglobin volume (HGB) were negatively correlated ($P < 0.05$). Univariate analysis showed that ISS stage, treatment protocol, immunofixation electrophoresis (IFE), ratio of red cell distribution width to platelet count (RPR), monocyte count (MONO), lactate dehydrogenase, and immunoglobulin G were significantly associated with the three-year overall survival (OS). IFE, treatment protocol, and β2-MG significantly affected progression-free survival ($P < 0.05$). Multivariate analysis showed that the treatment protocol, ISS stage, RPR, MONO, and IFE were independent prognostic factors for three-year OS ($P < 0.05$).
CONCLUSIONS: BMPC%, CysC, and β2-MG were positively correlated with both clinical staging systems and RBC and HGB were negatively correlated. RPR and MONO affect MM prognosis and the established prognostic model can guide patient prognosis.

Keywords: Multiple myeloma, clinical staging, non-genetic predictors, prognostic model, monocyte count

1. Introduction

Multiple myeloma (MM) is a systemic hematological malignancy that is usually incurable. The World Health Organization classifies MM as a lymphoproliferative B-cell disease [1]. There is an excess amount of myeloma (M) protein, a monoclonal immunoglobulin (Ig), in the serum of patients with MM. A small group of MM is classified as unsecreted MM when M protein cannot be detected in the serum. The incidence of MM is 1.6 cases per 100 000 persons per year, accounting for approximately 10% of all hematological malignancies, and is continuously increasing in China [2].

The clinical manifestations of MM are unclear and can be easily ignored. The symptoms reported by pa-

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tients with MM on presentation are often non-specific and may already have been present for an extended period. Anemia of unknown origin is found in 73% of patients, bone pain in 58%, and fatigue in 32%. Approximately 25% of patients report unexplained weight loss, and renal function is often impaired [3]. In addition to clinical history and physical examination, the diagnosis of MM involves clinical chemistry, cytogenetic analysis of the bone marrow, and radiological investigation to detect bone changes [4].

The prognosis of MM is heterogeneous, and factors affecting prognosis include host factors, tumor burden, genetic abnormalities, and response to treatment [5]. In recent years, several new therapeutic agents have been developed and approved for the treatment of MM, including proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), monoclonal antibodies (mAbs), as well as histone deacetylase (HDAC) inhibitors [6,7], and have improved the prognosis of MM patients in multiple ways. PIs, such as bortezomib, carfilzomib, and ixazomib, have shown efficacy in inducing apoptosis of MM cells and sensitizing them to chemotherapy [8]. IMiDs, such as lenalidomide and pomalidomide, have immunomodulatory effects, including enhancing the activity of T cells and natural killer cells against MM cells. The use of mAbs, such as daratumumab and elotuzumab, has led to improved immune-mediated tumor targeting and killing of MM cells [9]. Finally, HDAC inhibitors, such as panobinostat and vorinostat, have demonstrated the ability to induce apoptosis and inhibit the proliferation of tumor cells in MM [10]. The development and use of these new agents have significantly improved the prognosis of MM patients, leading to increased response rates, prolonged progression-free survival (PFS), and improved overall survival (OS).

Recently, researchers have found that patients with MM carrying the same genetic factors usually have different prognoses, suggesting a contribution of non-genetic factors [11]. The Durie-Salmon (D-S) stage and international staging system (ISS) are the most common clinical staging systems used for patients with MM. D-S staging classifies tumor burden into three stages based on serum/urine M protein, hemoglobin, X-ray examination, tumor cell count, and serum calcium of the patients. The ISS divides MM into three stages according to the levels of albumin and serum β2-microglobulin (β2-MG) [12]. Recently, the prognosis of MM has significantly improved with the widespread application of new therapeutic agents, such as thalidomide, bortezomib, and lenalidomide [13]. Consequently, the value of some important prognostic factors may gradually decrease. Therefore, there is a need to summarize and stratify the risk factors affecting the prognosis of MM in a multi-directional manner and to establish an effective prognostic evaluation system, which can guide clinical management. The clinical manifestations and biological characteristics of tumor cells in patients with MM are significantly heterogeneous, and the survival of patients varies greatly. In this study, we investigated the relationship between non-genetic indicators and prognosis in newly diagnosed patients with MM who received therapy at the First Affiliated Hospital of Guangzhou University of Chinese Medicine and established a prognostic model to provide risk stratification support for patients.

2. Materials and methods

This was a single-center retrospective clinical study. A total of 110 patients diagnosed with MM at the First Affiliated Hospital of Guangzhou University of Chinese Medicine between September 2005 and December 2018 were enrolled in this study. The study was approved by the First Affiliated Hospital of Guangzhou University of Chinese Medicine and conformed to the Helsinki Declaration of 1964 (revised in 2013) concerning human and animal rights. Due to the investigation being carried out through retrospective review of medical records and no foreseeable impact on the rights and/or welfare of the participants involved, ethics approval was not required. Additionally, consent from study participants was not required because the study only involved a retrospective review of medical records. The First Affiliated Hospital of Guangzhou University of Chinese Medicine granted Ethical approval to carry out the study within its facilities (Ethical Application Ref: K-2022-033).

2.1. Inclusion criteria

Patients included in the study met the international diagnosis of MM and were staged according to the D-S and ISS criteria [14]. In addition, the included patients were treated according to their normal clinical conditions and could cooperate with the improvement of various examinations. Meanwhile, inclusion criteria included good reading ability, ability to respond, and clear consciousness. Treatment options included chemotherapy with bortezomib and conventional chemotherapy without bortezomib.

2.2. Exclusion criteria

The exclusion criteria included patients to whom medication was not administered; who underwent hematopoietic stem cell transplantation; who were pregnant or lactating women; with any serious concomitant systemic disorder or uncontrollable infection; with decompensated heart, lung, or renal failure; and to whom chemotherapy was intolerable.

2.3. Observational index

All clinical variables were collected from electronic medical records held by the First Affiliated Hospital of Guangzhou University of Chinese Medicine, including age, sex, time of initial diagnosis, first symptom, underlying disease, clinical stage, treatment plan, clinical classification, bone marrow plasma cell percentage (BMPC%), white blood cell count (WBC), neutrophil count (NEU), lymphocyte count (LYM), monocyte count (MONO), red blood cell count (RBC), hemoglobin volume (HGB), red blood cell distribution width (RDW), platelet count (PLT), IgA, IgG, total serum calcium (Ca), urine hormone (urea), creatinine (Cre), alkaline phosphatase (ALP), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), cystatin C (CysC), β2-MG, remission time, and recurrence time. The ratios of RDW to PLT (RPR [RDW/PLT]), PLT to LYM (PLR [PLT/LYM]), and NEU to LYM (NLR [NEU/LYM]) were calculated.

2.4. Experimental instruments and methods

Serum immunofixation electrophoresis (IFE) was performed using automatic capillary electrophoresis (Sebia). Serum β2-MG, Ca, urea, Cre, ALP, ALT, LDH, CysC, and other biochemical parameters were measured using an AU5421 automatic biochemical analyzer (Olympus) and a Cobas 701 automatic biochemical analyzer (Roche). WBC, NEU, LYM, MONO, RBC, HGB, RDW, PLT, and other blood analysis indicators were measured using an XE-5000 automatic blood cell analyzer (Sysmex) and a BC6800 blood analyzer (Mindrayer). IgA and IgG levels were measured by immunoturbidimetry using an automatic biochemical analyzer DXC800 (Beckman Coulter).

2.5. Outcomes and measurements

The primary outcome was OS obtained at initial diagnosis to the date of death or the end of follow-up and from the date of known survival in patients who were lost to follow-up. The secondary outcome was PFS, which was the time from the first treatment to disease progression, recurrence, death, or termination of follow-up.

2.6. Statistical analyses

SPSS (version 27.0 for Windows, IBM, USA) and GraphPad Software (San Diego, California, USA) were used for statistical analysis and mapping of data. Quantitative data were expressed as mean $\pm$ standard deviation ($\bar{x} \pm s$). Qualitative data were expressed as the number of cases and percentages. Univariate analysis was performed using the Log-rank test. We performed univariate analysis using logistic regression models to assess the association between outcomes and each clinical factor. A P-value < 0.05 was considered statistically significant in this study. Multivariate logistic regression analyses were performed using variables that were identified as having associations with outcomes in the univariate analysis at $P < 0.05$. Finally, the risk scoring model was constructed by R (version 3.6.3) software based on the statistically significant results from the multivariate logistic regression analyses.

3. Results

3.1. Demographic and baseline clinical characteristics

Between September 2005 and December 2018, 110 eligible patients from the First Affiliated Hospital of Guangzhou University of Chinese Medicine were enrolled in the study. Underlying medical conditions were present in 69.1% of the patients. Hypertension, diabetes, coronary heart disease, and kidney stones are common in patients with MM. The most common first symptom reported was ostealgia (77.3%), followed by anemia (10.9%). Ostealgia mainly included pain in the lower back, rib, hip, and calf. Overall characteristics of the patients are presented in Table 1, alongside the statistics of the clinical test results.

3.2. Intergroup comparison of D-S and ISS stage

According to the grouping of the D-S and ISS stages, a comparative analysis between the observational index and grouping was carried out. In the three groups of the D-S stage, the results from the analysis showed that RBC, HGB, RDW, IgA, Cre, urea, ALP, CysC, and β2-MG levels were statistically significant between the three groups ($P < 0.05$). Correlation analysis showed that BMPC%, RPR, CysC, and β2-MG were positively correlated with the D-S stage ($P < 0.05$), whereas RBC, HGB, RDW, PLT, and IgA were negatively corre-

Table 1
The baseline characteristics of the participants

Characteristics	Number	Percentage (%)	x ± s/(M, IQR)
Case, N	110	–	–
Sex			
Male	58	52.7	–
Female	52	47.3	–
Underlying disease			
Yes	76	69.1	–
No	34	30.9	–
Regimen			
Bortezomib included	45	40.9	–
Bortezomib not included	69	59.1	–
Immunofixation electrophoresis			
Light chain type	19	17.3	–
IgA type	24	21.8	–
IgG type	62	56.4	–
Other	5	4.5	–
The first symptom			
Ostealgia	85	77.3	–
Anemia	12	10.9	–
Other	13	11.8	–
Age	110	–	(61, 13)
BMPC (%)	110	–	(27.5, 31.00)
WBC (*109/L)	110	–	(5.48, 2.66)
NEU (*109/L)	110	–	(2.94, 2.16)
LYM (*109/L)	110	–	(1.795, 0.95)
MONO (*109/L)	110	–	(0.45, 0.25)
RBC (*1012/L)	110	–	3.164 ± 0.787
HGB (g/L)	110	–	89.78 ± 20.180
RDW (%)	110	–	(15.45, 3.88)
PLT (*109/L)	110	–	198.76 ± 91.439
NLR	110	–	(1.625, 1.30)
PLR	110	–	111.95 ± 61.115
RPR	110	–	(0.10, 0.17)
IgG (g/L)	95	–	(14.95, 49.19)
IgA (g/L)	93	–	(0.357, 1.470)
Ca (mmol/L)	110	–	(2.28, 0.3)
Cre (umol/L)	110	–	(92, 103)
UREA (mmol/L)	110	–	(6.06, 4.49)
ALP (U/L)	103	–	(78, 40)
ALT (U/L)	110	–	(14, 11)
LDH (U/L)	84	–	(152.5, 64)
CysC (mg/L)	96	–	(1.205, 1.06)
β2-MG (mg/L)	110	–	(4.175, 5.24)

lated with the D-S stage ($P < 0.05$). Among the three ISS groups, the analysis results showed significant differences in BMPC%, RBC, HGB, IgG, Cre, urea, ALT, CysC, and β2-MG ($P < 0.05$). Correlation analysis showed that BMPC%, MONO, Cre, urea, CysC, and β2-MG were positively correlated with the ISS stage ($P < 0.05$), whereas RBC, HGB, and ALT were negatively correlated with the ISS stage ($P < 0.05$). The individual results are provided in Table 2. In addition, the Kruskal-Wallis test was used for multiple pairwise comparisons of the observational index, with differences between the three groups. Detailed results are presented in Tables 3 and 4.

3.3. Univariate and multivariate analysis of count data

Cox univariate and multivariate analyses were performed on factors, including sex, underlying disease, treatment protocol, D-S stage, ISS stage, and IFE. The results of univariate analysis showed that ISS stage, treatment plan, and IFE type had significant effects on the three-year OS of patients with MM ($P < 0.05$), while treatment regimen and IFE had significant effects on the three-year PFS of patients with MM ($P < 0.05$). Cox multivariate regression analysis showed that ISS stage, treatment regimen, and IFE were independent prognostic factors for OS ($P < 0.05$), while IFE

Table 2
Correlation analysis of observational indexes with D-S and ISS stage

Characteristics	Normality test (p)	D-S stage (p)	ISS stage (p)	D-S stage correlation	ISS stage correlation
BMPC (%)	0.000	0.059	0.016*	0.299*	0.305*
WBC (*10^9/L)	0.000	0.544	0.671	−0.216	0.008
NEU (*10^9/L)	0.000	0.741	0.444	−0.220	0.045
LYM (*10^9/L)	0.000	0.162	0.837	−0.077	−0.106
MONO (*10^9/L)	0.000	0.803	0.057	0.010	0.346*
RBC (*10^{12}/L)	0.200	0.000*	0.006*	−0.431*	−0.306*
HGB (g/L)	0.200	0.000*	0.002*	−0.056*	−0.326*
RDW (%)	0.037	0.004*	0.768	0.264*	−0.021
PLT (*10^9/L)	0.190	0.403	0.926	−0.294*	−0.028
NLR	0.000	0.692	0.722	−0.145	0.143
PLR	0.078	0.719	0.624	−0.178	−0.068
RPR	0.000	0.082	0.247	0.311*	−0.067
IgG (g/L)	0.000	0.716	0.005*	0.061	−0.221
IgA (g/L)	0.000	0.001*	0.194	−0.389*	−0.104
Ca (mmol/L)	0.000	0.217	0.712	−0.042	0.068
Cre (umol/L)	0.000	0.013*	0.000*	0.253	0.550*
UREA (mmol/L)	0.000	0.038*	0.000*	0.237	0.553*
ALP (U/L)	0.000	0.016*	0.293	0.164	−0.091
ALT (U/L)	0.000	0.087	0.009*	−0.110	−0.334*
LDH (U/L)	0.001	0.860	0.681	−0.038	−0.066
CysC (mg/L)	0.000	0.011*	0.000*	0.316*	0.610*
β_2-MG (mg/L)	0.000	0.001*	0.000*	0.392*	0.610*

Note: *represents $p < 0.05$, which is statistically significant.

Table 3
Results of multiple comparisons between D-S stages and test indicators

Stage		N	RBC ($\bar{x}$)	HGB ($\bar{x}$)	RDW ($\bar{x}$)	IgA ($\bar{x}$)	Cre ($\bar{x}$)	Urea ($\bar{x}$)	ALP ($\bar{x}$)	CysC ($\bar{x}$)	β_2MG ($\bar{x}$)
I		19	3.8258	115.58	14.6579	10.40493	105.05	6.4726	114.05	1.3113	3.2435
II		21	3.0195	89.14	15.0286	14.04874	100.71	7.4981	72.37	1.5605	4.3611
III		70	2.8186	79.71	16.5814	7.94671	170.9	8.7253	71.23	1.8672	6.6273
	H		13.780	27.010	11.21	13.495	8.702	6.538	8.228	9.063	13.204
III/I	p		0.000*	0.000*	0.010*	0.012*	0.035*	0.032*	0.012*	0.011*	0.003*
II/I	p		0.001*	0.000*	0.121	0.185	0.210	0.138	0.224	0.389	0.265
III/II	p		0.126	0.224	0.348	0.013*	0.004*	0.852	0.223	0.456	0.365

Note: *represents $p < 0.05$, which is statistically significant.

Table 4
Results of multiple comparisons between ISS stages and test indicators

Stage		N	RBC ($\bar{x}$)	HGB ($\bar{x}$)	Cre ($\bar{x}$)	Urea ($\bar{x}$)	ALT ($\bar{x}$)	CysC ($\bar{x}$)	β_2MG ($\bar{x}$)	BMPC ($\bar{x}$)	IgG ($\bar{x}$)
I		21	3.4467	101.6	103.67	5.9895	17.57	1.1818	2.1925	28.05	20.0822
II		41	3.11	88.02	105.46	6.7226	17.67	1.3027	4.2903	31.9	41.1766
III		48	2.779	80.85	197.98	9.9973	15.17	2.2161	8.4318	42.77	24.9037
	H		5.416	6.517	8.702	6.538	4.888	9.063	13.204	8.233	10.717
III/I	p		0.002*	0.000*	0.000*	0.000*	0.089	0.000*	0.000*	0.169	0.096
II/I	p		0.232	0.025	0.253	0.328	0.246	0.188	0.001*	0.536	0.232
III/II	p		0.315	0.126	0.002*	0.002*	0.009*	0.000*	0.001*	0.046*	0.004*

Note: *represents $p < 0.05$, which is statistically significant.

and treatment regimen were independent prognostic factors for PFS ($P < 0.05$) (Table 5). The Kaplan-Meier survival analysis of predictors for OS, including treatment protocol and ISS stage, is shown in Fig. 1A and B.

3.4. Univariate and multivariate analysis of measurement data

Table 6 shows the analysis of measurement data using univariate and multivariate analysis models. The

Table 5
Univariate and multivariate Cox proportional hazards regression models of count data for 3-year OS and PFS in MM patients

Factors	*N*	3-year OS mean (month)	3-year PFS mean (month)	Univariate		Multivariate					
				p-value for OS	*p*-value for PFS	OS			PFS		
						HR	95.0% CI	*p*-value	HR	95.0% CI	*p*-value
Gender				0.538	0.904						
Male	58	26.93	29.58								
Female	52	26.73	27.12								
Comorbidities				0.888	0.994						
Yes	76	27.15	29.54								
No	34	26.11	27.04								
Treatment protocol				0.015*	0.073*	0.458	0.251–0.833	0.011*	0.370	0.143–0.962	0.041*
Bortezomib included	45	30.24	34.40								
Bortezomib not included	65	24.47	25.46								
D-S stage				0.138	0.281						
I	19	24.31	25.99								
II	21	30.85	32.02								
III	70	26.31	28.61								
ISS stage				0.020*	0.109			0.044*			
I	21	23.76	26.27			0.465	0.216–1.001	0.05			
II	41	30.61	30.59			1.054	0.522–2.127	0.883			
III	48	24.91	25.03								
Immunoglobulins				< 0.001*	0.024*			0.001*			0.033*
Light chain	19	30.47	31.62			1.770	0.742–4.224	0.198	0.856	0.230–3.194	0.817
IgA	24	25.25	29.05			1.425	0.640–3.176	0.386	1.347	0.467–3.885	0.582
IgG	62	27.67	26.748			11.062	3.252–37.628	< 0.001*	30.226	2.660–343.470	0.006
Others	5	10.20	5.00								

HR = Hazard Ratio. $^*p < 0.05$.

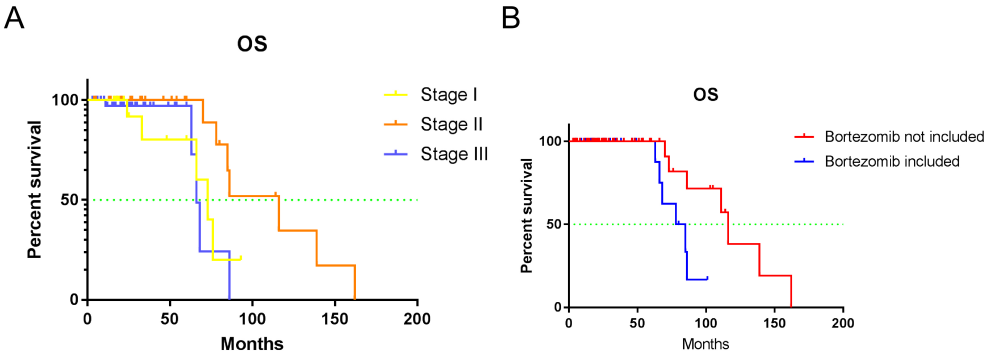

Fig. 1. Kaplan-Meier survival analysis of predictors for OS, including treatment protocol and ISS stage. Kaplan-Meier survival analysis for A) ISS stage ($P < 0.05$) and B) treatment protocol ($P < 0.05$). OS: overall survival; ISS: international staging system.

results from the univariate analysis showed that RPR, MONO, IgG, and LDH had significant effects on the three-year OS of patients with MM, while only β2-MG had significant effects on the three-year PFS ($P < 0.05$). Cox multivariate analysis showed that RPR and MONO were independent prognostic factors for OS ($P < 0.05$).

3.5. Establishment of the prognostic model

RPR and MONO showed statistical significance in multiple factors and were used to establish the prognostic model performed using R (v3.6.3); the results showed that MONO = 0.023 and RPR = −1.982. The risk score for each patient was calculated according to the following formula: Risk score = 0.023*MONO +

Table 6
Univariate and multivariate Cox proportional hazards regression models of measurement data for 3-year OS and PFS in MM patients

Factors	Univariate				Multivariate		
	OS		PFS		OS		
	HR	p-value	HR	p-value	HR	95.0% CI	p-value
Age (year)	1.019	0.155	1.001	0.931			
BMPC (%)	0.995	0.488	0.994	0.555			
WBC (*10^9/L)	1.043	0.284	1.093	0.234			
NEU (*10^9/L)	1.036	0.447	1.136	0.117			
LYM (*10^9/L)	1.083	0.178	0.896	0.620			
MONO (*10^9/L)	1.097	0.090	1.038	0.646	1.105	0.983–1.242	0.045*
RBC (*10^{12}/L)	1.070	0.668	1.000	0.999			
HGB (g/L)	1.006	0.265	0.999	0.911			
RDW (%)	0.968	0.477	1.010	0.870			
PLT (*10^9/L)	1.001	0.534	0.999	0.749			
NLR	1.003	0.947	1.072	0.181			
PLR	1.002	0.244	1.003	0.185			
RPR	0.02	0.003*	0.099	0.127	0.037	0.002–0.887	0.042*
IgG (g/L)	0.987	0.019*	0.994	0.366			
IgA (g/L)	1.006	0.254	1.003	0.785			
Ca (mmol/L)	1.445	0.249	1.766	0.170			
Cre (umol/L)	1.001	0.548	1.001	0.501			
UREA (mmol/L)	1.003	0.909	1.015	0.711			
ALP (U/L)	1.003	0.125	1.001	0.707			
ALT (U/L)	0.990	0.417	0.976	0.223			
LDH (U/L)	1.004	0.043*	1.003	0.184			
CysC (mg/L)	1.145	0.271	1.151	0.352			
β_2-MG (mg/L)	1.045	0.156	1.089	0.043*			

HR = Hazard Ratio. *$p < 0.05$.

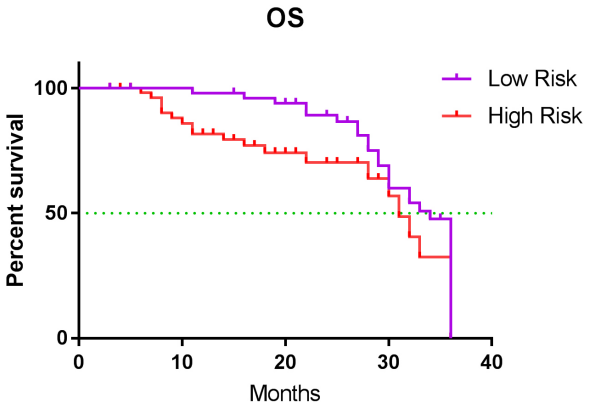

Fig. 2. Kaplan-Meier survival analysis of the high- and low-risk groups.

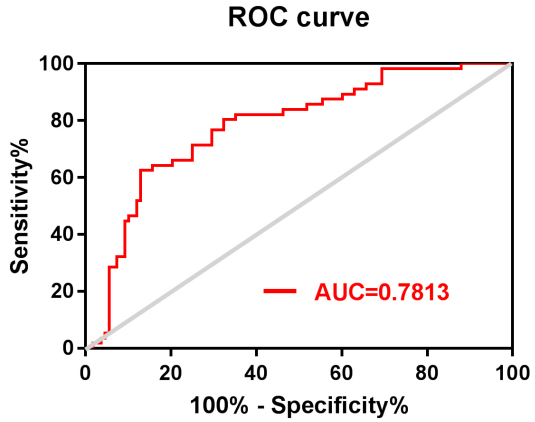

Fig. 3. ROC curve of the risk score of three-year mortality of patients with MM. ROC: receiver operating characteristic; MM: multiple myeloma.

(−1.982)*RPR. According to the median score, patients with MM were divided into high- and low-risk groups (Table 7). The OS of the two groups was significantly different ($P < 0.05$) (Table 8). The Kaplan-Meier survival analysis is shown in Fig. 2. The receiver operating characteristic (ROC) curve was constructed according to the risk score to predict the three-year mortality of patients with MM, with an area under the curve (AUC) of 0.781 (Fig. 3).

4. Discussion

MM is a malignant disease characterized by clonal proliferation of plasma cells, which tends to occur in the elderly population. In our study, the onset age of MM ranged from 31 to 84 years, with a median of 61 and a concentration between 50 and 70 years (68 cases, 61.8%), which is similar to the results of a retrospective

Table 7
Risk score for MM patients

Patient	RPR	MONO (*10^9/L)	Risk score	Risk
1	0.06	1.25	−0.085	High
2	0.08	0.203	−0.148	High
3	0.07	0.525	−0.136	High
4	0.09	0.352	−0.170	High
5	0.06	0.263	−0.115	High
6	0.05	0.421	−0.088	High
7	0.06	0.323	−0.116	High
8	0.11	0.57	−0.208	Low
9	0.10	0.36	−0.183	Low
10	0.07	0.46	−0.129	High
11	0.18	0.19	−0.352	Low
12	0.06	0.62	−0.109	High
13	0.11	0.24	−0.220	Low
14	0.13	0.18	−0.259	Low
15	0.22	0.43	−0.433	Low
16	0.06	0.5	−0.098	High
17	0.05	0.43	−0.085	High
18	0.04	0.36	−0.077	High
19	0.08	0.26	−0.153	High
20	0.10	0.67	−0.181	Low
21	0.06	0.87	−0.101	High
22	0.10	0.68	−0.176	High
23	0.09	0.65	−0.169	High
24	0.06	0.59	−0.098	High
25	0.30	0.35	−0.587	Low
26	0.07	0.78	−0.121	High
27	0.31	0.61	−0.595	Low
28	0.11	0.52	−0.209	Low
29	0.46	0.3	−0.900	Low
30	0.31	0.39	−0.608	Low
31	0.10	0.72	−0.182	Low
32	0.05	0.39	−0.083	High
33	0.11	12.9	0.088	High
34	0.13	0.21	−0.245	Low
35	0.05	1.48	−0.069	High
36	0.10	0.56	−0.192	Low
37	0.08	0.56	−0.155	High
38	0.21	7.0	−0.256	Low
39	0.09	0.38	−0.174	High
40	0.09	0.40	−0.169	High
41	0.12	0.35	−0.233	Low
42	0.13	0.44	−0.241	Low
43	0.22	0.19	−0.438	Low
44	0.06	0.24	−0.123	High
45	0.19	0.36	−0.364	Low
46	0.05	0.29	−0.091	High
47	0.09	0.34	−0.164	High
48	0.08	0.37	−0.142	High
49	0.05	0.36	−0.084	High
50	0.09	0.27	−0.175	High
51	0.11	0.24	−0.204	Low
52	0.06	0.40	−0.111	High
53	0.08	0.67	−0.140	High
54	0.10	0.60	−0.179	Low
55	0.07	0.69	−0.113	High
56	0.07	0.45	−0.128	High
57	0.06	2.40	−0.068	High
58	0.06	0.75	−0.094	High
59	0.19	0.28	−0.360	Low
60	0.07	0.44	−0.135	High
61	0.04	0.56	−0.070	High
62	0.48	0.33	−0.951	Low
63	0.04	1.27	−0.043	High
64	0.46	0.16	−0.905	Low
65	0.22	0.26	−0.427	Low
66	0.07	0.04	−0.130	High
67	0.05	0.58	−0.079	High
68	0.09	0.39	−0.173	High
69	0.07	0.38	−0.129	High
70	0.03	0.53	−0.050	High
71	0.44	0.65	−0.856	Low
72	0.12	0.28	−0.241	Low
73	0.04	7.1	0.083	High
74	0.05	0.69	−0.082	High
75	0.06	0.45	−0.100	High
76	0.10	0.84	−0.181	Low
77	0.11	0.79	−0.190	Low
78	0.06	0.94	−0.095	High
79	0.17	0.23	−0.340	Low
80	0.06	0.47	−0.110	High
81	0.05	0.44	−0.087	High
82	0.36	0.14	−0.714	Low
83	0.08	0.84	−0.141	High
84	0.07	1.61	−0.105	High
85	0.07	0.29	−0.133	High
86	0.05	0.23	−0.086	High
87	0.19	0.2	−0.366	Low
88	0.05	0.41	−0.099	High
89	0.10	0.39	−0.196	Low
90	0.14	0.42	−0.264	Low
91	0.13	0.44	−0.246	Low
92	0.07	0.7	−0.114	High
93	0.18	0.08	−0.347	Low
94	0.10	0.43	−0.196	Low
95	0.19	0.47	−0.358	Low
96	0.44	0.36	−0.862	Low
97	0.36	0.43	−0.709	Low
98	0.59	0.25	−1.154	Low
99	0.70	0.52	−1.375	Low
100	0.51	0.32	−1.010	Low
101	0.42	0.68	−0.826	Low
102	0.56	0.51	−1.094	Low
103	0.74	0.51	−1.456	Low
104	0.34	0.32	−0.669	Low
105	0.44	0.43	−0.859	Low
106	0.24	0.45	−0.474	Low
107	0.40	0.2	−0.795	Low
108	0.41	0.32	−0.807	Low
109	0.48	0.22	−0.947	Low
110	0.48	0.17	−0.943	Low

Table 8
Comparison of risk scores in MM patients

Risk score	N	Three-year OS mean (month)	p-value
High risk	56	24.911	0.015*
Low risk	54	28.833	

*$p < 0.05$.

study in China [2]. The prognosis of patients with MM is markedly heterogeneous, and early clinical manifestations lack specificity. In our study, the primary symptoms of MM were bone pain (77.3%), followed by anemia (10.9%), and other symptoms, such as bleeding and foam urine, accounting for a small proportion, which is consistent with results from a previous study [15]. Bone pain is often regarded as the primary symptom of MM because it is difficult for patients to ignore and cannot be missed during diagnosis and treatment.

In clinical practice, the most common current prognostic assessment systems are D-S and ISS staging [16,17]. In our study, 17.3%, 19.1%, and 63.6% of the patients were grouped into stages I, II, and III, respectively, according to D-S staging, suggesting that most of the patients with MM were in the mid or late stages of the disease when they were first diagnosed. Univariate and multivariate analyses showed that there was no significant difference in the prognosis between patients grouped according to the D-S stages. In terms of ISS groups, 19.1%, 37.3%, and 43.6% of the patients were classified as stage I, II, and III, respectively. Univariate analysis showed that the different ISS stages were closely related to the OS of patients with MM, suggesting that ISS staging may guide the prognosis of patients with MM better than D-S staging.

In our study, we found that BMPC%, CysC, and β2-MG levels in patients at stage III of the D-S and ISS were significantly higher than those in patients at stage I, which indicated that levels of CysC and β2-MG were positively correlated with the D-S and ISS stages. As sensitive indicators of glomerular filtration rate, β2-MG and CysC also directly reflect the tumor burden in patients with MM [18]. Serum LDH is an important enzyme in glucose metabolism, which is widely distributed in human tissues and is mainly used for the diagnosis of myocardial infarction and malignant tumors. Serum LDH levels are very low under normal circumstances, but in tumors and cell metabolism disorders, especially glucose metabolism disorders, the levels of serum LDH are increased [19,20]. The results of our univariate analysis showed that LDH was a prognostic factor influencing the three-year OS of patients with MM ($P < 0.05$).

With the development of immunosuppressants and protease inhibitors, bortezomib has become the first-line therapy for MM. As a PI, it can reduce the level of cytokines by reversibly binding to the 26S proteasome, thereby reducing its activity, which blocks the degradation pathways of various intracellular proteins, induces apoptosis of tumor cells, and inhibits the growth and proliferation of tumor cells [21,22]. In our study, the treatment regimens were divided into bortezomib and non-bortezomib groups. Univariate and multivariate analyses showed that the treatment regimens, including bortezomib, had better three-year OS and PFS ($P < 0.05$), suggesting that bortezomib can improve the prognosis of patients with MM to a certain extent.

Anemia is a major clinical manifestation in patients with MM. The infiltration of myeloma cells can directly destroy red blood cells, and the production of erythropoietin decreases owing to the renal involvement of MM [23]. In our study, RBC and HGB in patients were negatively correlated with their D-S and ISS stages, suggesting that the RBC and HGB not only can be used as screening indicators for anemia in patients with MM but also have guiding value for clinical staging and curative effects. In the pathogenesis of MM, tumor-associated macrophages derived from circulating monocytes can induce angiogenesis as well as inhibit growth factors and cytokines involved in the immune response, thereby promoting tumor progression [24]. Both univariate and multivariate analyses showed that the MONO had a significant impact on OS in patients with MM. In addition, the MONO was positively correlated with the ISS stage in between-group comparisons; therefore, the MONO was higher in patients at D-S or ISS stage III than in those with stage I. Therefore, monocytes could serve as a factor in the prognosis of MM. The RPR is often considered to have a close relationship with inflammation and tumors. According to some studies, the RPR reflects the inflammatory state of the tumor-related microenvironment and plays an important role in the proliferation and metastasis of tumor cells [25,26]. Our results of the univariate analysis showed that the RPR had a significant effect on the OS and PFS of patients with MM, while the results of the multivariate analysis showed that the RPR only had a significant effect on OS. The establishment of a prognostic model based on the MONO and RPR can be used to monitor the tumor microenvironment of MM and infer tumor progression. These two non-genetic indicators are easier to measure and are not affected by nutritional status. Most importantly, they have good prognostic values. In our prognostic model, the mean OS of the high-risk group was 24.911 months, and the mean OS time of the low-risk group was 28.833 months. The risk of death was significantly higher in the high-risk group than in the low-risk group ($P < 0.05$). The ROC curve based on the risk score of the model showed an AUC > 0.5, indicating that the model had a moderate diagnostic value and a certain reference value for the prognosis of MM patients.

Our study shares some common limitations with similar retrospective studies, including selection bias in patients and treatment due to the study design, as well as a potentially small sample size due to being conducted at a single center. We acknowledge these limitations, which should be considered when interpreting our findings. However, our study also had important strengths. We used a conceptual model to optimize our investigative approach, allowing us to identify pertinent and modifiable factors of MM that can be targeted to prevent adverse clinical outcomes. Our findings suggest that non-genetic predictors are modifiable risk factors for MM and can be targeted in future treatment strategies to improve patient outcomes. In addition, we proposed a prognostic model based on the RPR and MONO as risk factors that have important prognostic value for MM patients. The model can divide patients into low-and high-risk groups based on different prognostic indexes, enabling clinicians to tailor treatment plans accordingly. This approach can improve patient outcomes and reduce treatment-related toxicities. Risk stratification is crucial for MM patients, and our proposed prognostic model has significant clinical implications. It highlights the importance of individualized treatment plans based on the risk factors of patients, which can improve patient outcomes and reduce the risk of adverse events. Nevertheless, further research is needed to validate our proposed model in larger, multicenter cohorts and identify additional prognostic indicators to further refine risk stratification. We also recognize the need for exploring the identification of modifiable risk factors for MM in greater detail to identify new therapeutic targets.

5. Conclusion

In conclusion, the levels of CysC and β2-MG were positively correlated with the D-S and ISS stages, while RBC and HGB levels were negatively correlated. The prognosis of patients with MM can be influenced by many factors, among which, bortezomib, RPR, and MONO can significantly affect the prognosis of MM patients. Therefore, RPR and MONO should be studied further to validate their value as prognostic factors to guide patient risk stratification. Policies and treatments targeting these factors are important for the treatment of patients with MM.

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Declaration of conflicting interests

The authors declare no conflict of interest.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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