

Combined immune score predicts the prognosis of newly diagnosed multiple myeloma patients in the bortezomib-based therapy era

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Abstract

To investigate the effect of a combined immune score including the lymphocyte-to-monocyte ratio (LMR) and uninvolved immunoglobulin (u-Ig) levels on the prognosis of newly diagnosed multiple myeloma (NDMM) patients treated with bortezomib.

Clinical data of 201 NDMM patients were retrospectively analyzed. Patients with $LMR \geq 3.6$ and $LMR < 3.6$ were scored 0 and 1, respectively. Patients with preserved u-Ig levels, suppression of 1 u-Ig, and suppression of at least 2 u-Igs were scored 0, 1, and 2, respectively. The immune score, established from these individual scores, was used to separate patients into good (0–1 points), intermediate (2 points), and poor (3 points) risk groups. The baseline data, objective remission rate (ORR), whether receive maintenance treatment regularly and overall survival of patients before treatment were analyzed.

The ORR of the good-risk group was significantly higher than that of the intermediate-risk group (75.6% vs 57.7%, $P = .044$) and the poor-risk group (75.6% vs 48.2%, $P = .007$). The multivariate analysis results showed that age ≥ 65 years, International Staging System stage III, platelet count $\leq 100 \times 10^9/L$, lactate dehydrogenase (LDH) $> 250 U/L$, serum calcium $> 2.75 mmol/L$, no receipt of regular maintenance treatment, $LMR < 3.6$, suppressed u-Igs = 1, suppressed u-Igs ≥ 2 , intermediate-risk group and poor-risk group were independent predictors of poor overall survival.

In the bortezomib era, the LMR, u-Ig levels, and the immune score play an important role in the prognosis of NDMM patients. Among them, the immune score showed the strongest prognostic value, and it could be a beneficial supplement for the early identification of high-risk patients.

Abbreviations: ASCT = autologous stem cell transplantation, BAFF = B cell-activating factor belonging to the TNF family, BCMA = B cell maturation antigen, CR = complete remission, DS = Durie-Salmon, ISS = International Staging System, LDH = serum lactate dehydrogenase, LMR = absolute lymphocyte count/absolute monocyte count, M protein = monoclonal protein, MM = multiple myeloma, MR = minimal remission, NDMM = newly diagnosed multiple myeloma, ORR = objective remission rate, OS = overall survival, PD = disease progression, PFS = progression free survival, PLT = platelet, PR = partial remission, sCR = strict complete remission, SD = stable disease, u-Igs = uninvolved immunoglobulins, VGPR = very good partial remission.

Keywords: bortezomib, immune, lymphocyte-to-monocyte ratio, multiple myeloma, uninvolved immunoglobulins

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The authors have no conflicts of interest to disclose.

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

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1. Introduction

Multiple myeloma (MM) is a malignant plasma cell tumor. There is significant heterogeneity in its clinical features, treatment response, and prognosis, and the overall survival (OS) of patients varies from < 1 year to > 10 years.^[1] Studies have confirmed that the disease progression of MM is related to immune dysfunction.^[2] Immunotherapy is promising in the treatment of MM, and it is urgent to find immune-related biomarkers that can stratify patients according to immune status.^[3] Immune-related indicators in the peripheral blood are easy to obtain, and their predictive value in the prognosis of MM patients has become a hot research topic.

Most MM patients have “immune paralysis,” which means that they have high levels of monoclonal immunoglobulins and low levels of uninvolved immunoglobulins (u-Igs) in the serum and/or urine. Studies have demonstrated that patients with u-Ig suppression have poorer disease control rates and lower long-term survival rates than patients with preserved u-Igs.^[4] Furthermore, recent studies have shown that the absolute lymphocyte count, the absolute monocyte count, and their ratio absolute lymphocyte count / absolute monocyte count (LMR) can reflect the immune state of the organism and play an important role in predicting the prognosis of various blood tumors and solid

tumors.^[5,6] For MM patients, a low LMR at initial diagnosis has been proven to be associated with a poor prognosis. Some scholars have proposed integrating the LMR with more detailed data, which may produce a meaningful prognostic system.^[7] In view of these ideas, Sweiss et al.^[8] proposed an immune score based on the LMR and immunoglobulin levels for the first time and confirmed that this score can predict the treatment-free survival rate of MM patients after autologous stem cell transplantation (ASCT).

In recent years, proteasome inhibitors have been widely used in clinical practice. It is important to determine whether the immune-related indicators assessed at initial diagnosis still have prognostic significance.^[7] We hypothesized that the LMR and u-Ig levels could be used to evaluate the survival time of newly diagnosed MM (NDMM) patients, further established an immune grouping based on these 2 levels, analyzed their correlation with various prognostic factors and OS, and discussed their prognostic value for MM patients.

2. Materials and methods

2.1. Patients

This study assessed clinical data from NDMM patients ($n=251$) seen at Henan Provincial People's Hospital and Henan Cancer Hospital between October 2012 and February 2019. All patients were diagnosed according to the 2014 International Myeloma Working Group diagnostic criteria. The exclusion criteria were as follows: biclonal or nonsecretory MM, any treatment for plasma cell disease before diagnosis, plasma cell leukemia, monoclonal gammopathy of undetermined significance, septicemia, severe acquired immunodeficiency disease, and other malignant tumors or critical organ dysfunction and complications. During the treatment process, 7 patients received ASCT, and 2 patients received CAR-T cell treatment, which were excluded due to the small sample size. A total of 242 patients were identified, of which 41 were lost to follow-up and 201 were included in the analysis.

This study was approved by the Ethics Committee of Henan Provincial People's Hospital and conforms to the requirements of the Declaration of Helsinki. This was a retrospective study, so informed consent was not required, and all patients were not identified.

2.2. Observation index and definition

All patients received one of the following bortezomib-containing chemotherapy regimens: the BD regimen (bortezomib 1.3 mg/m^2 , d 1, 4, 8, 11; dexamethasone 20 mg, d 1–2, 4–5, 8–9, 11–12), the BDT regimen (bortezomib 1.3 mg/m^2 , d 1, 4, 8, 11; thalidomide 100–200 mg/night; dexamethasone 20 mg, d 1–2, 4–5, 8–9, 11–12), or the BCD regimen (bortezomib 1.3 mg/m^2 , d 1, 4, 8, 11; cyclophosphamide 500 mg/m^2 , d 1, 8; dexamethasone 20 mg, d 1–2, 4–5, 8–9, 11–12). The dose was adjusted according to patient tolerance. Efficacy evaluation was performed after 4 courses: strict complete remission (sCR), complete remission (CR), very good partial remission (VGPR), partial remission (PR), minimal remission (MR), stable disease (SD), and disease progression (PD). Objective remission rate (ORR) = sCR rate + CR rate + VGPR rate + PR rate. After 6 to 8 cycles of chemotherapy, maintenance therapy was administered (lenalidomide + dexamethasone, thalidomide + dexamethasone or

bortezomib alone). Follow-up was performed to record whether the patient was on regular maintenance treatment.

The peripheral blood hemoglobin level, lymphocyte count, mononuclear cell count, platelet (PLT) count, serum calcium level, serum creatinine level, serum lactate dehydrogenase (LDH) level, serum albumin level, $\beta 2$ microglobulin level, and M protein type were recorded 1 week before the first chemotherapy cycle. Immunoglobulin levels were measured by nephelometry. The LMR was calculated using the peripheral blood white blood cell counts.

The cut-off value for the LMR was obtained from a previous study included 372 patients, $\text{LMR} \geq 3.6$ yielded the greatest differential to segregate cohorts.^[9] Patients were divided into low LMR ($\text{LMR} < 3.6$) and high LMR ($\text{LMR} \geq 3.6$) groups. Normal immunoglobulins were defined as uninvolved immunoglobulins (u-Igs). u-Ig suppression was defined as u-Ig levels falling below the lower limit of the normal range, that is, $\text{IgG} < 630\text{ mg/dL}$, $\text{IgA} < 74\text{ mg/dL}$, and $\text{IgM} < 40\text{ mg/dL}$. According to these criteria, patients were divided into the preserved u-Ig group, the suppressed u-Igs = 1 group, and the suppressed u-Igs ≥ 2 group.

2.3. Follow-up

All patients were followed up using electronic medical records or telephone calls. Follow-up was performed to record whether the patient was on regular maintenance treatment and the OS of the patients. The OS was defined as the time from diagnosis to death or to the last follow-up.

2.4. Statistical analysis

SPSS v.25 (IBM Corp., Armonk, NY) was used for the statistical analysis. The percentage of cases was used to represent the classified count data. Comparisons between groups were made by the chi-square test. The Kaplan–Meier method was used for survival analysis and univariate analysis of prognostic factors. The median follow-up time was calculated by the reversed Kaplan–Meier method. Multivariate analysis of prognostic factors was performed using the Cox regression model. Differences with $P < .05$ were considered statistically significant.

3. Results

3.1. General clinical data

Among the 201 patients included in the study, there were 108 men (53.7%) and 93 women (46.3%). The average age was $60 (59.87 \pm 10.21)$ years old, and there were 63 patients (31.3%) ≥ 65 years old. In terms of M protein type, there were 78 cases (38.8%) of IgG myeloma, 64 cases (31.8%) of IgA myeloma, 40 cases (19.9%) of light-chain myeloma, and 19 cases (9.5%) of IgD myeloma. In terms of International Staging System (ISS) stage, there were 22 patients (10.9%) in stage I, 64 patients (31.8%) in stage II, and 115 patients (57.2%) in stage III. There were 82 patients (40.8%) in the low LMR group, and 119 patients (59.2%) in the high LMR group. For u-Ig groups, 25 patients (12.4%) were divided into the preserved u-Ig group, 37 patients (18.4%) were divided into the suppressed u-Igs = 1 group, and 139 patients (69.2%) were divided into the suppressed u-Igs ≥ 2 group. A total of 121 patients (60.2%) received regular maintenance treatment (Table 1).

Table 1	
Patients' baseline characteristics.	
Characteristic	All patients (n=201)
Sex	
Male	108 (53.7%)
Female	93 (46.3%)
Age, yrs	
<65	138 (68.7%)
≥65	63 (31.3%)
ISS stage	
I	22 (10.9%)
II	64 (31.8%)
III	115 (57.3%)
M protein	
IgG	78 (38.8%)
IgA	64 (31.8%)
IgD	19 (9.5%)
Light chain	40 (19.9%)
Hemoglobin, g/L	
≥100	54 (26.9%)
<100	147 (73.1%)
Platelet count, 10 ⁹ /L	
>100	158 (78.6%)
≤100	43 (21.4%)
β2 microglobulin, mg/L	
<5.5	88 (43.8%)
≥5.5	113 (56.2%)
LDH, U/L	
≤250	166 (82.6%)
>250	35 (17.4%)
Creatinine, μmol/L	
≤177	134 (66.7%)
>177	67 (33.3%)
Serum calcium, mmol/L	
≤2.75	162 (80.6%)
>2.75	39 (19.4%)
Plasma cells, %	
≤40%	107 (53.2%)
>40	94 (46.8%)
Maintenance treatment	
Yes	121 (60.2%)
No	80 (39.8%)
LMR	
≥3.6	119 (59.2%)
<3.6	82 (40.8%)
Suppressed u-Ig	
0	25 (12.4%)
1	37 (18.4%)
≥2	139 (69.2%)

ISS=International Staging System, LDH=lactic dehydrogenase, LMR=lymphocyte-to-monocyte ratio, M protein=monoclonal protein, plasma cells=bone marrow plasma cells, u-Ig=uninvolved immunoglobulins.

3.2. Analysis of prognostic factors for OS

The last follow-up time in this study was July 2020, with a median follow-up of 49 months (range 17–87 months). The median OS in this study was 36.7 (32.6–40.8) months. The univariate analysis showed that age ($P<.001$), ISS stage ($P=.001$), PLTs ($P<.001$), β2 microglobulin ($P<.001$), LDH ($P<.001$), creatinine ($P<.001$), serum calcium ($P<.001$), receipt of maintenance treatment ($P<.001$), LMR ($P<.001$), and u-Ig suppression ($P<.001$) were prognostic factors for OS in MM patients. Incorporating these factors into the multivariate analysis showed that age ≥65 years old (hazard ratio [HR] 1.709,

95% confidence interval [95% CI] 1.160–2.518, $P=.007$), ISS stage III (HR 2.208, 95% CI 1.175–4.148, $P=.014$), PLT count $\leq 100 \times 10^9/L$ (HR 2.326, 95% CI 1.512–3.577, $P<.001$), LDH >250 U/L (HR 2.014, 95% CI 1.288–3.148, $P=.002$), calcium >2.75 mmol/L (HR 1.664, 95% CI 1.069–2.589, $P=.024$), no receipt of regular maintenance treatment (HR 2.496, 95% CI 1.729–3.602, $P<.001$), LMR <3.6 (HR 1.908, 95% CI 1.324–2.751, $P=.001$), suppressed u-Igs=1 (HR 2.181, 95% CI 1.075–4.423, $P=.031$), and suppressed u-Igs=2 (HR 3.257, 95% CI 1.757–6.035, $P<.001$) were independently associated with poor OS (Table 2).

3.3. Establishment of the combined immune score

The above results showed that low LMR and suppression of ≥ 1 u-Igs were independent negative prognostic factors (Figs. 1 and 2). We applied K Sweiss method^[8] with slight modifications. According to the HR of the variable in the multivariate analysis, the coefficient with the smallest absolute value was taken as the baseline, the coefficient of other variables was divided by the coefficient, and the resulting value was rounded to the nearest whole number to obtain the risk score of the variable. We scored the LMR ≥ 3.6 group as 0 points and the LMR <3.6 group as 1 point. Patients with preserved u-Ig scored 0, those with suppression of 1 u-Ig scored 1, and those with suppression of at least 2 u-Igs scored 2. According to the combined score, the following immune groups were established: the good-risk group (0–1 points), the intermediate-risk group (2 points), and the poor-risk group (3 points).

3.4. Comparison of baseline characteristics between different immune groups

There were no significant differences in sex, age, ISS stage, M protein type, hemoglobin, PLTs, β2 microglobulin, LDH, bone marrow plasma cell ratio, or whether maintenance treatment was received between the immune groups. However, the numbers of patients with creatinine >177 μmol/L ($\chi^2=6.623$, $P=.036$), and patients with serum calcium >2.75 mmol/L ($\chi^2=7.029$, $P=.030$) in the poor-risk group were significantly higher than those in the intermediate-risk group and good risk group (Table 3).

3.5. Multivariate analysis of factors including the immune group

Incorporating immune grouping into the multivariate analysis showed that the intermediate-risk group (HR 2.207, 95% CI 1.327–3.668, $P=.002$), poor-risk group (HR 4.754, 95% CI 2.724–8.296, $P<.001$), age ≥65 years old (HR 1.785, 95% CI 1.211–2.632, $P=.003$), ISS stage III (HR 2.191, 95% CI 1.166–4.115, $P=.015$), PLT count $\leq 100 \times 10^9/L$ (HR 2.105, 95% CI 1.375–3.222, $P=.001$), LDH >250 U/L (HR 2.036, 95% CI 1.305–3.179, $P=.002$), calcium >2.75 mmol/L (HR 1.668, 95% CI 1.081–2.574, $P=.021$), and no receipt of regular maintenance treatment (HR 2.471, 95% CI 1.718–3.554, $P<.001$) were independent negative prognostic factors for OS (Table 4).

3.6. Comparison of curative effects between different immune groups

To evaluate the efficacy after 4 courses of chemotherapy, the chi-square test was used to compare the relationship between the

Table 2
Univariate and multivariate analysis of factors associated with OS.

Characteristic	Univariate analysis		Multivariate analysis		
	Median OS, mo	P value	HR	95% CI	P value
Sex					
Male	28	.270			
Female	35				
Age, yrs					
<65	37	<.001	1		.007
≥65	18		1.709	1.160–2.518	
ISS stage					
I	54	.001	1		.048
II	38		1.831	0.960–3.493	.066
III	25		2.208	1.175–4.148	.014
Hemoglobin, g/L					
≥100	40	.093			
<100	29				
Platelet count, 10 ⁹ /L					
>100	38	<.001	1		<.001
≤100	15		2.326	1.512–3.577	
β2 microglobulin, mg/L					
<5.5	40	<.001			
≥5.5	25				
LDH, U/L					
≤250	37	<.001	1		.002
>250	17		2.014	1.288–3.148	
Creatinine, μmol/L					
≤177	38	<.001	1		.490
>177	19		1.169	0.750–1.821	
Serum calcium, mmol/L					
≤2.75	37	<.001	1		.024
>2.75	16		1.664	1.069–2.589	
Plasma cells, %					
≤40	38	.071			
>40	28				
Maintenance treatment					
Yes	43	<.001	1		<.001
No	19		2.496	1.729–3.602	
LMR					
≥3.6	38	<.001	1		.001
<3.6	20		1.908	1.324–2.751	
Suppressed u-IgG					
0	55	<.001	1		<.001
1	40		2.181	1.075–4.423	.031
≥2	25		3.257	1.757–6.035	<.001

ISS=International Staging System, LDH=lactic dehydrogenase, LMR=lymphocyte-to-monocyte ratio, OS=overall survival, plasma cells=bone marrow plasma cells, u-IgG=uninvolved immunoglobulins.

index and the curative effect. The results showed that the ORR in all patients was 58.7%, and the ORR of the good-risk group was significantly higher than that of the intermediate-risk group (75.6% vs 57.7%, $P=.044$) and that of the poor-risk group (75.6% vs 48.2%, $P=.007$).

3.7. Comparison of OS between different immune groups

Kaplan–Meier analysis showed that there were significant differences in OS among different immune groups. The OS of the poor-risk group was significantly shorter than the OS of the intermediate-risk group and that of the good-risk group (20.34 [15.98–24.70] months vs 35.12 [30.60–39.63] months, $P<.001$; 20.34 [15.98–24.70] months vs 55.27 [46.68–63.86] months, $P<.001$) (Fig. 3).

In various subgroups with a poor prognosis (age ≥65 years old, ISS stage III, PLT count $\leq 100 \times 10^9/L$, LDH >250 U/L, calcium

>2.75 mmol/L, and no receipt of regular maintenance treatment), the immune score could still refine the risk stratification. Further Kaplan–Meier analysis in these subgroups showed that the OS of the poor-risk group was significantly shorter than the OS of the intermediate-risk group and that of the good-risk group:

- Among patients ≥65 years of age (11.38 [7.31–15.45] months vs 28.15 [20.64–35.66] months, $P=.001$; 11.38 [7.31–15.45] months vs 41.08 [25.94–56.21] months, $P=.001$) (Fig. 4A).
- Among patients with ISS stage III (17.46 [11.32–23.60] months vs 29.76 [24.29–35.24] months, $P<.001$; 17.46 [11.32–23.60] months vs 44.43 [34.28–54.57] months, $P<.001$) (Fig. 4B).
- Among patients with PLT counts $\leq 100 \times 10^9/L$ (10.17 [5.32–15.02] months vs 20.47 [13.64–27.30] months, $P<.001$;

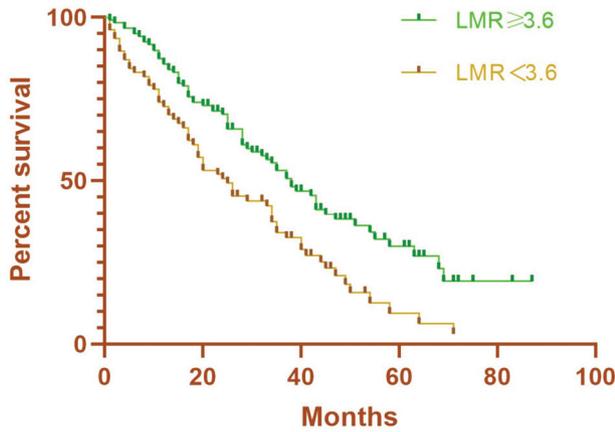


Figure 1. Comparison of OS between different LMR groups ($P < .001$). LMR = absolute lymphocyte count/absolute monocyte count, OS = overall survival.

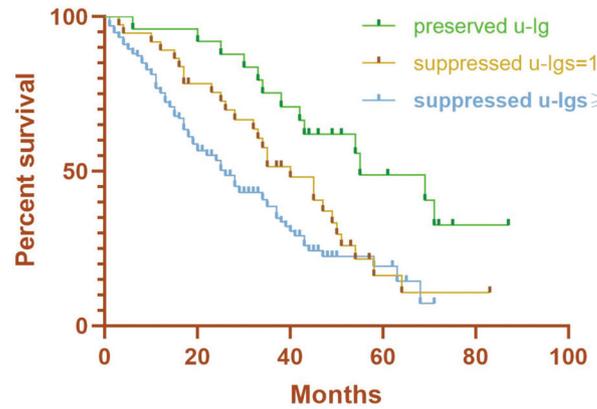


Figure 2. Comparison of OS between different u-Ig groups ($P < .001$). OS = overall survival; u-Igs = uninvolvement immunoglobulins.

Table 3

Comparison of baseline characteristics between different immune groups.

Characteristic	Immune group			χ^2	P value
	Good risk	Intermediate risk	Poor risk		
Sex					
Male	24 (58.5%)	49 (47.1%)	35 (62.5%)	3.944	.139
Female	17 (41.5%)	55 (52.9%)	21 (37.5%)		
Age, yrs					
<65	31 (75.6%)	72 (69.2%)	35 (62.5%)	1.923	.382
≥65	10 (24.4%)	32 (30.8%)	21 (37.5%)		
ISS stage					
I	7 (17.1%)	9 (8.7%)	6 (10.7%)	2.731	.604
II	14 (34.1%)	32 (30.8%)	18 (32.1%)		
III	20 (48.8%)	63 (60.6%)	32 (57.1%)		
M protein					
IgG	16 (39.0%)	35 (33.7%)	27 (48.2%)	5.728	.454
IgA	12 (29.3%)	40 (38.5%)	12 (21.4%)		
IgD	4 (9.8%)	10 (9.6%)	5 (8.9%)		
Light chain	9 (22.0%)	19 (18.3%)	12 (21.4%)		
Hemoglobin, g/L					
≥100	13 (31.7%)	24 (23.1%)	17 (30.4%)	1.596	.450
<100	28 (68.3%)	80 (76.9%)	39 (69.6%)		
Platelet count, $10^9/L$					
>100	33 (80.5%)	87 (83.7%)	38 (67.9%)	5.510	.064
≤100	8 (19.5%)	17 (16.3%)	18 (32.1%)		
$\beta 2$ microglobulin, mg/L					
<5.5	21 (51.2%)	42 (40.4%)	25 (44.6%)	1.426	.490
≥5.5	20 (48.8%)	62 (59.6%)	31 (55.4%)		
LDH, U/L					
≤250	38 (92.7%)	86 (82.7%)	42 (75.0%)	5.148	.076
>250	3 (7.3%)	18 (17.3%)	14 (25.0%)		
Creatinine, $\mu\text{mol/L}$					
≤177	34 (82.9%)	67 (64.4%)	33 (58.9%)	6.623	.036
>177	7 (17.1%)	37 (35.6%)	23 (41.1%)		
Serum calcium, mmol/L					
≤2.75	37 (90.2%)	86 (82.7%)	39 (59.6%)	7.029	.030
>2.75	4 (9.8%)	18 (17.3%)	17 (30.4%)		
Plasma cells, %					
≤40%	24 (60.0%)	55 (53.9%)	28 (51.9%)	0.654	.721
>40%	16 (40.0%)	47 (46.1%)	26 (48.1%)		

ISS = International Staging System, LDH = lactic dehydrogenase, M protein = monoclonal protein, plasma cells = bone marrow plasma cells.

Table 4
Multivariate analysis of factors affecting OS, including the immune group.

Characteristic	Multivariate analysis		
	HR	95% CI	P value
Age, yrs			
<65	1		.003
≥65	1.785	1.211–2.632	
ISS stage			
I	1		.051
II	1.790	0.942–3.404	.076
III	2.191	1.166–4.115	.015
Platelet count, 10 ⁹ /L			
>100	1		.001
≤100	2.105	1.375–3.222	
LDH, U/L			
≤250	1		.002
>250	2.036	1.305–3.179	
Creatinine, μmol/L			
≤177	1		.540
>177	1.147	0.739–1.780	
Serum calcium, mmol/L			
≤2.75	1		.021
>2.75	1.668	1.081–2.574	
Maintenance treatment			
Yes	1		<.001
No	2.471	1.718–3.554	
Immune group			
Good risk	1		<.001
Intermediate risk	2.041	1.231–3.382	.006
Poor risk	4.287	2.454–7.489	<.001

ISS=International Staging System, LDH=lactic dehydrogenase.

- 10.17 [5.32–15.02] months vs 36.50 [26.34–46.66] months, $P < .001$) (Fig. 4C).
- (d) Among patients with LDH > 250 U/L (11.57 [5.56–17.59] months vs 22.55 [15.23–29.87] months, $P = .009$; 11.57 [5.56–17.59] months vs 38.50 [29.68–47.32] months, $P = .009$) (Fig. 4D).
- (e) Among patients with calcium > 2.75 mmol/L (12.32 [5.94–18.71] months vs 28.67 [17.82–39.51] months, $P = .008$; 12.32 [5.94–18.71] months vs 44.00 [26.65–61.35] months, $P = .008$) (Fig. 4E).

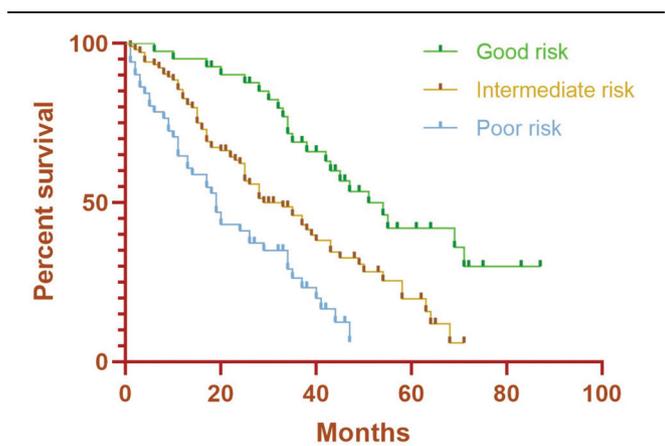


Figure 3. Comparison of OS between different immune groups ($P < .001$). OS=overall survival.

- (f) Among patients not receiving regular maintenance treatment (10.93 [6.07–15.78] months vs 25.51 [19.86–31.17] months, $P < .001$; 10.93 [6.07–15.78] months vs 45.44 [31.03–59.84] months, $P < .001$) (Fig. 4F).

4. Discussion

The prognostic factors of MM are complex, and new indicators and stages are frequently proposed. Durie/Salmon (DS) staging and ISS staging have been the most commonly used methods for prognostic assessment in the past. However, the number of osteolytic lesions in the DS staging assessment depends on the subjectivity of the observer, and the adverse effect of renal damage on prognosis can be improved by proteasome inhibitor treatment^[10]; thus, the predictive efficacy of the DS staging system is gradually declining. The ISS staging system is simpler and more reliable, but it is not accurate enough to judge the prognosis with only 2 indicators. Our results confirm the value of ISS stage III but indicate that ISS stages I and II are not independent prognostic factors when other variables are considered. This is likely due to the presence of β2 microglobulin, which is associated with renal insufficiency and does not accurately reflect tumor load. In recent years, molecular genetic abnormalities have been used to better determine prognosis. However, studies have shown that bortezomib-based treatment can improve the negative impact of specific cytogenetic abnormalities on prognosis.^[11] Moreover, due to the limitations of equipment and economic conditions, genetic detection is still not widely used in low/middle-income countries. Therefore, simple and easily available indicators are still needed to assist in the assessment of patient prognosis.

Immune dysfunction is an important characteristic of MM that can lead to infection and can promote tumor cell growth and increase drug resistance. MM cells inhibit the immune response in the bone marrow microenvironment by inducing functional defects in T cells and B cells, upregulating the inhibition pathway, producing excessive amounts of proinflammatory cytokines, and promoting the proliferation and immune escape of malignant plasma cells.^[12] Lymphocytes are an important cell component of the immune response of the body, and a low lymphocyte count reflects immunosuppression, which has been proven to be associated with a poor prognosis in patients with a variety of tumors.^[13] Monocytes also play an important role in the tumor microenvironment. TNF and IL-1 secreted by monocytes can increase the tumor burden. In addition, monocyte-derived cells, including macrophages, marrow-derived suppressor cells, and dendritic cells, participate in the construction of an immunosuppressive microenvironment conducive to the survival of MM cells.^[14] Tumor-associated macrophages, also derived from circulating monocytes, play an important role in the proliferation of MM cells and protect them from chemotherapy-induced apoptosis.^[15] The LMR represents the relative strength of the host immune system (mean lymphocytes) and tumor-induced immune dysfunction (mean monocytes, reflecting tumor-associated macrophages) and can be used to assess the extent of host immunosuppression. Several studies in recent years have shown that the LMR has an important impact on the survival of MM patients. The progression-free survival (PFS) and OS times in the low LMR group were shorter than those in the high LMR group among NDMM patients treated with bortezomib-based therapies.^[7,9] Our study showed that a low LMR was associated with a poor prognosis and had predictive value independent of

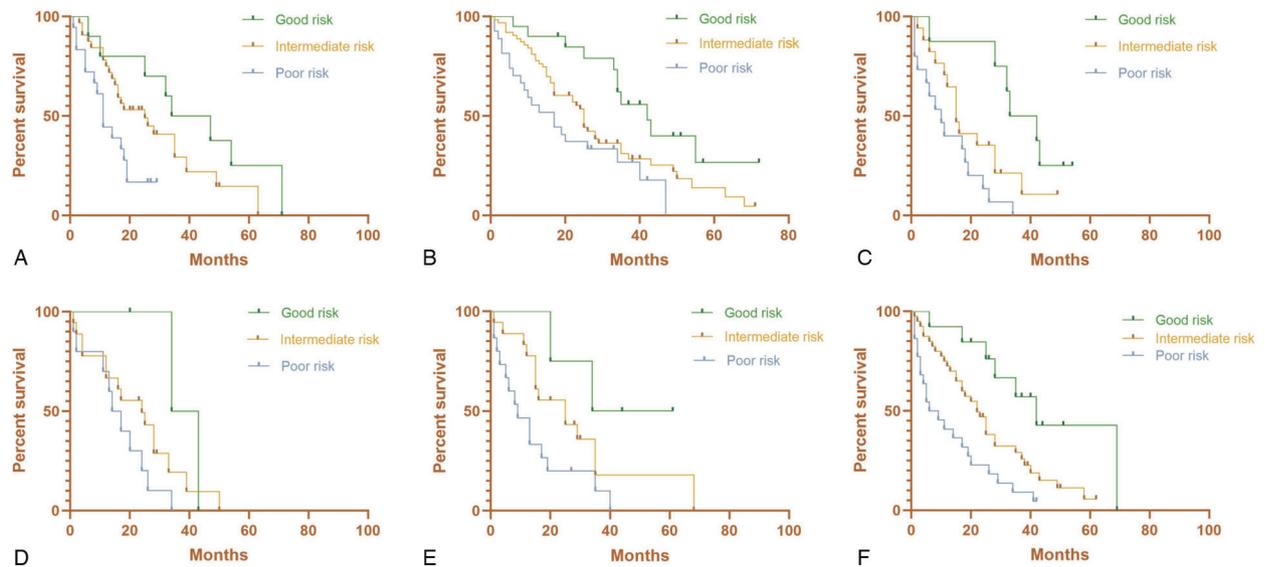


Figure 4. (A) Comparison of OS between different immune groups among patients with age > 65 years old ($P = .001$). (B) Comparison of OS between different immune groups among patients with ISS III ($P < .001$). (C) Comparison of OS between different immune groups among patients with PLT count $\leq 100 \times 10^9/L$ ($P < .001$). (D) Comparison of OS between different immune groups among patients with LDH > 250 U/L ($P = .009$). (E) Comparison of OS between different immune groups among patients with calcium > 2.75 mmol/L ($P = .008$). (F) Comparison of OS between different immune groups among patients who did not receive regular maintenance treatment ($P < .001$). ISS=International Staging System, LDH=serum lactate dehydrogenase, OS=overall survival, PLT=platelet.

other common prognostic factors in clinical practice. This demonstrates that bortezomib fails to reverse the negative prognostic effects of immunosuppression, as represented by a low LMR.

Suppression of u-Ig is associated with a reduced rate of immunoglobulin synthesis in peripheral blood B lymphocytes, which is a common feature in MM patients.^[16] Suppression of u-Ig increases the risk of progression to MM in patients with monoclonal gammopathy of undetermined significance and smoldering MM.^[17,18] This phenomenon also has important clinical significance in NDMM patients. Gao et al^[4] analyzed the clinical data of 147 MM patients receiving bortezomib-based treatment and found that after 6 courses of treatment, compared with patients with suppressed u-Ig at initial diagnosis, patients with preserved u-Ig were more likely to achieve at least VGPR or CR and had a longer PFS. A large retrospective study also found that approximately 85% to 90% of NDMM patients had u-Ig suppression, with IgG-type and IgA-type suppression in the majority of patients. Further study found that u-Ig suppression at initial diagnosis was independently associated with short-term disease control and a low survival rate.^[19] In our study, u-Ig suppression occurred in 87.6% of patients before treatment, which was similar to the results reported in the literature. In the u-Ig suppression groups, IgG myeloma and IgA myeloma also accounted for the majority of cases (in the suppressed u-Ig=1 group: IgG 29.7%, IgA 43.3%; in the suppressed u-Ig suppression=2 group: IgG 42.5%, IgA 30.2%), but the difference was not statistically significant ($P = .071$). A possible reason is that the sample size was not enough, or there could be more IgD patients in China. The mechanism of u-Ig suppression remains unclear. A possible explanation is that bone marrow stromal cells attached to MM cells secrete lower levels of supportive factors (IL-7) and higher levels of suppressor factors (TGF- β 1 and MIP-1 β) that affect pre-B cell survival,^[20] which

may explain the inhibition of B lymphocytes in the bone marrow of MM patients. Some scholars have also proposed that the molecular mechanism of u-Ig suppression is mediated by the interaction between B cell maturation antigen (BCMA) and its ligands B cell-activating factor belonging to the TNF family (BAFF) and a proliferation-inducing ligand, which stimulate the differentiation of B cells and the production of antibodies.^[21] Studies have confirmed that BCMA has a high level of dissolution in the serum of MM patients.^[22] Soluble BCMA isolates circulating BAFF and thus prevents BAFF from inducing signals that stimulate B cell development, leading to a decrease in polyclonal antibody levels in MM patients.^[23]

Bortezomib plays an immunomodulatory role as well as a cytotoxic role. In our study, both low LMR and u-Ig suppression were independent negative prognostic factors. We combined the 2 factors into a single score and established immune groups, and found that patients in the poor-risk group were more likely to have creatinine > 177 $\mu\text{mol/L}$ and serum calcium > 2.75 mmol/L. Analysis of the curative effect showed that the ORR of the good-risk group was significantly higher than that of the intermediate-risk group and that of the poor-risk group. Survival analysis showed that the OS of patients in the good-risk group, intermediate-risk group, and poor-risk group decreased successively, and the differences were statistically significant. Compared with the LMR or u-Ig level alone, the immune group classification was the strongest prognostic factor (HR 4.754, 95% CI 2.724–8.296, $P < .001$). This result suggests that even under the immunomodulatory effect of bortezomib, the immune score can still be a strong independent predictor of the prognosis of NDMM patients. Further analysis showed that the immune group was still a prognostic factor in patient subgroups with a poor prognosis (advanced age, ISS stage III, low PLT count, high LDH, hypercalcemia, and no receipt of regular maintenance treatment) and could further refine the risk stratification and

assist in prognosis assessment. And for these higher-risk patients, earlier and more effective treatments should be explored.

In conclusion, in the bortezomib-based chemotherapy era, the immune score can be used as a simple and reliable prognostic indicator for MM patients in low/middle-income countries and can be a beneficial supplement for the early identification of high-risk patients. At the same time, it can also help predict early treatment response. In view of the significance of immune group indicators in the tumor microenvironment, immune group classification may guide the future use of some immunotherapies or monocyte-blocking drugs and the early identification of patients who may benefit from these treatments. On the other hand, there are still some limitations to this study. The examination results during treatment were insufficient to evaluate the relationship between immune indicators and PFS. Due to patient economic and compliance reasons, the molecular genetic data were insufficient and were not included in the statistical analysis; thus, the influence of cytogenetics cannot be excluded. Moreover, our study was conducted in a small cohort, and more clinical studies are needed to prove our hypothesis. The immune response and tumor biology are so complex that a few biomarkers are not enough to accurately predict the prognosis of patients. In the future, the integration of multiple immune response parameters, such as immunophenotypes, protein expression, and genomic features, will be important for early risk identification and for guiding immunotherapy use.

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Author contributions

All authors participated in project approval, data collation and analysis, and manuscript revision. In addition, all authors approved the final manuscript.

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