Ultra-High-Risk Group of Multiple Myeloma: A Real-World Study Based On Two Different Prognostic Evaluation Systems

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Abstract

Recently, two prognostic evaluation systems based on different angles, UK Myeloma Research Alliance proposed UK Myeloma Research Alliance Risk Profile(MRP) and chinese inflammatory prognostic scoring index(IPSI), have shown prognostic differences in newly diagnosed multiple myeloma(MM) patients without transplantation. However, there is no relevant research on whether there is a difference in the evaluation of the two systems. Here, we used these two systems to evaluate the prognosis of 160 patients with MM based on bortezomib without transplantation from January 2007 to June 2018. It was found that the evaluation of patients at medium and low risk was similar, but in the high-risk group of MRP, IPSI could be further stratified, and in the high-risk group of IPSI, MRP could also be further stratified. It is suggested that myeloma patients with high risk factors of MRP and IPSI are ultra high risk patients with poor prognosis.

Introduction

Multiple myeloma(MM) is a malignant plasma cell disease, in which the malignant proliferation of plasma cells in the bone marrow produces a large number of monoclonal immunoglobulins or their fragments, resulting in damage to related organs or tissues, accounting for about 10% of hematological tumors[1]. In recent years, based on the application of proteasome inhibitors and immunomodulatory inhibitors, the prognosis of patients with MM has been significantly improved. For different patients, screening patients with different risk stratification through the corresponding prognosis evaluation system also provides guidance and help for clinical diagnosis and treatment. In 2019, UK Myeloma Research Alliance proposed UK Myeloma Research Alliance Risk Profile(MRP) based on non-transplant patients[2], while inflammatory prognostic scoring index(IPSI) was proposed in China[3], both of which are based on blood and biochemical indicators that are easy to obtain clinically. Both of them can evaluate the prognosis of newly diagnosed non-transplant MM patients treated with proteasome inhibitors. However, at present, there is no related research on the comparison of the two prognostic scoring systems. Through the retrospective analysis of the same group of data, this study discusses the differences, advantages and disadvantages of the two prognostic scoring systems.

Materials And Methods

Patient Eligibility and Treatment

242 MM patients were collected from the Wuxi People's Hospital from January 2007 to June 2018 and the clinical and laboratory data (such as age, sex, β2 microglobulin, ISS stage, etc.) were analyzed. Excluding those who did not use bortezomib, 160 patients were enrolled in the study. Diagnostic criteria for disease diagnosis and staging with reference to the International Myeloma Working Group (IMWG) and International Prognostic Stage System (ISS).[4]

In IPSI, patients with high red cell distribution width(RDW) (RDW>14) were given a score of 1; patients with high neutrophil-to-lymphocyte ratio(NLR) (NLR>2) or low PLT (PLT≤150) were given a score of 2, thus patients were grouped into high-risk group (4–5 points), intermediate-risk group (3 points) and low-risk group (0–2 points).

MRP score combines WHO PS score, ISS stage, age and CRP, and obtains one by the calculation method of (PS score -2) * 0.199+ (age -74.4)*0.0165+ (ISS stage-2) * 0.212 [log (CRP+1)-2.08] * 0.0315，0.256≤ score ≤，0.0283 is the middle risk group; The score >，0.0283 is the low risk group.

All patients were treated with bortezomib-containing therapy for induction and consolidation, including bortezomib, 1.3 mg/m^2, subcutaneous injection at days 1, 8, 15, and 22; dexamethasone, 20-40 mg, PO or intravenous injection at days 1, 8, 15, and 22 (VD). bortezomib, 1.3 mg/m^2, subcutaneous injection at days 1, 8, 15, and 22; liposomal doxorubicin, 25 mg/m2, intravenous drip at day 1; dexamethasone, 20-40 mg, PO or intravenous injection at days 1, 8, 15, and 22(VAD). bortezomib, 1.3 mg/m^2, subcutaneous injection at days 1, 8, 15, and 22; thalidomide, 100-200mg po at d1-21; dexamethasone, 20-40 mg, PO or intravenous injection at days 1, 8, 15, and 22(VTD).And the maintenance treatment was carried out by thalidomide. Hematopoietic stem cell transplantation was not performed as a result of financial status or by personal choice including those not qualified for transplantation.

Statistical Analysis

The differences in numerical variables between groups were tested using the Kruskal-Wallis and Mann-Whitney methods. The counting variables were assessed using the χ2 test, and corrected using Fisher's precision test, where correction was required. The Kaplan-Meier method was used in survival analysis and the log-rank test was used to test survival difference. $p < 0.05$ was considered to indicate statistical significance.

Result

The basic information of the patients in the study is as follows in Table 1.

The correlation analysis of MRP and IPSI showed that in MRP low-risk group 36.25%，58/160，, medium-risk group 25%，40/160，, high-risk group 38.75%，62/160，, and in IPSI low-risk group 30%，48/160，, medium-risk group 37.5%，60/160，, high-risk group 32.5%，52/160，. The correlation analysis showed that there was no correlation between the two staging systems(r=-0.062，p=0.433).(Table 2)

Through Kaplan-Meier survival analysis, all patients showed differences in prognosis on OS (p=0.019, 48 months *vs* 30 months *vs* 32 months) and PFS(p=0.013, 31 months *vs* 24 months *vs* 22 months) by MRP, similarly, in the IPSI group, it still shows such differences in OS(p=0.058, 38 months *vs* 23 months *vs* 22 months) and PFS(p=0.02, 54 months *vs* 40 months *vs* 29 months) seemingly.(Figure 1)

It was found that the evaluation of patients at low and medium risk was similar(Figure 2)(p>0.05), but in the high-risk group of MRP, IPSI could be further stratified in OS(p=0.027, 40 months *vs* 32 months *vs* 27 months) and PFS(p=0.055, 25 months *vs* 21 months *vs* 14months)(Figure 3A), and in the high-risk group of IPSI, MRP could also be further stratified in OS(p=0.033, 35 months *vs* 24 months *vs* 27 months) and PFS(p=0.039, 25 months *vs* 15 months *vs* 14 months)(Figure 3B).Their respective baseline tables are as follows.(Table 3, Table 4).

Further including all patients in the study, our study can find similar results in 242 patients (including those who were treated only with thalidomide). It was found that the ultra-high risk patients (defined as patients with both MRP high-risk and IPSI high-risk patients) had significantly shorter OS(p□0.001, 18 months *vs* 39 months) and PFS(p□0.001, 12 months *vs* 26 months) compared to the other patients(Figure 4) when there is no other bias in the baseline data table 5.

Discussion

At present, MM is still an incurable disease, but with the successive application of proteasome inhibitors, immunomodulators, monoclonal antibody drugs and autologous hematopoietic stem cell transplantation, the prognosis of MM patients has been significantly improved. In China, due to various reasons, few patients are willing to carry out autologous hematopoietic stem cell transplantation, and most patients only choose drug treatment. there is a need to choose an appropriate prognosis score to select appropriate induction, maintenance and consolidation programs. In recent years, with the continuous development of molecular detection technology, the corresponding second-generation sequencing and gene expression techniques have been gradually applied to predict the prognosis of MM. EMC-92, Inid-14, Mayo SMART staging and other gene-based prognostic indicators have been put forward [5–6]. In addition, some scholars have put forward the point of view of double hit and triple hit according to the high-risk genetic factors. [7–8] But for most developing countries, it is not mature to improve such expensive and complex laboratory conditions, hindering further cytogenetic analysis of prognostic stratification. Therefore, the relatively simple staging system without molecular genetic parameters has also become a research hotspot, such as MRP based on tumor load and host factors and IPSI based on inflammatory factors proposed in 2019 all avoid molecular genetic parameters and show good prognostic value in newly diagnosed MM patients treated with protease inhibitors. This provides a new direction for us to evaluate the prognosis of this kind of patients.

The MRP combines the four factors of WHO ECOG, age, ISS stage and CRP, including both tumor factors and host factors, while the IPSI creatively evaluates the prognosis of MM patients from the perspective of inflammation, combined with RDW, NLR and PLT, and selects patients with different prognostic grades. At present, there are few real-world studies related to MRP and IPSI. In addition to the data from the British Myeloma Research Alliance, Redder et al counted 1377 multiple myeloma patients over the age of 65 who were not eligible for transplantation in Denmark, and concluded that the MRP high-risk group had a higher early mortality rate than the low-risk group, and the MRP high-risk group had shorter duration of treatment and poorer treatment response[9]. Unfortunately, there is no other research data on IPSI at

present. In this study, because the patients included in IPSI were patients based on bortezomib treatment, initially only patients who had been treated with bortezomib were studied, and both of them can show that there are statistical differences in OS and PFS stratification of non-transplant patients based on bortezomib treatment.The sample was then further extended to all patients (including patients who were treated only with thalidomide at an early stage), and similar conclusions could be obtained.

In this study, through the MRP and IPSI analysis of the same group of data, both of them can show that there are statistical differences in OS and PFS stratification of non-transplant patients based on bortezomib treatment, but by comparison, there are still some similarities and differences between them.

Among the subgroups of MRP, IPSI did not show prognostic significance in patients with low and moderate risk of MRP, but in the high-risk subgroup of MRP, the OS and PFS of patients with high-risk IPSI were shorter; Similarly, MRP in the high-risk subgroup of IPSI can further stratify the prognosis of patients. Considering that MRP and IPSI evaluate patients from different angles, it can be considered that patients with both MRP high-risk factors and IPSI high-risk factors have worse prognosis and shorter survival time than general high-risk patients, and belong to ultra-high-risk patients. For such ultra-high-risk patients, if autologous hematopoietic stem cell transplantation can be performed after evaluation, it is recommended that transplantation be carried out as soon as possible to improve the prognosis; if the patient is really unable to perform transplantation or has no intention to transplant, it may be necessary to add immunotargeted therapy with monoclonal antibodies such as daratumumab[10], and new immunomodulators may even enter clinical trials to further benefit. Of course, this needs to be assessed by further evidence-based research on this type of patients in the future.

In the actual process of clinical diagnosis and treatment, the factors affecting the prognosis of MM are complex. In recent years, a variety of new prognostic scoring systems about MM are constantly emerging, most of which require a variety of genetic testing. The MRP and IPSI scoring system avoids the relevant genetic indicators, and can also confirm its evaluation effect in the relevant clinical verification, indicating the value of application in the current medical conditions, especially through comparative analysis, it shows that the two systems have combined and complementary effects in some patients, which is helpful to further stratify the discrimination of this kind of patients and provide early warning for the next step of treatment. Of course, with the continuous development of scientific and technological conditions, the corresponding molecular biotechnology can be widely carried out in clinical practice. It is believed that it can provide patients with more accurate and applicable prognosis and treatment strategies in the future.

Statement of Ethics

This study was conducted as a retrospective analysis of patient data and was approved by the Wuxi People's Hospital clinical new technology and Scientific Research Ethics Committee.(No.KYLLS200612). Written informed consent was obtained from all patients. This research project complied with the guidelines for human studies and was conducted ethi-cally in accordance with the World Medical Association Declara-tion of Helsinki.

Declarations

Conflict of Interest Statement

All of the authors have no conflicts of interest to declare.

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Author Contributions

JIAN-NAN YE and KE-WA MA conceived and designed the analysis, collected the data, and drafted the paper.YONG-QIN CAO and XIN ZHOU performed the statistical analysis.CHAO SUN reviewed and revised the paper.

Data Availability Statement.

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Tables

Table1 Clinical characteristics of all patients

Characteristic	Median
Age	64.5（40-84）
Gender Man	88（55%）
Female	72（45%）
ISS stage I stage	11（6.875%）
II stage	60（37.5%）
III stage	89（55.625%）
Hemoglobin（g/L）	85（37-163）
Platelet（*109/L）	136（33-329）
CRP(mg/L)	5（0-160）
Neutrophil-to-lymphocyte ratio （2	96（60%）
WHO ECOG 0 score	9（5.625%）
1 score	27（16.845%）
2 score	49（30.625%）
3 score	64（40%）
4 score	11（6.875%）
Red cell distribution width（%）	15.1（11.7-31.3）
Lactate Dehydrogenase（U/L）	136.5（50-1105）
Creatinine（umol/L）	98（30-1176）
Serum Ca2+（mmol/L）	2.22（1.38-5.35）
Albumin(g/L)	29.9（11.7-64）
β2 microglobulin(mg/L)	6（1.5-81.8）
Proportion of Tumor Cells（%）	32.25（10-92）
Monoclonal protein IgA	51（31.875%）
IgD	2（1.25%）
IgG	65（40.625%）
Light chain disease	23（14.375%）
Non-secreting	19（11.875%）

Table 2.160 patients were divided into groups of prognosis by MRP and IPSI

		MRP			Total
		Low-risk(3 score)	Medium-risk(2 score)	High-risk(1 score)	
IPSI	Low-risk(1 score)	21	9	18	48
	Medium-risk(2 score)	19	19	22	60
	High-risk(3 score)	18	12	22	52
Total		58	40	62	160

Table3 Clinical characteristics of patients in the high-risk group of MRP

Characteristic	Median
Age	68（40-84）
Gender Man	39（62.9%）
Female	23（37.1%）
ISS stage I stage	0（0%）
II stage	16（25.8%）
III stage	46（74.2%）
Hemoglobin（g/L）	82.5（45-163）
Platelet（*109/L）	144（42-329）
CRP(mg/L)	16（0-160）
Neutrophil-to-lymphocyte ratio ≥2	43（69.4%）
WHO ECOG 0 score	1（1.7%）
1 score	3（4.8%）
2 score	18（29%）
3 score	33（53.2%）
4 score	7（11.3%）
Red cell distribution width（%）	15.25（11.2-31.3）
Lactate Dehydrogenase（U/L）	127.5（50-1102）
Creatinine（umol/L）	104（48-1176）
Serum Ca2+（mmol/L）	2.29（1.38-5.35）
Albumin(g/L)	27.2（11.7-44.5）
β2 microglobulin(mg/L)	8.2（1.8-81.8）
Proportion of Tumor Cells（%）	31（10-89）

Table4 Clinical characteristics of patients in the high-risk group of IPSI

Characteristic	Median
Age	63.5（43-80）
Gender Man	31（59.6%）
Female	21（40.4%）
ISS stage I stage	4（7.7%）
II stage	11（21.2%）
III stage	37（71.1%）
Hemoglobin（g/L）	77（37-147）
Platelet（*109/L）	114（34-154）
CRP(mg/L)	5.2（0-160）
WHO ECOG 0 score	2（3.8%）
1 score	8（15.4%）
2 score	21（40.4%）
3 score	18（34.6%）
4 score	3（5.8%）
Red cell distribution width（%）	15.1（11.7-26.3）
Lactate Dehydrogenase（U/L）	145.5（50-602）
Creatinine（umol/L）	115（47-918）
Serum Ca2+（mmol/L）	2.25（1.38-3.6）
Albumin(g/L)	28.8（11.7-48.2）
β2 microglobulin(mg/L)	9.64（2.62-36.9）
Proportion of Tumor Cells（%）	32.5（10-82）

Table5.Patient characteristics between the ultra-high risk patients and the other patient.

	The ultra-high risk patients(n=35)	The other patient(n=207)	*p*
Age（year）	68（43-82）	64（40-83）	0.012
Sex			
Male	23	114	0.24
Female	12	93	
ECOG			
0-2	14	111	0.136
3-4	21	96	
ISS stage			
Stage I/II	6	103	0.000
Stage III	29	104	
Haemoglobin (g/L)	88（40-135）	84（37-163）	0.983
Platelets（$\times 10^9$/L）	118（26-154）	151（16-345）	0.000
Lymphocyte count （$\times 10^9$/L）	1.02（0.34-2.65）	1.3（0.16-3.95）	0.004
C-Reactive Protein（mg/L）	14（0-160）	4（0-160）	0.016
LDH, (U/L)	145(50-1221)	136(44-1102)	0.183
Creatinine, (μmol/L)	163（39-918）	92（30-1176）	0.013
Ca^{2+}（mmol/L）	2.52（1.38-4.05）	2.2（1.39-5.35）	0.006
Albumin, (g/L)	27.5（11.7-40.8）	29.5（11.5-64）	0.067
Plasmocytoma（%）	33（10-95）	31（10-95）	0.357
Treatment scheme			
Include bortezomi	22	138	0.66
Traditional chemotherapy	13	69	

Figures

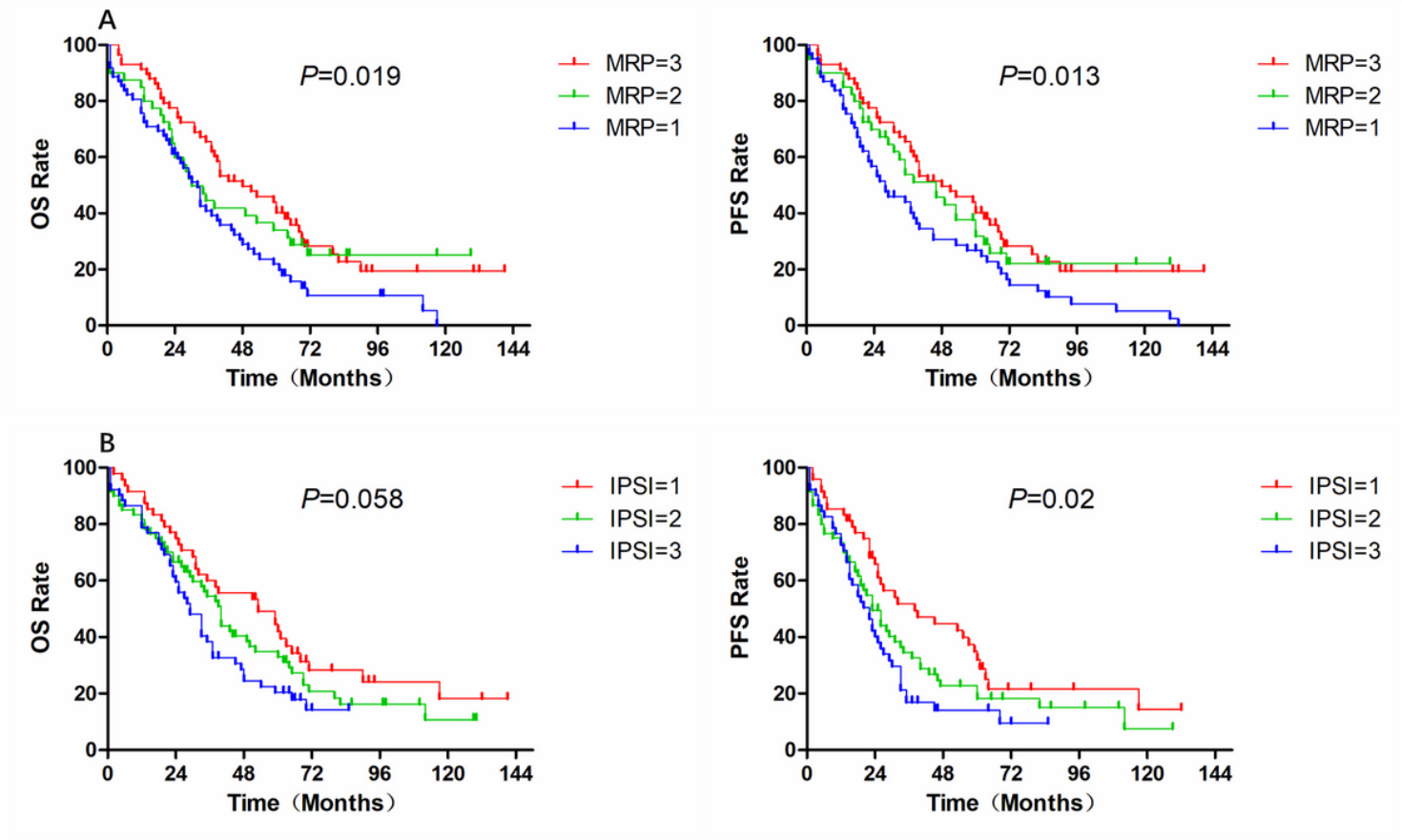

Figure 1

(A)Survival curve of MRP in all patients with OS and PFS (B)Survival curve of IPSI in all patients with OS and PFS

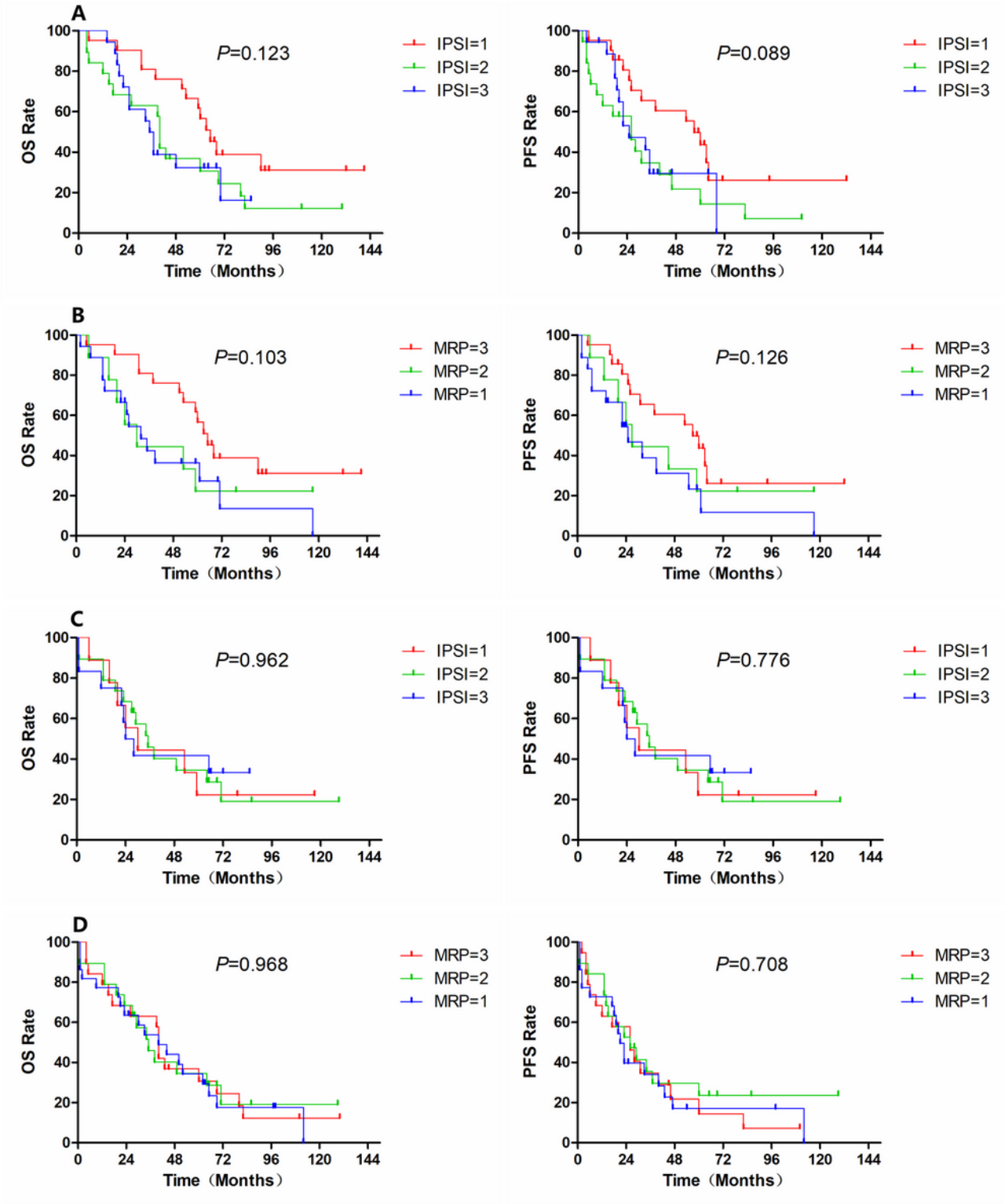

Figure 2

(A)Survival curve of OS and PFS based on MRP low-risk group patients according to IPSI (B)Survival curve of OS and PFS based on IPSI low-risk group patients according to MRP (C)Survival curve of OS and PFS based on MRP medium-risk group patients according to IPSI (D)Survival curve of OS and PFS based on IPSI medium-risk group patients according to MRP

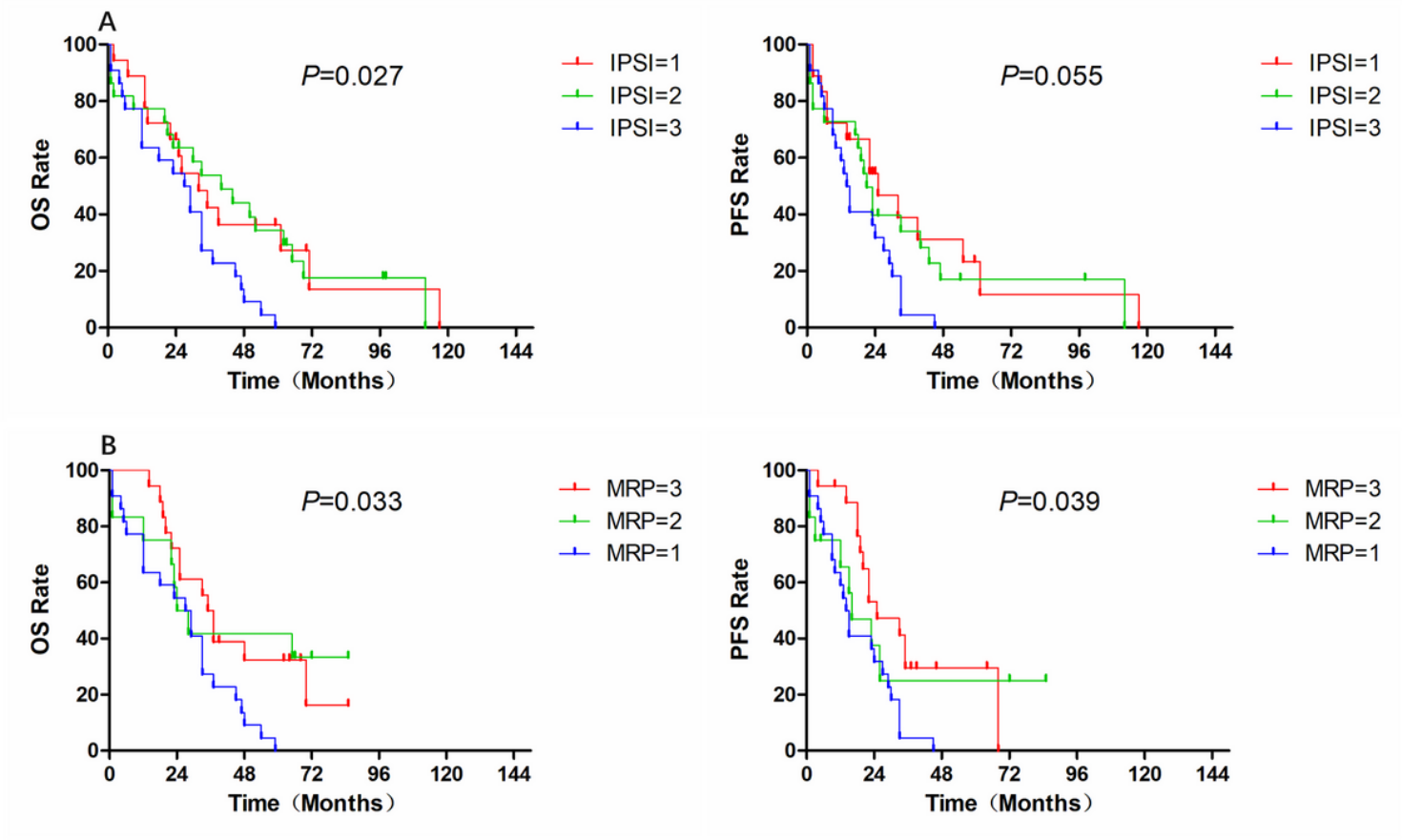

Figure 3

(A)Survival curve of OS and PFS based on MRP high-risk group patients according to IPSI (B)Survival curve of OS and PFS based on IPSI high-risk group patients according to MRP

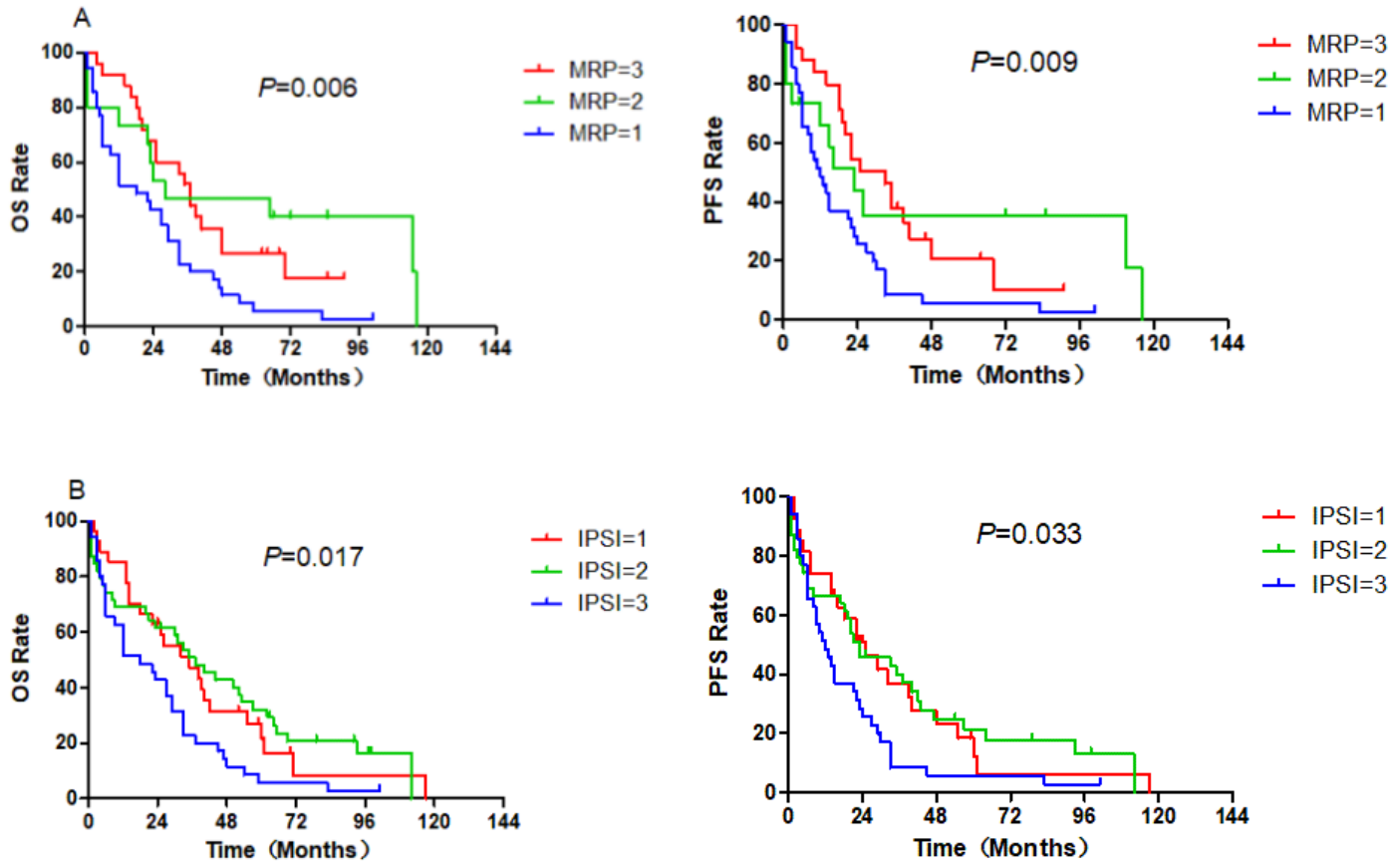

Figure 4

Survival curve of OS and PFS between the ultra-high risk patients and the other