ORIGINAL RESEARCH

Evaluation of the UK Myeloma Research Alliance Risk Profile in Chinese Patients with Newly Diagnosed Multiple Myeloma without Autologous Stem Cell Transplantation

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Purpose: Recently, the British Myeloma Research Alliance put forward a Myeloma Risk Profile (MRP) for the first time to stratify the prognosis risk of non-transplanted patients with multiple myeloma. However, only limited studies have evaluated the applicability of this model in the Chinese population. This study aimed to estimate the prognostic value of MRP in newly diagnosed multiple myeloma patients without autologous stem cell transplantation in China.

Patients and Methods: Patients with multiple myeloma in Wuxi People's Hospital from January 1, 2007, to June 30, 2018 were evaluated based on the MRP score, and the relationship between the clinical outcome of patients with MM and the score was analyzed retrospectively.

Results: First, significant differences were observed in the overall survival (OS) (P<0.05) and progression-free survival (PFS) (P<0.05) between the low-, middle-, and high-risk groups. Second, in the bortezomib treatment subgroup and complex chromosome karyotype subgroup, OS and PFS were significantly shorter in the high-risk group than in the low-risk group (P<0.05). Third, the depth of remission still showed prognostic significance in the high-risk MRP group.

Conclusion: MRP is also applicable in Chinese patients with newly diagnosed MM who did not undergo transplantation, as it is simple and cost effective; hence, it is worth popularizing.

Keywords: multiple myeloma, myeloma risk profile, bortezomib, complex chromosome karyotype, prognosis

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Introduction

GA scoring, R-ISS staging, and mSMART staging based on host and tumor factors, respectively, provide beneficial clinical value for estimating the prognosis of multiple myeloma.[1–3] However, mSMART staging mainly focuses on cytogenetics, while GA scoring pays attention to the host factors and is rather complicated. In clinical practice, these staging systems have certain limitations. In 2019, the British Myeloma Research Alliance put forward a Myeloma Risk Profile (MRP) for the first time to stratify the prognosis risk of non-transplant patients with multiple myeloma.[4] This prognosis model combines host factors and tumor load burden, which is simple and feasible. MRP shows a good prognosis in transplant-ineligible

MM patients. However, only a few relevant studies have reported the applicability of this model in the real-world setting, especially in the Chinese population. In this study, the prognosis of 242 newly diagnosed non-transplanted MM patients was analyzed retrospectively to determine whether this scoring model is beneficial for predicting the clinical outcomes.

Patients and Methods
Patients

A total of 242 patients with newly diagnosed multiple myeloma in the Department of Hematology of Wuxi People's Hospital from January 1, 2007 to June 30, 2018 were included in this study. Among them, 82 patients used traditional non-bortezomib-based (such as COMP, VAD, etc.) chemotherapy schemes due to personal and disease factors, while 160 used a protocol containing bortezomib (such as PAD, VTD, etc.). All patients were administered with thalidomide (75–150 mg) as maintenance treatment during the intermission period of chemotherapy. None of the MM patients included in the study underwent hemato-poietic stem cell transplantation due to personal and dis-ease factors. This research was carried out under agreements from the patients along with a written informed consent. It was approved by the ethics committee of the Affiliated Wuxi People's Hospital, Nanjing Medical University, and conducted in accordance with the Declaration of Helsinki.

Follow-Up Parameters

The following parameters were evaluated: age, sex, WHO PS score, C-reactive protein (CRP), serum albumin (ALB), serum β2-microglobulin (β2-GM), ISS stage, lactate dehy-drogenase (LDH), hemoglobin (Hb), serum creatinine (Cr), serum Ca2+, chromosomal karyotype, tumor cell ratio of bone marrow smear, treatment plan, remission depth after chemotherapy, comorbidities, total survival time (OS), and progression-free survival (PFS); the depth of remission after chemotherapy refers to the IMWG con-sensus criteria in 2016.[5]

MRP Score

The MRP score is calculated by combining the WHO PS score, ISS stage, age, and CRP, and is obtained using the following formula: (PS score − 2) × 0.199+ (age − 74.4) × 0.0165 + (ISS stage − 2) * 0.212+ [log (CRP+1) − 2.08] × 0.0315. Individuals with a score of < −0.256 were

classified as the low-risk group, while those with a score of −0.256 ≤ score ≤ −0.0283 and > −0.0283 were classified as the medium-risk group and high-risk group respectively.[6]

Statistical Methods

For the continuous data, the Kruskal–Wallis nonparametric test was used to compare the differences among the groups. For the counting data, the chi-square test was used to compare the differences among groups, while the Fisher's exact test was used for correction of multiple comparisons when needed. The Kaplan-Meier method was used for survival analysis, while the Log rank test was used for the analysis of survival difference. A P value of <0.05 was considered significant.

Results
Prognosis of the Overall Population

Based on the MRP score, 242 patients were divided into three groups: low-risk, medium-risk, and high-risk groups. As shown in Table 1, except for Cr level, other factors such as sex, Hb, LDH, serum Ca2+ level, tumor cell ratio, chemotherapy reaction, comorbidities, chromosome karyo-type, and treatment plan were not significantly different.

As shown in Figure 1, the median OS of the low-risk, medium-risk, and high-risk groups were 48, 37, and 29 months, respectively; meanwhile, the median PFS of the low-risk, medium-risk, and high-risk groups were 31, 25, and 20 months, respectively. There were significant differ-ences in OS (P=0.003) and PFS (P=0.007) among the three groups, and the OS and PFS in the medium-risk and high-risk groups were shorter.

Prognosis of Different MRP Stratifications in the Treatment Subgroup Receiving Bortezomib

The 160 patients who received bortezomib regimen were divided into low-risk, medium-risk, and high-risk groups. As shown in Table 2, the serum Cr level in the high-risk group increased significantly, while the other baseline characteristics such as sex, Hb, and so on were not sig-nificantly different.

As shown in Figure 2A and B, the median OS of the low-risk, medium-risk, and high-risk groups were 48, 30, and 32 months, respectively, while their median PFS were 31, 24, and 22 months, respectively. The median OS

Table 1 Clinical Characteristics of Overall Patients of Different MRP Stratification

Clinical Parameters	Low Risk (n=80)	Medium Risk (n=61)	High Risk (n=101)	P value
Age	61 (44-75)	65 (47–83)	68 (40–84)	
≥65	22 (27.5%)	32 (52.5%)	69 (68.3%)	
<65	58 (72.5%)	29 (47.5%)	32(31.7%)	
PS score				
0	8 (10.0%)	2 (3.3%)	1 (0.9%)	
1	17 (21.3%)	10 (16.4%)	4 (4.0%)	
2	34 (42.5%)	22 (36.1%)	27 (26.7%)	
3	20 (25.0%)	24 (39.3%)	60 (59.4%)	
4	1 (1.3%)	3 (4.9%)	9 (8.9%)	
CRP (mg/L)	1 (0–24)	5 (0.5–87)	12 (0.8–160)	
ISS Staging				
I	13 (16.3%)	1 (1.6%)	0 (0.0%)	
II	45 (56.3%)	22 (36.1%)	28 (27.7%)	
III	22 (27.5%)	38 (62.3%)	73 (72.3%)	
Gender				0.388
Male	41 (51.2%)	34 (55.7%)	62 (61.4%)	
Female	39 (48.8%)	27 (44.3%)	39 (38.6%)	
Hemoglobin (g/L)	89.5 (43–148)	82 (37–149)	83 (40–163)	0.081
Platelet (*10^9/L)	134 (41–324)	141 (16–301)	146 (26–345)	0.692
Lymphocyte count (*10^9/L)	1.213 (0.16–3.95)	1.24 (0.21–3.73)	1.31 (0.3–3.308)	0.729
Lactate Dehydrogenase (U/L)	132.5 (64–602)	142 (66–1036)	128 (44–1221)	0.295
Creatinine (umol/L)	82.1 (30.3–778.3)	91.8 (38.5–755.1)	113.3 (39.5–1176.7)	**0.001**
Serum Ca^{2+} (mmol/L)	2.2 (1.84–4.79)	2.2 (1.39–3.72)	2.22 (1.38–5.35)	0.135
Tumor Cell Ratio (%)	27 (1.5–92)	33 (2–95)	33 (1–95)	0.289
Response				0.108
CR/VGPR	51 (63.7%)	30 (49.2%)	50 (49.5%)	
<VGPR	29 (36.3%)	31 (50.8%)	51 (50.5%%)	
Hypertension				0.521
NO	52 (65.0%)	34 (55.7%)	60 (59.4%)	
YES	28 (35%)	27 (44.3%)	41 (40.6%)	
Diabetes				0.130
NO	68 (85.0%)	57 (93.4%)	83 (82.2%)	
YES	12 (15%)	4 (6.6%)	18 (17.8%)	
Treatment Options				0.291
With bortezomib	58 (72.5%)	40 (65.5%)	62 (61.4%)	
Without bortezomib	22 (27.5%)	21 (34.4%)	39 (38.6%)	
Karyotype				0.273
Complex karyotype	19 (27.9%)	11 (23.4%)	11 (16.4%)	
Noncomplex karyotype	49 (72.1%)	36 (76.6%)	56 (83.6%)	

Note: Bold values indicate significance.
Abbreviations: CR, complete response; VGPR, very good partial response.
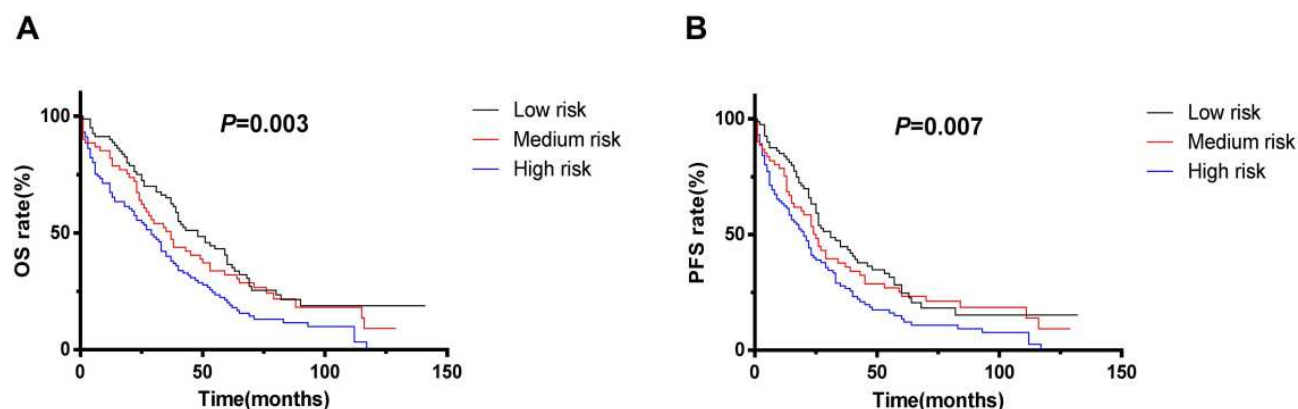
Figure 1 (**A**) The medium OS of overall 242 patients in MRP low-risk, medium-risk and high-risk groups were 48 months, 37 months and 29 months respectively. (**B**) The medium PFS of overall 242 patients in MRP low-risk, medium-risk and high-risk groups were 31 months, 25 months and 20 months respectively.
Abbreviations: OS, the overall survival time; PFS, the progression-free survival time.

(P=0.019) and median PFS (P=0.013) were significantly different among the three groups.

Meanwhile, patients treated with bortezomib were divided into three groups by ISS stage as we found that there was a certain correlation between the MRP scoring system and ISS staging (Spearman correlation coefficient, r=0.408, P<0.05). The median OS of patients in the ISS I, ISS II, and ISS III groups were 65, 43, and 33 months, respectively; their median PFS were 57 months, 26 months, and 25 months, respectively. However, no significant difference was observed in the OS and PFS (P>0.05) in the ISS I, ISS II, and ISS III groups (Figure 2C and D).

MRP-Stratified Prognosis of Patients with Complex Chromosome Karyotype Abnormality

Of the 242 newly diagnosed non-transplanted MM patients, 182 underwent chromosome tests (including G+R banding, FISH) due to personal preference and presence of economic conditions. Among the 182 patients, 41 had complex chromosomal karyotype abnormalities (According to G+R banding and FISH detection, three or more kinds of chromosomal abnormalities were defined as complex karyotype, and those if they did not reach the standard of complex karyotype or no abnormalities were defined as others.) as shown on the results of G+R banding and FISH. In this subgroup, no significant differences were observed in other baseline characteristics except serum Cr level and serum Ca2+ level in the MRP low-risk group and middle-high-risk group (Table 3). The median OS and PFS of the MRP-stratified low-risk group were 31 months and

25 months, respectively, while those of the MRP-stratified medium-to-high-risk groups were 12 months and 8 months, respectively. The OS (P=0.004) and PFS (P=0.007) were significantly shorter in the middle-to-high-risk group than in the low-risk group (Figure 3).

Prognostic Significance of Remission Depth in Different MRP Groups

The baseline characteristics of MRP patients in the low-risk group and medium-risk group, patients with VGPR and above after treatment, and patients without VGPR are shown in Tables 4 and 5, and no significant difference was found except Ca2+ in Table 4. After treatment, no significant difference was observed in the OS and PFS (P>0.05) in different remission degrees (VGPR and above or below VGPR) between the two groups (Figure 4A–D). In the MRP high-risk group, after treatment, the median OS and PFS of patients with VGPR and above were 44 months and 32 months, respectively, while those of patients with remission degree below VGPR were 12 months and 8 months, respectively. There were significant differences in the OS (P<0.0001) and PFS (P<0.0001) between the two groups with different remission degrees (Figure 4E and F), although the tumor cell ratio was higher in those with remission degree below VGPR (Table 6).

Discussion

MM remains an incurable disease. In recent years, many studies have focused on the risk assessment of MM. Based on host factors, the GA score proposed by IMWG in 2015 was an additive scoring system (range: 0–5) based on age,

Table 2 Clinical Characteristics of Patients Treated with Bortezomib of Different MRP Stratification

Clinical Parameters	Low Risk (n=58)	Medium Risk (n=40)	High Risk (n=62)	P value
Age	59.5 (44–75)	65 (47–83)	68 (40–84)	
≥65	13 (22.4%)	23 (57.5%)	43 (69.4%)	
<65	45 (77.6%)	17 (42.5%)	19 (30.6%)	
PS score				
0	6 (10.3%)	2 (5.0%)	1 (1.6%)	
1	16 (27.6%))	8 (20.0%)	3 (4.8%)	
2	20 (34.5%)	11 (27.5%)	18 (29.1%)	
3	15 (25.9%)	16 (40.0%)	33 (53.2%)	
4	1 (1.7%)	3 (7.5%)	7 (11.3%)	
CRP (mg/L)	1 (0–24)	4 (0.5–87)	16 (0.8–160)	
ISS Staging				
I	11 (19.0%)	0 (0.0%)	0 (0.0%)	
II	28 (48.3%)	16 (40.0%)	16 (25.8%)	
III	19 (32.7%)	24 (60.0%)	46 (74.2%)	
Gender				0.129
Male	26 (44.8%)	23 (57.5%)	39 (62.9%)	
Female	32 (55.2%)	17 (42.5%)	23 (37.1%)	
Hemoglobin (g/L)	92.5 (43–148)	80.5 (37–146)	82.5 (45–163)	0.068
Platelet (*10^9/L)	135 (41–324)	133 (33–301)	144 (42–329)	0.701
Lymphocyte count (*10^9/L)	1.24 (0.160–3.950)	1.126 (0.210–3.450)	1.27 (0.340–3.070)	0.687
Lactate Dehydrogenase (U/L)	129 (64–602)	142 (87–1036)	127.5 (50–1102)	0.438
Creatinine (umol/L)	82.75 (30.3–778.3)	92.6 (38.5–527.5)	103.9 (43.3–1176.7)	**0.022**
Serum Ca^{2+} (mmol/L)	2.2 (1.92–2.98)	2.2 (1.39–3.68)	2.285 (1.38–5.35)	0.100
Tumor Cell Ratio (%)	28 (1.5–92.0)	33 (2.0–86.0)	31 (5.0–89.0)	0.279
Response				0.085
CR/VGPR	40 (69.0%)	19 (47.5%)	34 (54.8%)	
<VGPR	18 (31.0%)	21 (52.5%)	28 (45.2%)	
Hypertension				0.935
NO	34 (58.6%)	22 (55.0%)	35 (56.5%)	
YES	24 (41.4%)	18 (45.0%)	27 (43.5%)	
Diabetes				0.341
NO	50 (86.2%)	37 (92.5%)	51 (82.3%)	
YES	8 (13.8%)	3 (7.5%)	11 (17.7%)	
Karyotype				0.998
Complex karyotype	10 (21.3%)	6 (20.7%)	9 (20.9%)	
Noncomplex karyotype	37 (78.7%)	23 (79.3%)	34 (79.1%)	

Note: Bold values indicate significance.

comorbidities, and cognitive and physical conditions and was developed to identify three groups: fit, intermediate fitness, and frail. It was used to predict mortality and the risk of toxicity in older myeloma patients.[1] Compared with the IMWG scoring strategy, Murillo et al developed the Fried weakness scoring model, which excluded age and found that the Fried model was significantly associated with risk of death and a better predictor of survival.[7]
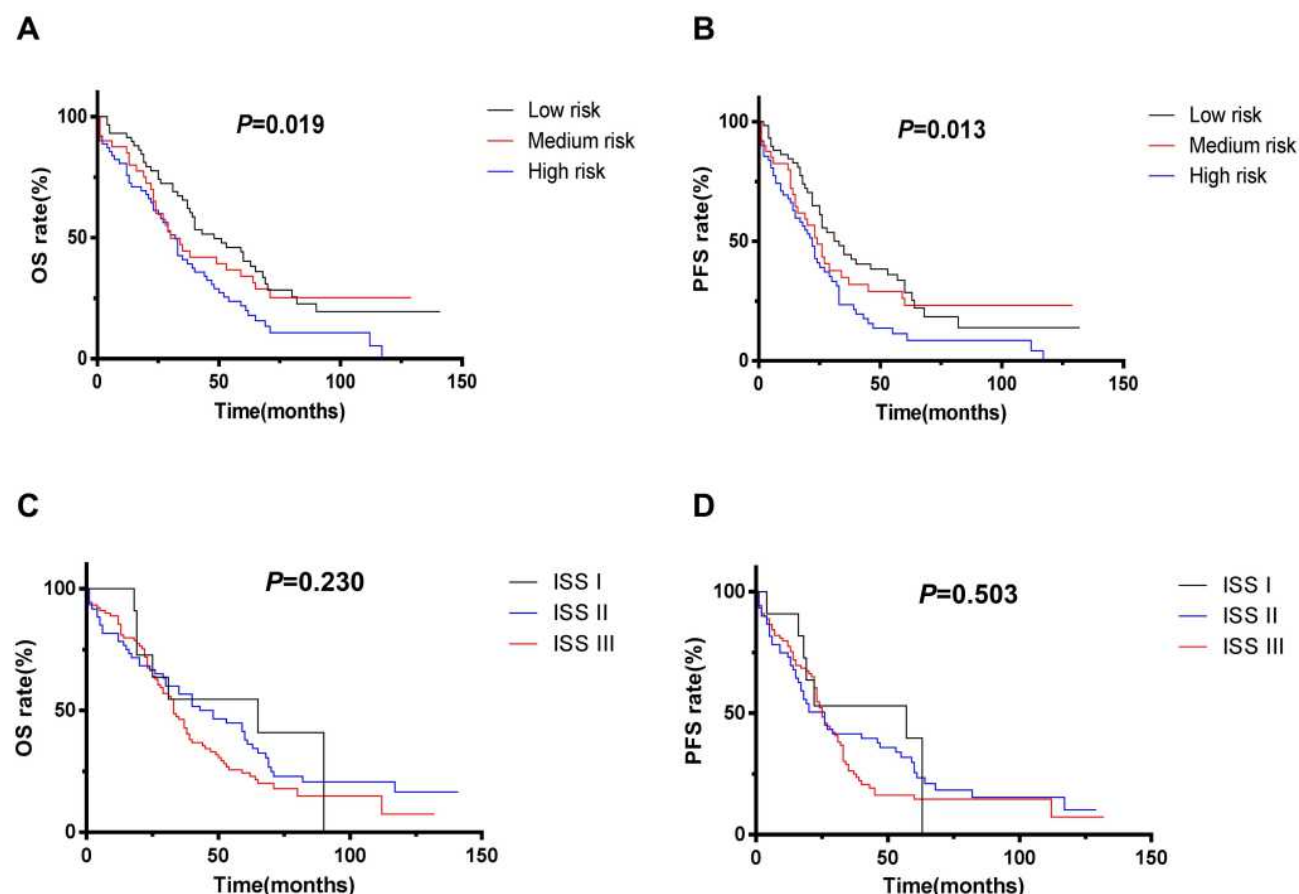
Figure 2 (**A**) The medium OS of patients treated with bortezomib in MRP low-risk, medium-risk and high-risk groups were 48 months, 30 months and 32 months respectively; (**B**) the median PFS of patients treated with bortezomib in MRP low-risk, medium-risk and high-risk groups were 31 months, 24 months and 22 months respectively; (**C**) the medium OS of patients treated with bortezomib in ISS I, ISS II and ISS III groups were 65 months, 43 months and 33 months respectively; (**D**) the median PFS of patients treated with bortezomib in ISS I, ISS II and ISS III groups were 57 months, 26 months and 25 months respectively.

Facon et al have also put forward a different prognosis assessment model for MM; they used an ECOG PS-containing frailty scale as a predictive measure of clinical outcomes in patients with transplant-ineligible NDMM and documented that frail patients have worse PFS and OS compared with nonfrail patients.[8] On the contrary, based on tumor factors, Kim et al and Liu et al successively put forward the MPI and IPSI risk assessment models, and confirmed their survival relevance with MM.[9,10] The MPI comprised NLR, PLT, and CRP, while the IPSI consisted of RDW, NLR, and PLT. Both models played an important role in the prognosis of NDMM in the bortezomib-based chemotherapy era and identified that inflammatory factors affect the prognosis of MM.[9,10] Of course, ISS and RISS are still more commonly used in the clinical setting. In 2019, the British Myeloma Research Alliance first proposed the prognosis evaluation model of MRP composed of physical fitness score, age, ISS stage, and CRP using the data from the NCRI Myeloma XI study

[NCRI-XI, n=1852] and the MRC Myeloma IX study [MRC-IX, n=520]. They found that the median OS values of the low-risk, medium-risk, and high-risk MRP groups in the NCRI-XI and MRC IX studies were 60, 44, and 25 months and 49, 34, and 20 months respectively; meanwhile, their median PFS values were 20, 17, 12, months and 15, 13, and 9 months, respectively. These results indicated that MRP could predict early mortality and had a good prognostic value in older MM patients who are not suitable for transplantation.[4] They found that MRP has a prognostic value in patients with different treatment schemes and in those with high-risk genetic abnormalities defined base on the MRP criteria,[4] which may indirectly reflect that MRP had better prognostic value than RISS.

However, few studies have verified whether MRP can be implemented in the real-world setting. Redder et al made a retrospective analysis and found that the median OS of the low-risk MRP group was 55 months, while those of the high-risk and median-risk groups were 13.9 months and 35.9

Table 3 Clinical Characteristics of Patients with Complex Chromosomal Karyotype of Different MRP Stratification

Clinical Parameters	Low Risk (n=19)	Medium and High Risk (n=22)	P value
Age ≥65 <65	62 (44–75) 5 (26.3%) 14 (73.7%)	62.5 (48–76) 9 (40.9%) 13 (59.1%)	

PS score
  0
  1
  2
  3
  4
	2 (1.5%)
	4 (21.1%)
	10 (52.6%)
	3 (15.8%)
	0 (0.0%)
		0 (0.0%)
		2 (9.1%)
		9 (40.9%)
		10 (45.5%)
		1 (4.5%)	

CRP (mg/L)	1 (0–5)	12 (2–160)	

ISS Staging
  I
  II
  III
	2 (1.5%)
	11 (57.9%)
	6 (31.6%)
		0 (0.0%)
		4 (18.2%)
		18 (81.8%)	

Gender
  Male
  Female
	13 (68.4%)
	6 (31.6%)
		12 (54.5%)
		10 (45.5%)
			0.522

Hemoglobin (g/L)	83 (61–122)	80 (45–131)	0.601
Platelet (*10^9/L)	106 (43–201)	115 (64–238)	0.464
Lymphocyte count (*10^9/L)	1.143 (0.160–2.982)	1.39 (0.470–3.734)	0.657
Lactate Dehydrogenase (U/L)	138 (73–356)	187.5 (50–1221)	0.166
Creatinine (umol/L)	80.4 (43.9–363.7)	191.55 (53.8–755.1)	**0.010**
Serum Ca^{2+} (mmol/L)	2.14 (1.84–4.79)	2.345 (1.8–4.05)	**0.019**
Tumor Cell Ratio (%)	33 (1.5–81.5)	35 (4.5–95)	0.548
Response CR/VGPR <VGPR	12 (63.2%) 7 (36.8%)	12 (54.5%) 10 (45.5%)	0.577

Hypertension
  NO
  YES
	16 (84.2%)
	3 (15.8%)
		13 (59.1%)
		9 (40.9%)
			0.098

Diabetes
  NO
  YES
	13 (68.4%)
	6 (31.6%)
		20 (90.9%)
		2 (9.1%)
			0.115

Treatment Options
  With bortezomib
  Without bortezomib
	10 (52.6%)
	9 (47.4%)
		15 (68.2%)
		7 (31.8%)
			0.352

Note: Bold values indicate significance.

months, respectively. The PFS in the high-risk group showed a hazard ratio of 2.06, while that in the medium-risk group showed a hazard ratio of 1.39. Therefore, they showed consistent results in terms of the prognostic value of MRP score; that is, the high-risk group had a higher risk of early death and a shorter PFS.[6] They also found that the high-risk group had much higher Cr, lower Hb, and higher LDH levels, which differed from the results of our study.[6] In addition,
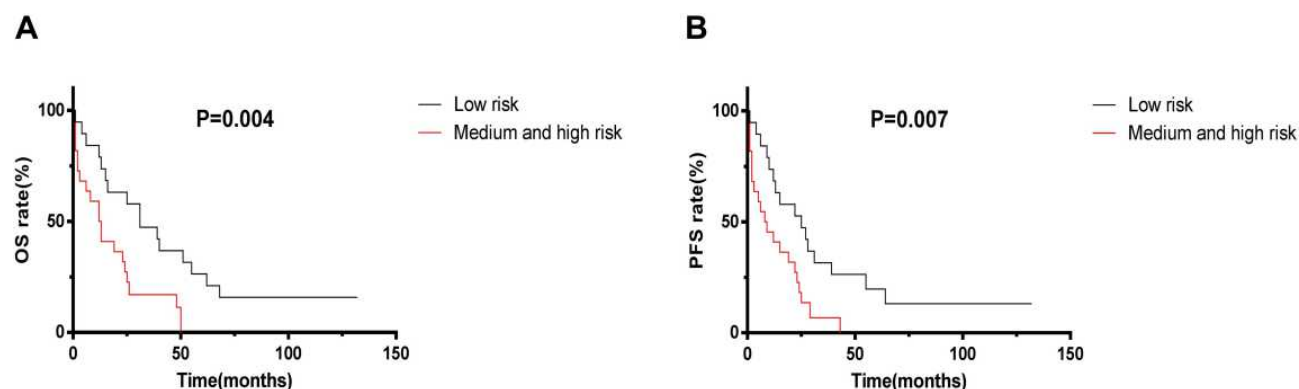
Figure 3 (**A**) The medium OS of patients with complex chromosome karyotype abnormality in MRP low risk group and medium-and-high risk group were 31 months and 12 months respectively. (**B**) The median PFS of patients with complex chromosome karyotype abnormality in MRP low risk group and medium-and-high risk group were 25 months and 8 months respectively.

patients in the high-risk group had shorter treatment durations and worse treatment responses.[6]

In China, in addition to patients who were not suitable for transplantation after undergoing a medical evaluation, some patients were unable to undergo transplantation due to personal factors (fear of transplantation, inability to understand and recognize this method because of low literacy levels, etc.) and objective conditions (such as economic constraints, and lack of care and support from their families) in the real world. Whether MRP is applicable to the above non-transplant patients remains unclear. This study retrospectively analyzed 242 newly diagnosed non-transplanted MM patients in China and found that MRP, as a simple prognostic evaluation model, was also suitable for this patient group. Similar to the studies mentioned above, significant differences were found in the OS and PFS among the different MRP risk groups. MM patients who used the treatment regimen containing bortezomib can still carry out prognosis stratification using the MRP.

Significant differences were observed between this study and other foreign studies. First, the patients enrolled in this study were slightly different from those included in the study conducted in Britain and Denmark, but both were objectively evaluated as unsuitable for transplantation. However, this study included some non-transplant patients who preferred not to undergo this procedure or due to objective conditions. There are many such patients in China and other developing countries, and including them in this study may better reflect the actual real-world setting. Second, Redder et al found significant differences in the degree of remission among different MRP groups,[6] but no differences were found in this study either in general or in different subgroups. In our

opinion, this may be related to the differences in treatment schemes. According to Redder et al, there were significant differences in the treatment schemes among different MRP groups,[6] which may lead to bias in the degree of remission. By contrast, no MRP difference was noted between the different MRP groups in this study, and they showed relatively consistent results, which may reflect the prognosis of MRP patients more accurately. Of course, this difference may also exist due to racial differences, which requires further verification using a large sample size. Third, some studies found that patients with MM had a better prognosis if they achieved better remission after treatment.[11,12] In this study, among 242 MM patients, the OS and PFS of those with VGPR and above were longer (VGPR and above vs. less than VGPR patients' OS: 50 months vs. 27 months; PFS: 31 months vs. 16 months, $P<0.05$). Similarly, the patients in the high-risk group who had a treatment response above VGPR based on the MRP score showed similar prognosis; moreover, the depth of remission still showed prognostic significance in the high-risk MRP group. However, the remission depth of patients in the MRP low-risk group and middle-risk group did not show a correlation with survival time, which indicated that the remission depth has no prognostic significance in the low-risk and middle-risk groups based on the MRP score. Fourth, the high-risk genetic abnormalities defined by IMWG et al will seriously affect the prognosis of MM.[13,14] The prognosis of MM patients with complex karyotypes was also extremely poor.[15] Studies in the UK and Denmark have analyzed the prognosis of MM patients with high-risk genetic abnormalities, but no studies have reported the prognosis of MRP in patients with complex karyotypes. Our study found that in the complex karyotype subgroup with poor prognosis, the MRP model can be used to

Table 4 Clinical Characteristics of Low-Risk Patients with Different Remission Depth

Clinical Parameters	CR/VGPR (n=51)	<VGPR (n=29)	P value
Age	59 (44–73)	61 (44–75)	
≥65	14 (27.5%)	8 (27.6%)	
<65	37 (72.5%)	21 (72.4%)	
PS score			
0	5 (9.8%)	3 (10.3%)	
1	12 (23.5%)	5 (17.2%)	
2	19 (37.3%)	15 (51.7%)	
3	15 (29.4%)	5 (17.2%)	
4	0 (0.0%)	1 (3.4%)	
CRP (mg/L)	1 (0–7)	1 (0.8–24)	
ISS Staging			
I	10 (19.6%)	3 (10.3%)	
II	25 (49.0%)	20 (69.0%)	
III	16 (31.4%)	6 (20.7%)	
Gender			0.168
Male	23 (45.1%)	18 (62.1%)	
Female	28 (54.9%)	11 (37.9%)	
Hemoglobin (g/L)	91 (43–148)	88 (51–140)	0.896
Platelet ($*10^9$/L)	136 (57–288)	126 (41–324)	0.638
Lymphocyte count ($*10^9$/L)	1.226 (0.16–3.95)	1.05 (0.4–3.154)	0.278
Lactate Dehydrogenase (U/L)	130 (73–602)	135 (64–366)	0.502
Creatinine (umol/L)	83.1 (30.3–778.3)	81.9 (47.8–501.7)	0.652
Serum Ca^{2+} (mmol/L)	2.2 (1.98–4.79)	2.11 (1.84–2.64)	**0.027**
Tumor Cell Ratio (%)	30 (1.5–85)	27 (1.5–92)	0.775
Hypertension			0.808
NO	34 (66.7%)	18 (62.1%)	
YES	17 (33.3%)	11 (37.9%)	
Diabetes			0.336
NO	45 (88.2%)	23 (79.3%)	
YES	6 (11.8%)	6 (20.7%)	
Treatment Options			0.115
With bortezomib	40 (78.4%)	18 (62.1%)	
Without bortezomib	11 (21.6%)	11 (37.9%)	
Karyotype			1.000
Complex karyotype	12 (27.9%)	7 (28%)	
Noncomplex karyotype	31 (72.1%)	18 (72%)	

Note: Bold values indicate significance.

further stratify the prognosis of MM patients in this subgroup, which proves that the MRP model has the ability to evaluate the prognosis of MM patients based on the biological factors and has nothing to do with tumor invasiveness.

Fifth, even though both MRP and ISS can be used to stratify patients into three groups, the MRP comprises host factors such as age, WHO PS score, and tumor factors such as ISS and CRP, that can be utilized as a more comprehensive

Table 5 Clinical Characteristics of Medium-Risk Patients with Different Remission Depth

Clinical Parameters	CR/VGPR (n=30)	<VGPR (n=31)	P value
Age	65 (47–83)	64 (48–75)	
≥65	17 (56.7%)	15 (48.4%)	
<65	13 (43.3%)	16 (51.6%)	
PS score			
0	1 (3.3%)	1 (3.2%)	
1	6 (20.0%)	4 (12.9%)	
2	10 (33.3%)	12 (38.7%)	
3	12 (40.0%)	12 (38.7%)	
4	1 (3.3%)	2 (6.5%)	
CRP (mg/L)	5 (0.5–81)	4 (0.5–87)	
ISS Staging			
I	1 (3.3%)	0 (0.0%)	
II	13 (43.3%)	9 (29.0%)	
III	16 (53.3%)	22 (71.0%)	
Gender			0.306
Male	19 (63.3%)	16 (51.6%)	
Female	11 (36.7%)	15 (48.4%)	
Hemoglobin (g/L)	86 (49–149)	80 (37–146)	0.090
Platelet ($*10^9$/L)	153 (16–301)	133 (17–255)	0.197
Lymphocyte count ($*10^9$/L)	1.315 (0.36–3)	1.1 (0.21–3.734)	0.204
Lactate Dehydrogenase (U/L)	142.5 (66–1036)	142 (88–533)	0.795
Creatinine (umol/L)	92.95 (49–344.6)	89.7 (38.5–755.1)	0.891
Serum Ca^{2+} (mmol/L)	2.15 (1.39–3.3)	2.22 (1.86–3.72)	0.204
Tumor Cell Ratio (%)	33 (7–95)	33 (2–86)	0.862
Hypertension			0.609
NO	18 (60.0%)	16 (51.6%)	
YES	12 (40.0%)	15 (48.4%)	
Diabetes			0.612
NO	29 (96.7%)	28 (90.3%)	
YES	1 (3.3%)	3 (9.7%)	
Treatment Options			0.717
With bortezomib	19 (63.3%)	21 (67.7%)	
Without bortezomib	11 (36.7%)	10 (32.3%)	
Karyotype			0.740
Complex karyotype	5 (20.8%)	6 (26.1%)	
Noncomplex karyotype	19 (79.2%)	17 (73.9%)	

prognostic assessment tool. In addition, ISS was first proposed in 2003 and had a limited prognostic value in MM patients in the era of new drugs based on recent researches.[2] Similar with our previous published data,[16] ISS did not show significant prognostic value in these patients treated with bortezomib, while MRP still had a prognostic significance, which makes it necessary to study a new and simple scoring system such as MRP in the era of new drugs.
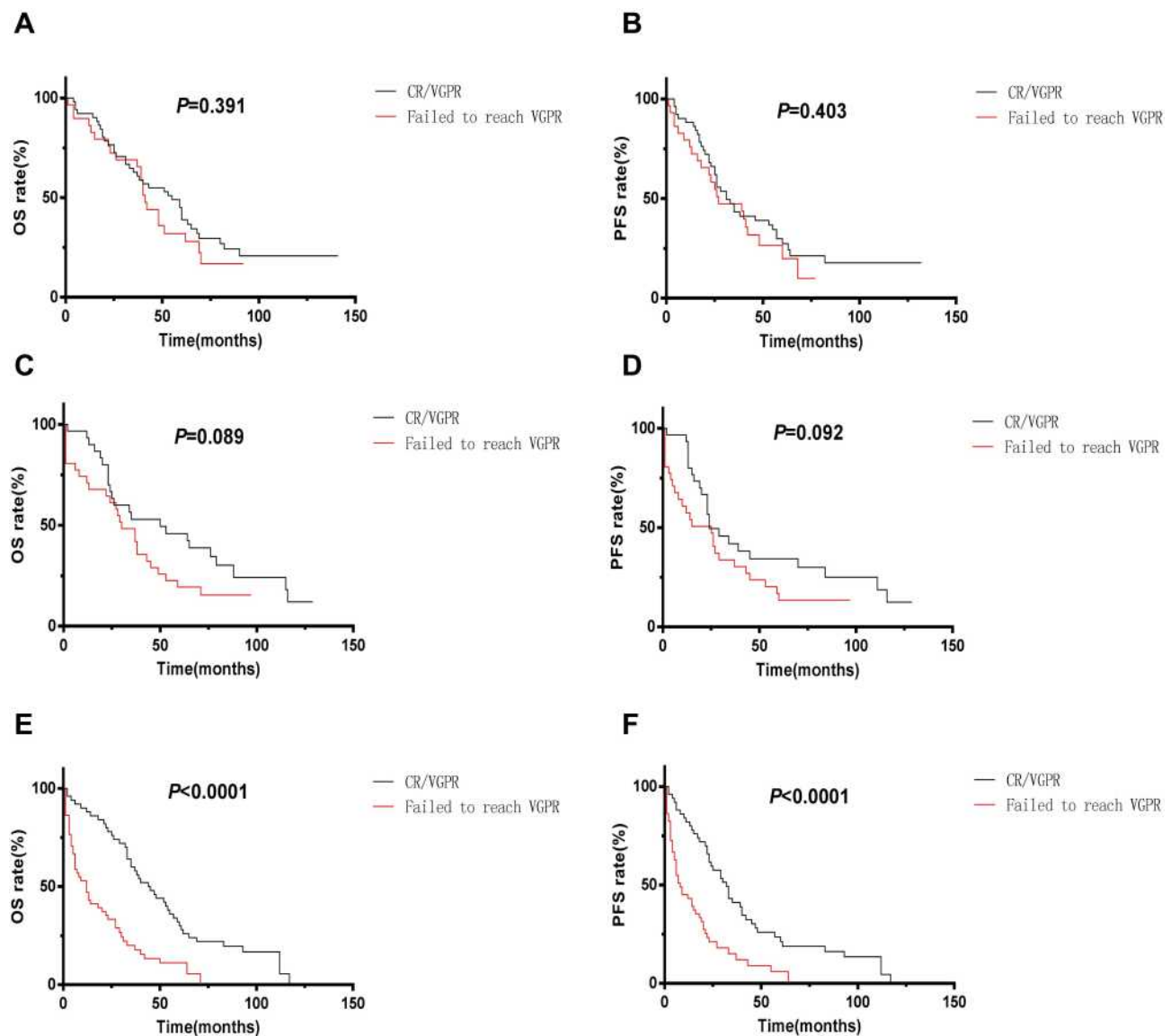
Figure 4 (**A**) The medium OS of MRP low-risk patients who reached CR/VGPR and failed to reach VGPR after treatment were 55 months and 41 months respectively. (**B**) The medium PFS of MRP low-risk patients who reached CR/VGPR and failed to reach VGPR after treatment were 31 months and 27 months respectively. (**C**) The medium OS of MRP medium-risk patients who reached CR/VGPR and failed to reach VGPR after treatment were 50 months and 30 months respectively. (**D**) The medium PFS of MRP medium-risk patients who reached CR/VGPR and failed to reach VGPR after treatment were 24 months and 25 months respectively.(**E**) The medium OS of MRP high-risk patients who reached CR/VGPR and failed to reach VGPR after treatment were 44 months and 12 months respectively. (**F**) The medium PFS of MRP high-risk patients who reached CR/VGPR and failed to reach VGPR after treatment were 32 months and 8 months respectively.

However, this study has some limitations. The number of clinical cases used in this study was relatively small, and this study was retrospective in nature, which could lead to bias. By contrast, due to economic constraints, some patients did not previously undergo complete cytogenetic examination; hence, only those patients with complete information underwent MRP analysis to determine the complex karyotype subsets. Third, due to the limited conditions, only the IMWG efficacy standard in 2016 can be used to judge the remission degree in the study population, but a more comprehensive MRD analysis to evaluate the MRP score cannot be carried out.

Conclusion

In summary, the prognostic value of MRP score in 242 newly diagnosed non-transplanted MM patients in China has been preliminarily verified, which can provide prognostic

Table 6 Clinical Characteristics of High-Risk Patients with Different Remission Depth

Clinical Parameters	CR/VGPR (n=50)	<VGPR (n=51)	P value
Age	66 (40–78)	71 (51–84)	
≥65	30 (60%)	39 (76.5%)	
<65	20 (405)	12 (23.5%)	
PS score			
0	0 (0.0%)	1 (2.0%)	
1	3 (6.0%)	1 (2.0%)	
2	12 (24.0%)	15 (29.4%)	
3	28 (48.0%)	32 (62.7%)	
4	7 (14.0%)	2 (3.9%)	
CRP (mg/L)	19 (0.8–160)	15 (1–109)	
ISS Staging			
I	0 (0.0%)	0 (0.0%)	
II	19 (38.0%)	9 (17.6%)	
III	31 (62.0%)	42 (82.3%)	
Gender			0.067
Male	26 (52%)	36 (70.6%)	
Female	24 (48%)	15 (29.4%)	
Hemoglobin (g/L)	82.5 (40–147)	83 (48–163)	0.865
Platelet (*10^9/L)	155 (26–279)	131 (42–345)	0.307
Lymphocyte count (*10^9/L)	1.30 (0.451–2.77)	1.31 (0.34–3.308)	0.862
Lactate Dehydrogenase (U/L)	127 (49–381)	131 (44–1221)	0.461
Creatinine (umol/L)	102.4 (39.5–956.6)	127.1 (54.2–1176.7)	0.072
Serum Ca^{2+} (mmol/L)	2.205 (1.38–5.35)	2.37 (1.79–4.05)	0.210
Tumor Cell Ratio (%)	26.75 (1–89)	36.5 (5–95)	**0.021**
Hypertension			0.159
NO	26 (52%)	34 (66.7%)	
YES	24 (48%)	17 (33.3%)	
Diabetes			0.309
NO	39 (78%)	44 (86.3%)	
YES	11 (22%)	7 (13.7%)	
Treatment Options			0.176
With bortezomib	34 (68%)	28 (54.9%)	
Without bortezomib	16 (32%)	23 (45.1%)	
Karyotype			0.746
Complex karyotype	5 (14.3%)	6 (18.8%)	
Noncomplex karyotype	30 (85.7%)	26 (81.3%)	

Note: Bold values indicate significance.

information for newly diagnosed MM patients treated with proteasome inhibitors. In addition, tumor biological factors, including genetic abnormalities or complex chromosome karyotypes, did not affect the prognostic stratification significance of the MRP model based on host biological factors. After treatment, the depth of remission still showed

prognostic value in the high-risk MRP group. Importantly, CRP, physical fitness score, age, and ISS staging (including β 2-microglobulin and albumin) are routine hematological and biochemical indexes, which are easy to obtain and have low economic burden. Moreover, the prognostic assessment model is simple and easy to operate; therefore, the model can be applied in the different levels of the health care system.

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Disclosure

The authors report no conflicts of interest in this work.

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