Article

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High Red Blood Cell Distribution Width to Platelet Ratio is an Independent Poor Prognostic Factor in Patients with Newly Diagnosed Multiple Myeloma

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Background: The red blood cell distribution width to platelet ratio (RPR) is an inflammatory marker that is a convenient and reliable prognostic indicator for several solid malignancies. However, the correlation between RPR and myeloma prognosis has not been reported. Therefore, this study aims to explore the correlation between RPR level and the prognosis of multiple myeloma (MM) patients.

Methods: We retrospectively analyzed 145 newly diagnosed patients with MM. The receiver operating characteristic curve (ROC) method was used to determine the RPR cut-off value. In addition, we studied the correlation between pre-treatment RPR levels and clinical characteristics, immunophenotype, cytogenetics, and its impact on the disease prognosis.

Results: The optimal cut-off value for RPR was 0.12 and was divided into high RPR and low RPR groups. Patients in the high RPR group are more likely to have anemia, thrombocytopenia, high β2-macroglobulinemia, a high percentage of bone marrow plasma cells, late-stage status by Dury-Salmon (DS) and international staging system (ISS) ($p < 0.05$). More notably, between the high RPR and low RPR groups, the incidence rates of CD56-positive, D13S319-positive, RB1-positive, and 1q21 amplification were statistically significant ($p < 0.05$). Additionally, survival analysis revealed that compared with patients in the low RPR group, the median progression-free survival (PFS) and overall survival (OS) of patients in the high RPR group were substantially shortened ($p < 0.05$). Multivariate analysis confirmed that RPR $\geq$0.12, D13S319-positive, and 1q21 amplification were independent risk factors for poor PFS and OS.

Conclusions: RPR is a practical and effective prognostic marker in newly diagnosed patients with MM, and a high RPR is an independent poor prognostic factor.

Keywords: multiple myeloma; red blood cell distribution width to platelet ratio; immunophenotype; cytogenetics; prognosis

Introduction

Multiple myeloma (MM) is a lymphocyte-mediated malignant tumor of the blood system, which is also a hematologic tumor with an abnormal clonal proliferation of plasma cells [1]. MM is diagnosed more often in the elder, and the current incidence in the population is increasing yearly. The normal bone marrow block in MM patients is infiltrated by malignant tumor cell proliferation because of the malignant proliferation of plasma cells, causing patients to present with symptoms such as anemia, kidney damage, infection, and hypercalcemia [2]. Due to the high heterogeneity of the disease, nearly all patients with MM eventually experience the adverse outcome of relapse and become refractory to treatment. According to data from randomized controlled trials, the median survival time of MM patients is about 6 years, and identifying prognostic biomarkers is critical to help optimize clinical treatment options and improve prognosis [3].

In newly diagnosed MM patients, circulating plasma cells, neutrophil-to-lymphocyte ratio, and other blood components are independent adverse prognostic factors [4–7]. The inflammatory response is involved in the proliferation and invasion of myeloma cells [8]. Red blood cell distribution width (RDW) is a parameter that indicates the volume of the red blood cell. Inflammatory cytokines impair the maturation of erythrocytes by regulating their proliferation and differentiation, and this results in the variable size of peripheral erythrocytes and increased RDW [9,10]. As an indicator of inflammation, RDW is related to the prognosis of various solid tumors and hematological tumors, including myeloma [7,11–13]. It has been suggested that high pre-treatment RDW levels in myeloma patients correlate with poor treatment response and accelerated disease pro-

gression [13]. In the blood system, a low platelet (PLT) count usually indicates a poor prognosis due to the abnormal proliferation of tumor cells and the suppression of normal hematopoiesis [14,15].

The RDW to PLT ratio (RPR) indicates systemic inflammation. Recently, several studies have confirmed that high RPR is an important marker of poor prognosis in various solid tumors [16,17]. However, the literature has not reported the relationship between RPR and immunophenotype, genetic characteristics, and prognosis of MM patients. Hence, we hypothesize that high RPR is important in predicting MM patients' prognosis. Therefore, this study aims to investigate the relationship between RPR and clinical characteristics in newly diagnosed MM patients using a retrospective analysis and to identify the relation of RPR to the immunophenotype and cytogenetics of MM patients and its impact on disease prognosis.

Patients and Methods

In this retrospective study, 145 patients with newly diagnosed MM participated. The samples were collected in Henan Provincial People's Hospital from May 2015 to December 2021. According to the International Myeloma Working Group (IMWG) diagnostic criteria in 2014 [18], all patients were diagnosed for the first time and had not received chemotherapy. The following cases were excluded: Monoclonal gammopathy of undetermined significance (MGUS), biclonal MM, amyloidosis, plasma cell leukemia, massive blood transfusion, severe acquired immunodeficiency disease, dysfunction and complications of solid organs, inflammatory disease including infection or collagen disease, and previous tumor.

We extracted all the clinical baseline parameters from the medical records, including age, sex, blood cell counts, and data and calculations related to RPR, albumin, β2-macroglobulinemia (β2-MG), creatinine (Cr), blood calcium, lactate dehydrogenase (LDH), immunoglobulin type, cell count of bone marrow plasma, immunophenotype, and collected and performed fluorescence in situ hybridization (FISH) for cytogenetic abnormalities before MM patients received initial chemotherapy. According to the European Myeloma Working Group [19], the positive threshold for del (13q14), 17p, and 1q21 amplification was 20%, and the positive threshold for fusion genes was 10%. In this study, probes were targeted at two main regions of del (13q14) involvement: LSI-RBl and LSI-D13S319.

RPR was calculated from the ratio of the red blood cell distribution width CV (coefficient of variation) (RDW-CV) to blood platelet count ($\times 10^9$/L) in peripheral blood.

Follow-Up and Survival Time

Follow-up was conducted until June 2022 by phone and involved inpatient case identification and outpatient review. The period from diagnosis to illness recurrence, progression, death, or the end of follow-up was defined as progression-free survival (PFS). The period from MM diagnosis to death or the end of follow-up was defined as overall survival (OS).

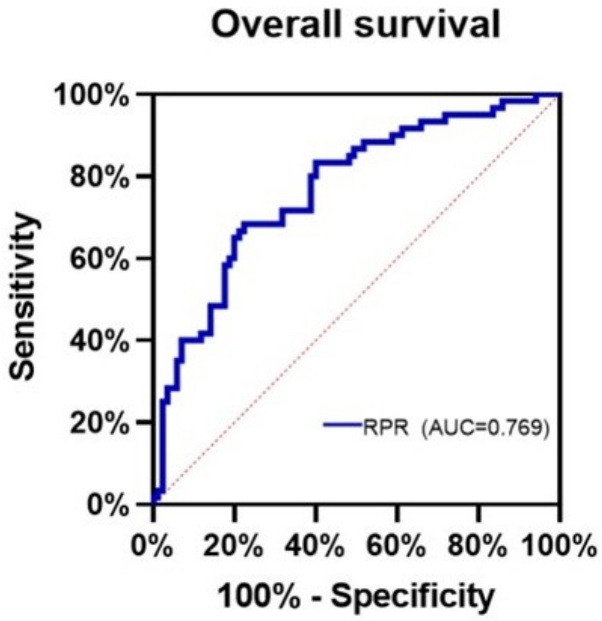

Fig. 1. ROC curve of RPR for predicting the prognosis of MM patients.

Statistical Analysis

SPSS version 21.0 (IBM Corporation, Armonk, NY, USA) was exploited for statistical analysis, and GraphPad Prism version 9.0 (GraphPad, San Diego, CA, USA) was used to make graphs. The ROC approach was used to establish the cut-off value for RPR, and the area under the curve (AUC) was recorded. Chi-square test or Fisher's exact probability method was used to analyze the variability of the constituent ratio between the two groups. Prognostic univariate analysis was performed using the Kaplan–Meier method, and survival between groups was performed using the log-rank test. In addition, factors affecting PFS and OS were analyzed using a Cox univariate regression model, and then the Cox regression model was used for multivariable analyses. A two-sided p-value < 0.05 was considered statistically significant.

Results

Baseline Characteristics

Among the 145 patients with primary MM, 79 (54.5%) were male, and 66 (45.5%) were female. The median age was 59 when patients were diagnosed (range 38–85 years). Forty-five (31.0%) patients were $\geq$65 years, and 100 (69.0%) patients were $<$65 years. The distribution of

Table 1. Relationship between RPR and clinical characteristics in newly diagnosed MM patients.

Project	RPR <0.12 (n = 84)	RPR ≥0.12 (n = 61)	χ^2	*p* value
Sex			0.873	0.350
Male	43 (51.2%)	36 (59.0%)		
Female	41 (48.8%)	25 (41.0%)		
Age (yrs)			2.189	0.139
≤65	62 (73.8%)	38 (62.3%)		
>65	22 (26.2%)	23 (37.7%)		
M protein			–0.052	0.959
IgG	36 (42.9%)	28 (45.9%)		
IgA	20 (23.8%)	11 (18.0%)		
Others	28 (33.3%)	22 (36.1%)		
DS stage			4.434	0.035
I–II	25 (29.8%)	9 (14.8%)		
III	59 (70.2%)	52 (85.2%)		
ISS stage			7.845	0.005
I–II	58 (69.0%)	28 (45.9%)		
III	26 (31.0%)	33 (54.1%)		
BM PCs (%)			5.154	0.023
≤30%	42 (50.0%)	19 (31.1%)		
>30%	42 (50.0%)	42 (68.9%)		
Hb (g/L)			25.434	0.000
≤85	25 (29.8%)	44 (72.1%)		
>85	59 (70.2%)	17 (27.9%)		
PLT ($\times 10^9$/L)			58.832	0.000
≤100	0 (0.0%)	33 (54.1%)		
>100	84 (100.0%)	28 (45.9%)		
Albumin (g/L)			1.712	0.191
≤35	46 (54.8%)	40 (65.6%)		
>35	38 (45.2%)	21 (34.4%)		
β2-MG (mg/L)			10.641	0.001
≤5.5	61 (72.6%)	28 (45.9%)		
>5.5	23 (27.4%)	33 (54.1%)		
Cr (μmol/L)			2.476	0.116
≤177	72 (85.7%)	46 (75.4%)		
>177	12 (14.3%)	15 (24.6%)		
LDH (U/L)			0.818	0.366
≤200	71 (84.5%)	48 (78.7%)		
>200	13 (15.5%)	13 (21.3%)		
Ca (mmol/L)			1.592	0.207
≤2.75	75 (89.3%)	50 (82.0%)		
>2.75	9 (10.7%)	11 (18.0%)		

cases by type was as follows: According to M protein typing, there were 64 cases (44.1%) of IgG (immunoglobulin G) type, 31 cases (21.4%) of IgA type, and 50 cases (34.5%) of the light chain and other types. According to Dury-Salmon (DS) staging, 10 cases (6.8%) were stage I, 24 cases (16.6%) were stage II, and 111 cases (76.6%) were stage III. According to the international staging system (ISS) staging, 21 cases (14.5%) were stage I, 65 cases (44.8%) were stage II, and 59 cases (40.7%) were stage III. A total of 89 patients (61.4%) were CD56+, and 63 patients (43.4%) were CD117+. Cytogenetic analysis was defined as interphase FISH in 49.0% (71/145) of D13S319+ patients, 48.3% (70/145) of RB1+ patients, and 53.1% (77/145) of 1q21 amplification patients. A total of 71.7% (104/145) of patients were IgH rearrangement, and 11.7% (17/145) were TP53 mutation.

The Optimal Cut-Off Values of RPR

The area under the curve (AUC) of MM patients with RPR = 0.12 in peripheral blood as the best cut-off value according to the ROC curve was 0.769, the sensitivity was 68.3%, and specificity was 77.6% (Fig. 1). Patients were

Table 2. Association of RPR with immunophenotype and cytogenetics in patients with newly diagnosed MM patients.

Project	Expression	RPR <0.12 (n = 84)	RPR ≥0.12 (n = 61)	χ^2	*p* value
CD56				10.641	0.001
	+	61 (72.6%)	28 (45.9%)		
	–	23 (27.4%)	33 (54.1%)		
CD117				2.336	0.126
	+	41 (48.8%)	22 (36.1%)		
	–	43 (51.2%)	39 (63.9%)		
D13S319				7.487	0.006
	+	33 (39.3%)	38 (62.3%)		
	–	51 (60.7%)	23 (37.7%)		
RB1				6.463	0.011
	+	33 (39.3%)	37 (60.7%)		
	–	51 (60.7%)	24 (39.3%)		
IgH				3.843	0.050
	+	55 (65.5%)	49 (80.3%)		
	–	29 (34.5%)	12 (19.7%)		
P53				0.197	0.657
	+	9 (10.7%)	8 (13.1%)		
	–	75 (89.3%)	53 (86.9%)		
1q21				6.575	0.010
	+	37 (44.0%)	40 (65.6%)		
	–	47 (56.0%)	21 (34.4%)		

Abbreviations: CD56+, CD56-positive; CD56–, CD56-negative; CD117+, CD117-positive; CD117–, CD117-negative; D13S319+, D13S319-positive; D13S319–, D13S319-negative; RB1+, RB1-positive; RB1–, RB1-negative; IgH+, IgH rearrangement; IgH–, non-IgH rearrangement; P53+, P53 mutation; P53–, non-P53 mutation; 1q21+, 1q21 amplification; 1q21–, non-1q21 amplification.

thereby classified into a high RPR group (RPR ≥0.12) and a low RPR group (RPR <0.12), with 61 and 84 cases in each group, respectively.

Relationship between RPR and Clinical Characteristics

We reanalyzed data profiles of patients with newly diagnosed MM before the first treatment. The χ^2 test was used to compare the baseline characteristics in the two groups (high RPR group: RPR ≥0.12 and low RPR group: RPR <0.12). The results showed that in the high RPR group of MM patients, there was a higher incidence of anemia (Hb ≤85 g/L), thrombocytopenia (PLT ≤100 × 10^9/L), high β2-MG (β2-MG >5.5 mg/L), increased bone marrow plasma cells (BM PCs >30%), DS stage III, and ISS stage III compared to the low RPR group ($p < 0.05$). At the same time, no statistically significant differences were found between the two groups in sex, age, M protein typing, albumin, Cr, LDH, or serum calcium (Ca) ($p > 0.05$) (Table 1).

Relationship between RPR and Immunophenotype

In our study, we mainly analyzed two immunophenotypes: CD56 and CD117. Sixty-one out of 84 patients (72.6%) were CD56+ in the low RPR group. In the high RPR group, 28 of 61 patients (45.9%) were CD56+, and the expression of CD56+ was remarkably lower in the high RPR group than in the low RPR group ($p = 0.001$). The expression of CD117 was not significantly different between the two groups ($p > 0.05$) (Table 2).

Relationship between RPR and Cytogenetics

We found that detection rates of D13S319+, RB1+, 1q21 amplification, and IgH rearrangement were significantly higher in primary MM patients in the high RPR group than in the low RPR group (D13S319: 39.3% vs 62.3%, $p = 0.006$; RB1: 39.3% vs 60.7%, $p = 0.011$; 1q21: 44.0% vs 65.6%, $p = 0.010$; IgH: 65.5% vs 80.3%, $p = 0.050$) (Table 2).

Relationship between RPR and Clinical Outcomes

The survival curve was drawn by the K–M method to compare the two groups of patients. The median PFS times in the high and low RPR groups of MM patients were 11 and 28 months ($p < 0.05$), and the median OS time in the high RPR group was 24 months ($p < 0.05$) (Fig. 2A,B). As further clarification of the influence of immunophenotype and cytogenetics on the adverse prognosis of RPR, the results showed significant differences in PFS and OS between the D13S319-positive and negative expression groups in the high RPR group (8 months vs 16 months, $p = 0.011$; 19 months vs 33 months, $p = 0.001$) (Fig. 2C,D). PFS and OS differed significantly between the RB1-positive and neg-

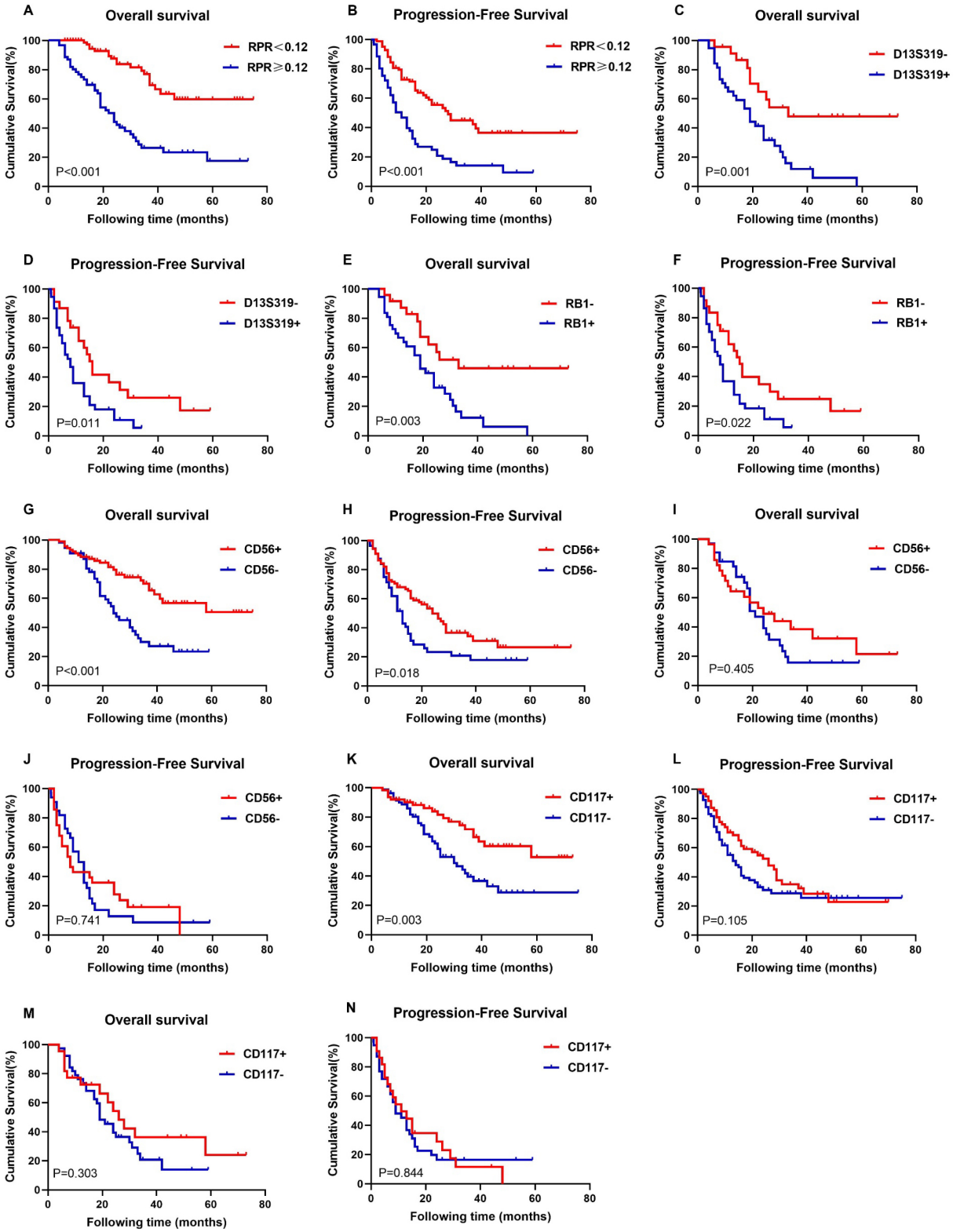

Fig. 2. Kaplan–Meier curves for OS and PFS. (A,B) Kaplan–Meier curves for OS and PFS according to RPR. (C,D) Kaplan–Meier curves for OS and PFS were plotted according to the expression of D13S319 in the high RPR group. (E,F) Kaplan–Meier curves for OS and PFS were plotted according to the expression of RB1 in the high RPR group. (G,H) Kaplan–Meier curves for OS and PFS were plotted according to CD56 expression. (I,J) Kaplan–Meier curves for OS and PFS were plotted according to CD56 expression in the high RPR group. (K,L) Kaplan–Meier curves for OS and PFS were plotted according to CD117 expression. (M,N) Kaplan–Meier curves for OS and PFS were plotted according to CD117 expression in the high RPR group.

Table 3. Univariate analysis of predictors of overall survival and progression-free survival time in patients with newly diagnosed MM.

Variable		Patients (n = 145)	PFS			OS		
			Median time (M)	χ^2	*p* value	Median time (M)	χ^2	*p* value
Sex				0.266	0.606		0.125	0.724
	Male	79	17			37		
	Female	66	16			41		
Age (yrs)				1.535	0.215		4.384	0.036
	≤65	100	17			58		
	>65	45	16			34		
M protein				0.047	0.829		0.047	0.829
	IgG	64	16			39		
	IgA	31	17			41		
	Others	50	21			34		
DS stage				3.294	0.07		1.423	0.233
	I–II	34	31					
	III	111	16			37		
ISS stage				12.470	0.000		9.579	0.002
	I–II	86	26			58		
	III	59	11			26		
BM PCs (%)				4.244	0.039		8.530	0.003
	≤30%	61	24					
	>30%	84	13			34		
Hb (g/L)				5.212	0.022		3.423	0.064
	≤85	69	13			34		
	>85	76	22					
PLT ($\times 10^9$/L)				12.007	0.001		27.218	0.000
	≤100	33	9			22		
	>100	112	22					
Albumin (g/L)				2.946	0.086		1.236	0.266
	≤35	86	16			37		
	>35	59	21					
β2-MG (mg/L)				9.949	0.002		9.621	0.002
	≤5.5	89	24			58		
	>5.5	56	11			25		
Cr (μmol/L)				4.591	0.032		6.933	0.008
	≤177	118	20			58		
	>177	27	9			33		
Ca (mmol/L)				3.373	0.066		2.481	0.115
	≤2.75	125	20			41		
	>2.75	20	9			30		
LDH (U/L)				3.808	0.051		4.070	0.044
	≤200	119	20			41		
	>200	26	11			26		
CD56				5.600	0.018		13.505	0.000
	+	89	24					
	–	56	13			24		
CD117				2.634	0.105		8.976	0.003
	+	63	26					
	–	82	14			30		

Table 3. Continued.

	D13S319				13.754	0.000		18.629	0.000
		+	71	11			28		
		–	74	28					
	RB1				12.304	0.000		16.556	0.000
		+	70	11			28		
		–	75	29					
FISH	IgH				0.505	0.477		0.099	0.753
		+	104	16			37		
		–	41	22			41		
	TP53				4.180	0.041		8.984	0.003
		+	17	8			23		
		–	128	19			42		
	1q21				6.852	0.009		12.693	0.000
		+	77	11			32		
		–	68	22					
RPR					21.043	0.000		31.291	0.000
		<0.12	84	29					
		≥0.12	61	11			24		

Table 4. Multifactorial analysis of predictors of overall survival and progression-free survival time in patients with newly diagnosed MM.

Variable	PFS			OS		
	HR	95% CI	*p* value	HR	95% CI	*p* value
CD56	0.50	0.29~0.86	0.013	0.39	0.22~0.68	<0.001
D13S319	2.58	1.44~4.61	0.001	2.76	1.56~4.89	<0.001
1q21	2.19	1.19~4.05	0.012	2.68	1.43~5.01	0.002
IgH	0.43	0.22~0.83	0.012	0.41	0.21~0.80	0.008
RPR ≥0.12	3.60	2.0~6.48	<0.001	3.39	1.9~5.94	<0.001

PFS, C-index = 0.78; OS, C-index = 0.8.

ative expression groups among patients in the high RPR group (8 months vs 15 months, $p = 0.022$; 19 months vs 33 months, $p = 0.003$) (Fig. 2E,F). The OS and PFS in CD56+ patients were significantly longer than in CD56– patients (Fig. 2G,H), but there was no significant difference in patients with high RPR (Fig. 2I,J). The OS in CD117+ patients was significantly longer than in CD117– patients, but there was no significant difference in PFS (Fig. 2K,L), and neither OS nor PFS was significantly different in the high RPR group (Fig. 2M,N). The differences in the positive detection rates of 1q21 amplification, IgH rearrangement, and TP53 mutation in patients with high RPR were not statistically significant ($p > 0.05$).

Univariate and Multivariate Analyses of OS and PFS

We analyzed a variety of prognostic factors for OS and PFS. Table 3 displays the results of the univariate Cox regression analysis. The results showed that CD56–, D13S319+, RB1+, 1q21 amplification, TP53 mutation, Cr >177 μmol/L, β2-MG >5.5 mg/L, PLT $\leq 100 \times 10^9$/L, Hb ≤85 g/L, BM PCs >30%, ISS stage III, and RPR ≥0.12 were significantly associated with PFS in MM patients ($p < 0.05$). CD56–, CD117–, D13S319+, RB1+, TP53 mutation, 1q21 amplification, LDH >200 U/L, Cr >177 μmol/L, β2-MG >5.5 mg/L, PLT $\leq 100 \times 10^9$/L, BM PCs >30%, ISS stage III, age >65 years, and RPR ≥0.12 were significantly associated with OS in MM patients ($p < 0.05$) (Table 3). Multifactorial results showed that RPR ≥0.12, D13S319+, and 1q21 amplification were independent risk factors for PFS and OS in newly diagnosed MM patients (Table 4, Figs. 3,4).

Discussion

RDW is one of the indicators commonly used in the clinical diagnosis of anemia. The inflammatory factors released by cells reduce the sensitivity of bone marrow hematopoietic stem cells to erythropoietin; Erythrocyte maturation was impaired, and the size of peripheral erythrocytes was increased [9]. Recent studies have discovered a significant correlation between RDW and the prognosis of different malignancies [11–13]. Zhou *et al.* [13] found that in MM patients, OS and PFS in patients with high RDW were decreased, and RDW decreased when pa-

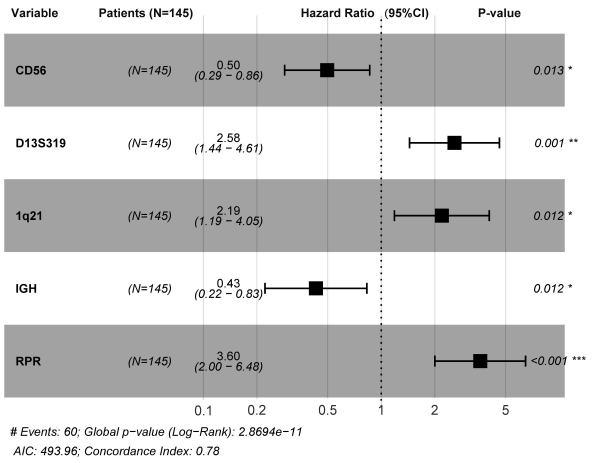

Fig. 3. Multifactorial analysis of the combination of multiple indicators of PFS. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

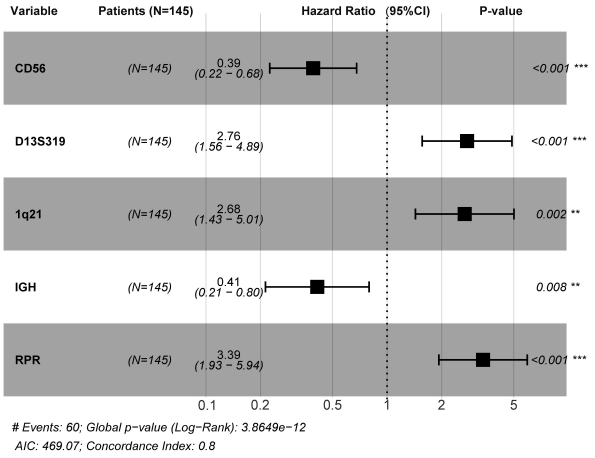

Fig. 4. Multifactorial analysis of the combination of multiple indicators of OS. $^{**}p < 0.01$, $^{***}p < 0.001$.

tients achieved complete remission (CR) after treatment, but RDW levels increased when the disease progressed. Thus, changes in RDW levels may somewhat reflect the disease state and prognosis. It has been reported that the inflammatory prognostic scoring index (IPSI), including three indicators: RDW, NLR (neutrophil to lymphocyte ratio), can be used to predict the prognosis and survival of patients with myeloma [7]. Li *et al.* [20] reported seven studies on RDW and the prognosis of hematological malignancies in a database and performed a meta-analysis. The results showed that elevated RDW could predict the shorter OS, event free survival (EFS), and PFS in patients with malignant hematological diseases, and when analyzed separately, these results were still applicable to different tumor subtypes (including MM).

Moreover, studies show that platelet is one of the indicators of inflammation, and myeloma patients are often accompanied by thrombocytopenia. The possible mechanism is the clonal proliferation of malignant plasma cells in the bone marrow, which affects the maturity of normal megakaryocytes. Malignant plasma cells release transforming growth factor-β1, which inhibits megakaryocyte colony-forming unit development and causes thrombocytopenia [21]. A low platelet count indicates a poor prognosis in MM [14,15].

Recently, a new risk parameter combining RDW and PLT count, namely the RDW/PLT ratio (RPR), has been applied to predict prognosis in various solid tumors [16,17]. In addition, breast cancer and colorectal cancer (CRC) patients reported by Bilgin *et al.* [22] also indicated that RPR could be used as a prognostic marker of CRC. However, there is no literature on the role of RPR in the prognosis prediction of myeloma. Our study found that the patients in the high RPR group had a greater tumor burden and a deeper degree of bone marrow suppression. Furthermore, our univariate and multifactorial prognostic analyses results suggest that RPR $\geq$0.12 is one of the independent influencing factors of OS and PFS in MM patients, and OS and PFS in patients with a high RPR group are significantly shorter, which indicates that a higher RPR ratio is one of the risk factors for MM prognosis.

Relevant research shows that the impact of cytogenetic and immunophenotypic abnormalities has an impact on the prognosis of patients with MM. Amplification of 1q21 is an indicator of poor prognosis in MM [23,24]. Our study also showed that OS and PFS were considerably shorter in 1q21 amplification patients compared with non-1q21 amplification patients, and this result is generally consistent with the above findings. MM patients with a 13q14 deletion often have poor prognoses [25,26]. We used two probes, LSI-RBl (for 13q14.1–14.2) and LSI-D13S319 (for 13q14.3), to detect del (13q14). The results showed that the two fragments were not missing in the same proportion, and 13q14.3 is more often in MM patients than 13q14.1–14.2. The OS and PFS of D13S319+ patients were shorter than those of D13S319– patients. The above findings held true in the high RPR group. OS and PFS were shorter in RB1+ patients than in RB1– patients. OS and PFS were substantially shorter in RB1+ patients with high RPR. Our results also suggest that patients with del (13q14) have poorer survival. Dysregulation of TP53 is a definite high-risk feature of MM patients [27]. Our findings suggest that patients with TP53 mutations have significantly shorter survival than patients with non-TP53 mutations. More importantly, we found that the incidence of D13S319+, RB1+, 1q21 amplification and CD56+ in the high RPR group was significantly higher than in the low RPR group, and the results suggest that the high RPR group is more prone to cytogenetic abnormalities.

CD56 is an adhesion molecule on neuron cells that mediates the homing of myeloma cells. When CD56 expression is absent, the direct adhesion of myeloma cells is weakened, thus forming a microenvironment conducive to the metastasis and invasion of tumor cells [28,29]. Many

studies have shown that the OS and/or PFS of MM patients with CD56+ are significantly longer than those of MM patients with CD56– [30]. The survival analysis results in this study show that MM patients with CD56+ expression have good OS and PFS, and in multifactorial analysis, CD56– was an independent risk factor for OS, which is generally consistent with the results of previous studies [31]. More importantly, we found that the CD56+ expression rate was significantly lower in the high RPR group compared with the low ratio group. However, there was no notable change in OS and PFS between CD56+ patients and CD56– patients in the high RPR group, suggesting that the prognostic role of peripheral blood RPR levels in MM patients may not be influenced by abnormal expression of the immunophenotype. There is a controversy about the effect of CD117 on the prognosis of myeloma patients [32,33], but our study confirmed that MM patients with CD117+ expression had good OS compared to those with CD117– (not reached vs 30 months). In multifactorial analysis, CD117– was not an independent risk factor for OS and PFS, which is consistent with the results of Shim *et al*. [34]. Our findings suggest that we are more likely to find cytogenetic abnormalities in the high RPR group. In the high RPR group, the prognosis of MM patients with or without del (13q14) was statistically significant. In contrast, in the high RPR group, the impact of CD56+, CD117+, IgH rearrangement, TP53 mutation and 1q21 amplification on the prognosis of MM patients were not statistically significant, which suggested that the effect of RPR on the prognosis of MM patients is not directly affected by chromosome karyotype to a large extent. The mechanism may be the interaction between the immune inflammatory response and the bone marrow microenvironment in MM patients, thus forming a microenvironment conducive to the growth of myeloma cells. To a certain extent, patients with high RPR can be considered high-risk.

RPR is a practical and effective prognostic marker in patients with MM, it can reflect inflammation in the body and evaluate the prognosis of the disease, but this was a single-center retrospective study, which carries the limitation of a small sample size. Even though we performed a multifactorial analysis of the results, we could not completely exclude the effect of confounding factors. Moreover, this study was also limited by FISH detection technology and the definition of the positive threshold. In the future, multicenter and large-sample research is still needed to explore further the clinical application value of RPR, which may support a simple, easy-to-detect, inexpensive, and time-sensitive new indicator for evaluating the prognosis of MM patients.

Conclusions

The current research results demonstrate that elevated RPR levels are more likely to have cytogenetic and immunophenotypic abnormalities and shorter PFS and OS. Therefore, RPR can be used as a biomarker for predicting the prognosis of MM patients. In addition, this result may assist in clinically individualized treatment.

Abbreviations

RDW, red blood cell distribution width; PLT, platelet; RPR, RDW to PLT ratio; DS, Dury-Salmon; ISS, international staging system; IMWG, International Myeloma Working Group; MGUS, monoclonal gammopathy of undetermined significance; CD56+, CD56-positive; CD56–, CD56-negative; CD117+, CD117-positive; CD117–, CD117-negative; D13S319+, D13S319-positive; D13S319–, D13S319-negative; RB1+, RB1-positive; RB1–, RB1-negative; IgH+, IgH rearrangement; IgH–, non-IgH rearrangement; P53+, P53 mutation; P53–, non-P53 mutation; 1q21+, 1q21 amplification; 1q21–, non-1q21 amplification; Hb, hemoglobin; LDH, lactate dehydrogenase; β2-MG, β2-macroglobulinemia; Cr, creatinine; OS, overall survival; PFS, progression-free survival.

Availability of Data and Materials

The datasets generated during the current study will not be made public because they will contain patient data, and the informed consent agreement does not include the sharing of data publicly. Upon a reasonable request, the corresponding author may provide an anonymized version of the data.

Author Contributions

XS and HW—performed the data acquisition, curation and reviewing the original draft; ML and YB—performed formal analysis, statistical analysis, writing-original draft; WL and XX—performed the interpretation of data, the project administration, Kaplan–Meier curves analysis and reviewing original draft; YC and KS—performed writing-review & editing, conceptualization and funding acquisition. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Medical Ethical Committee of Henan Provincial People's Hospital [(2018) Ethics Examination No. (51)]. Each participant signed a written informed consent form before enrolment.

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Conflict of Interest

The authors declare no conflict of interest.

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