



# Correlation between red blood cell distribution width/platelet count and prognosis of newly diagnosed diffuse large B-cell lymphoma

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## Background

Red blood cell distribution width/platelet count ratio (RPR) is a reliable prognostic assessment indicator for numerous diseases. However, no studies to date have examined the relationship between RPR and the prognosis of diffuse large B-cell lymphoma (DLBCL). Therefore, this study aimed to investigate the correlation between RPR and the clinical characteristics and prognosis of patients with diffuse large B-cell lymphoma.

## Methods

We retrospectively studied 143 patients with newly diagnosed DLBCL and used the median value as the RPR threshold. We also investigated the correlation of pretreatment RPR level with clinical characteristics and its impact on DLBCL prognosis.

## Results

Using the median value as the cut-off, patients with DLBCL were divided into a low RPR group ( $< 0.0549$ ) and a high RPR group ( $\geq 0.0549$ ). Patients in the high RPR group were older, had a later Ann Arbor stage, were prone to bone marrow invasion, and had a higher National Comprehensive Cancer Network International Prognostic Index score ( $P < 0.05$ ). A survival analysis showed that progression-free survival (PFS) ( $P = 0.003$ ) and overall survival (OS) ( $P < 0.0001$ ) were significantly shorter in the high versus low RPR group. A multifactorial Cox analysis showed that bone marrow invasion and elevated lactate dehydrogenase (LDH) were separate risk factors for PFS ( $P < 0.05$ ), while an RPR  $\geq 0.0549$  and elevated LDH were separate risk factors for OS ( $P < 0.05$ ).

## Conclusion

A high RPR ( $\geq 0.0549$ ) in patients with newly diagnosed DLBCL is an independent risk factor for a poor prognosis.

**Key Words** Red blood cell distribution width, Platelet count, Diffuse large B-cell lymphoma, Prognosis

## INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is an aggressive tumor derived from mature B-cells and the most prevalent kind of non-Hodgkin lymphoma [1]. With the advent of the rituximab era, the National Comprehensive Cancer Network IPI (NCCN-IPI) is now mostly used in clinical practice to assess the prognosis of DLBCL, which consists of five parameters – tumor stage, performance status, serum lactate dehydrogenase (LDH) level, age, and number of extra-

nodal involvement sites – and can more efficiently predict the survival rate of DLBCL patients [2]. However, the prognosis of patients with poor outcomes has not been fully elucidated, so new prognostic biomarkers are needed to better predict the prognosis of patients with DLBCL.

In addition, several studies have identified the prognostic significance of immunohistochemical features, molecular genetic markers, and biochemical markers in DLBCL [3], but these are usually accompanied by high cost, high technical skill requirements, and time-consuming procedures. Therefore, there is also a clinical need for a simple and easy-to-use

laboratory indicator to determine prognosis. Inflammation and tumors are closely related, and inflammatory cells in the tumor microenvironment can promote tumorigenesis and progression [4]. An increasing number of studies have verified the link between inflammation-related clinical indicators and cancer biological behavior and patient prognosis. These clinical indicators include lymphocyte-monocyte ratio, red blood cell distribution width (RDW), platelet count (PLT), and mean platelet volume (MPV) and have significant prognostic value in DLBCL [5-8]. The RDW to platelet ratio (RPR) is a newly proposed composite parameter index that plays an important role in predicting the prognosis of many diseases. Studies have shown that the RPR in the peripheral blood is an independent risk factor affecting the prognosis of glioblastoma and acute pancreatitis, while an elevated RPR index suggests a poor prognosis for breast cancer and multiple myeloma [9-12]. However, research is lacking on the prognostic relevance of RPR for patients with newly diagnosed DLBCL.

Therefore, this study retrospectively analyzed the relationship between RPR and clinical characteristics in newly diag-

nosed DLBCL patients and aimed to identify the prognostic assessment value of RPR in patients with newly diagnosed DLBCL.

## MATERIALS AND METHODS

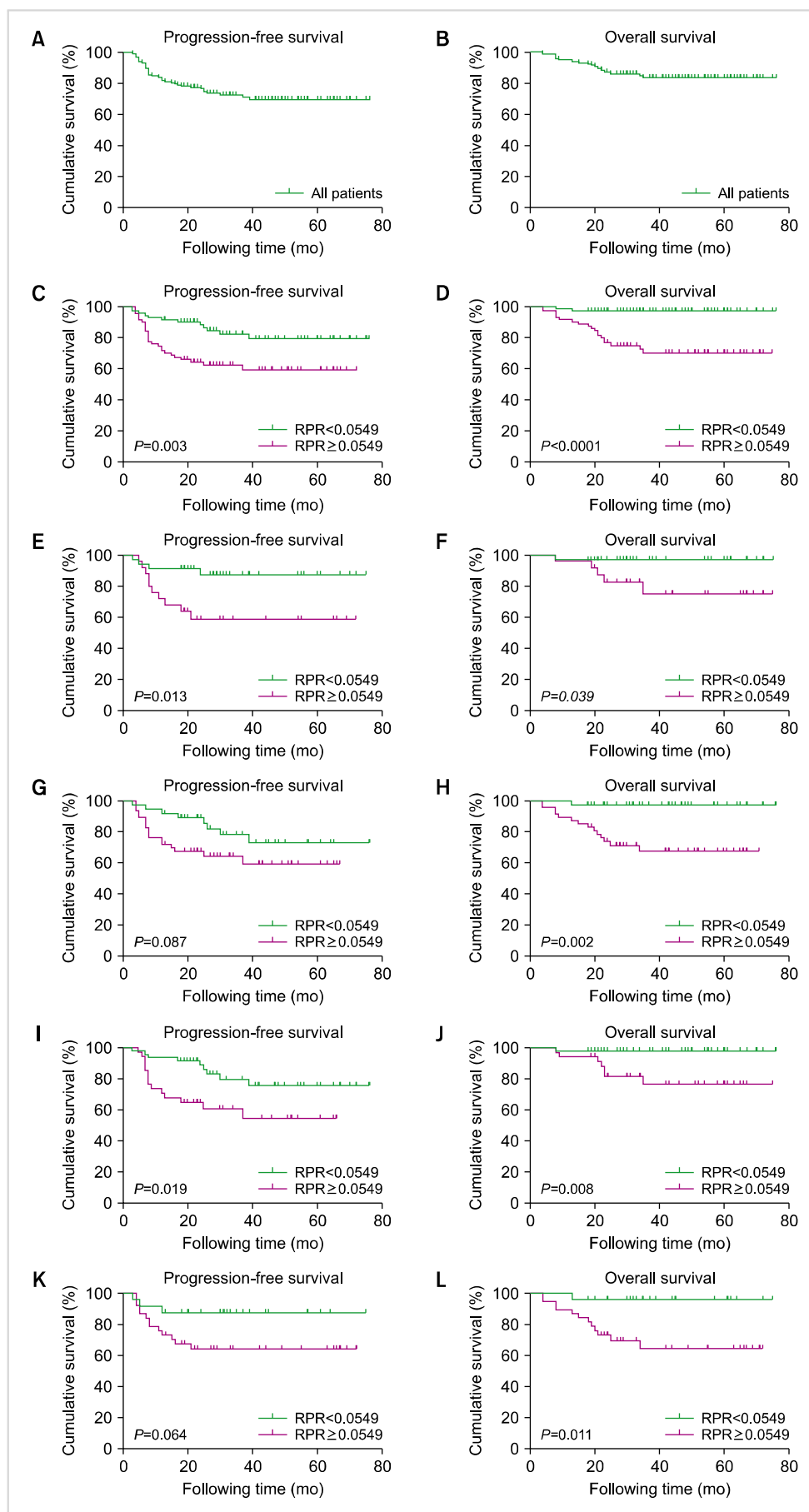
### Patients

From January 2017 to December 2021, 143 patients with newly diagnosed DLBCL qualified for the study. The study adhered to the principles of the Helsinki Declaration and was authorized by the Henan Provincial People's Hospital's Institutional Review Board. Patients with primary central nervous system DLBCL, autoimmune diseases, combined human immunodeficiency virus-positive and inflammatory-responsive diseases, malignancies, other hematologic diseases, and previous chemoradiotherapy were excluded. All clinical baseline characteristics were collected from medical records, including sex; age; Eastern Cooperative Oncology Group Physical Status Score (ECOG PS); B symptoms (weight loss, night sweats, and fever); Ann Arbor stage; Hans stage; LDH level;

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

Variable	RPR < 0.0549 (N=71)	RPR ≥ 0.0549 (N=72)	$\chi^2$	P
Sex			0.338	0.561
Male	36 (50.7%)	40 (55.6%)		
Female	35 (49.3%)	32 (44.4%)		
Age, years			5.241	0.022
≤60	47 (66.2%)	34 (47.2%)		
>60	24 (33.8%)	38 (52.8%)		
ECOG PS score			3.348	0.067
<2	61 (85.9%)	53 (73.6%)		
≥2	10 (14.1%)	19 (26.4%)		
B symptoms			2.786	0.095
No	57 (80.3%)	49 (68.1%)		
Yes	14 (19.7%)	23 (31.9%)		
Ann Arbor stage			11.826	0.001
I-II	42 (59.2%)	22 (30.6%)		
III-IV	29 (40.8%)	50 (69.4%)		
LDH			0.362	0.547
Normal	42 (59.2%)	39 (54.2%)		
Elevated	29 (40.8%)	33 (45.8%)		
Extranodal sites, N			3.002	0.083
<2	53 (74.6%)	44 (61.1%)		
≥2	18 (25.4%)	28 (38.9%)		
Bone marrow involvement			7.842	0.005
No	70 (98.6%)	62 (86.1%)		
Yes	1 (1.4%)	10 (13.9%)		
NCCN-IPI			6.220	0.013
0-3	50 (70.4%)	36 (50.0%)		
4-8	21 (29.6%)	36 (50.0%)		
Hans type			2.556	0.110
GCB	34 (47.9%)	25 (34.7%)		
Non-GCB	37 (52.1%)	47 (65.3%)		

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Physical Status; GCB, germinal center B-cell; LDH, lactate dehydrogenase; NCCN-IPI, National Comprehensive Cancer Network International Prognostic Index; RPR, red blood cell distribution width/platelet count.



**Fig. 1.** Kaplan-Meier curves of overall survival (OS) and progression-free survival (PFS). **(A, B)** Kaplan-Meier curves of PFS and OS in all patients. **(C, D)** Kaplan-Meier curves for PFS and OS according to red blood cell distribution width/platelet count (RPR). **(E, F)** Kaplan-Meier curves of PFS and OS were plotted according to RPR in the germinal center B-cell (GCB) group. **(G, H)** Kaplan-Meier curves of PFS and OS were plotted according to the RPR in the non-GCB group. **(I, J)** Kaplan-Meier curves of PFS and OS were plotted according to RPR in the group aged ≤ 60 years. **(K, L)** Kaplan-Meier curves of PFS and OS were plotted according to RPR in the group aged > 60 years.

number of extranodal lesions; International Comprehensive Cancer Network International Prognostic Index score; bone marrow morphology and biopsy results; RDW, PLT, and immunophenotype; ultrasound and computed tomography of the chest, abdomen, and pelvis; and whole-body positron emission tomography. RPR was calculated based on the laboratory parameters (RDW, PLT) at the time of the patient's initial diagnosis as  $RPR = RDW (\%) / PLT (\times 10^9 / L)$ .

### Follow-up and survival time

Follow-up by telephone and the review of inpatient and outpatient medical records was conducted until May 2023. Progression-free survival (PFS) was defined as the time from the date of diagnosis until disease progression, relapse, death, or the end of follow-up, while overall survival (OS) was defined as the time from the date of diagnosis until death or the end of follow-up.

### Statistical analysis

For the statistical analysis and graphing, GraphPad Prism version 8.0 and SPSS software version 25.0 were used. The chi-squared test was applied to analyze the correlation between RPR and DLBCL clinical factors. The Kaplan-Meier method was used to analyze PFS and OS using the log-rank test. In addition, Cox proportional risk regression models were used to perform univariate and multifactorial analyses of factors affecting PFS and OS. Values of  $P < 0.05$  were considered statistically significant.

## RESULTS

### Patients' baseline characteristics

Among the 143 patients with newly diagnosed DLBCL, 76 (53.1%) were male and 67 (46.9%) were female. The median age was 58 (8–86) years; 62 (43.4%) were  $> 60$  years

and 81 (56.6%) were  $\leq 60$  years. 114 patients (79.7%) had ECOG PS score  $< 2$  and 29 (20.3%) patients had  $\geq 2$ . By Ann Arbor tumor stage, 64 (44.8%) I or II, while 79 (55.2%) had III or IV. B symptoms were reported by 37 patients (25.9%). LDH level was elevated in 62 cases (43.4%). There were  $\geq 2$  extranodal lesions in 46 cases (32.2%). In 11 cases, bone marrow invasion was noted (7.7%). The NCCN-IPI score was low to intermediate risk (0–3) in 86 cases (60.1%) and intermediate to high risk (4–8) in 57 cases (39.9%). A total of 59 cases (41.3%) were germinal center B-cell (GCB) and 84 cases (58.7%) were non-GCB by Hans classification.

### Relationship between RPR and clinical characteristics

Since the sample data were not normally distributed, the median of 0.0549 was taken as the threshold value, and DLBCL patients were split into low ( $< 0.0549$ ) and high ( $\geq 0.0549$ ) RPR groups. The patients' baseline characteristics were compared between groups using the chi-squared test. The findings revealed that DLBCL patients in the high RPR group were older ( $> 60$  yr), had a higher Ann Arbor stage (stage III–IV), were prone to bone marrow invasion, and had a higher NCCN-IPI score than the low RPR group ( $P < 0.05$ ). However, sex, ECOG PS score, B symptoms, LDH level, number of extranodal locations, and Hans type did not differ significantly between groups ( $P > 0.05$ ) (Table 1).

### Relationship between RPR and clinical outcomes

The median follow-up in this study was 40 months (range, 18–76 mo), and the 3-year PFS and OS rates were 72.5% and 83.5%, respectively (Fig. 1A, B). The groups were compared using Kaplan-Meier survival curves. The survival of DLBCL patients was considerably worse in the high RPR group (3-year PFS rate: 62.5% vs. 82.5%,  $P = 0.003$ ; 3-year OS rate: 70.3% vs. 97.2%,  $P < 0.0001$ ) (Fig. 1C, D). To learn more about the predictive usefulness of RPR levels in differ-

**Table 2.** Univariate analysis of predictors of overall survival (OS) and progression-free survival (PFS) time in patients with newly diagnosed DLBCL.

Factor	PFS		OS	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Sex, male	0.966 (0.515–1.810)	0.913	0.818 (0.347–1.928)	0.646
Age $> 60$ years	0.983 (0.519–1.861)	0.959	2.338 (0.968–5.644)	0.059
Ann Arbor stage III–IV	3.093 (1.468–6.518)	0.003	8.135 (1.895–34.928)	0.005
B symptoms	2.720 (1.448–5.111)	0.002	2.827 (1.200–6.661)	0.017
ECOG PS score $\geq 2$	1.735 (0.863–3.488)	0.122	2.048 (0.826–5.076)	0.122
LDH elevated	2.603 (1.352–5.012)	0.004	6.124 (2.060–18.203)	0.001
Extranodal sites $\geq 2$	1.778 (0.943–3.353)	0.076	3.123 (1.315–7.417)	0.010
Bone marrow involvement	5.969 (2.816–12.653)	0.000	5.649 (2.188–14.585)	0.000
Hans type	1.281 (0.666–2.464)	0.459	1.775 (0.689–4.577)	0.235
NCCN-IPI $> 3$	2.988 (1.563–5.712)	0.001	7.174 (2.412–21.342)	0.000
RPR $\geq 0.0549$	2.644 (1.338–5.226)	0.005	10.349 (2.410–44.447)	0.002

Abbreviations: DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group Physical Status; LDH, lactate dehydrogenase; NCCN-IPI, National Comprehensive Cancer Network International Prognostic Index; RDW, red blood cell distribution width; PLT, platelet count; RPR, RDW to PLT ratio.

ent pathological staging and age groupings, a Kaplan-Meier analysis showed significant variations in PFS and OS between the low and high RPR groups in the GCB group (3-year PFS rate: 59.1% vs. 87.4%,  $P=0.013$ ; 3-year OS rate: 75.1% vs. 97.1%,  $P=0.039$ ) (Fig. 1E, F); in the non-GCB group, patients in the high RPR group had poorer OS (3-year OS rate: 67.7% vs. 97.3%,  $P=0.002$ ), but the PFS results were not statistically significant (Fig. 1G, H). The patients were split into two groups by age ( $\leq 60$  yr vs.  $> 60$  yr). Among patients aged  $\leq 60$  yr, the 3-year PFS rate (54.6% vs. 79.6%,  $P=0.019$ ) and 3-year OS rate (76.5% vs. 97.8%,  $P=0.008$ ) were significantly lower in the high versus low RPR group (Fig. 1I, J). Among patients aged  $> 60$  years, those in the low RPR group had significantly higher OS than those in the high RPR group, but there was not a significant distinction in PFS (Fig. 1K, L).

### Univariate and multivariate analyses of OS and PFS

We analyzed various prognostic factors affecting PFS and OS. Table 2 shows the results of the Cox regression univariate analysis. Ann Arbor stage III–IV, B symptoms, elevated LDH level, bone marrow invasion, NCCN-IPI  $> 3$ , and RPR  $\geq 0.0549$  were strongly related to PFS and OS in individuals with DLBCL ( $P < 0.05$ ). The multifactorial analysis results showed that bone marrow invasion and an elevated LDH level were separate risk factors for PFS and an elevated LDH level and RPR  $\geq 0.0549$  were separate risk factors for OS in patients with newly diagnosed DLBCL (Table 3).

## DISCUSSION

RDW is often used to analyze anemia type. The inflammatory factors released by cells inhibit the maturation of erythrocytes in the bone marrow, causing a significant number of immature erythrocytes to be released into the circulation, leading to an increased width of the peripheral blood erythrocyte distribution [13]. RDW is strongly correlated with the prognosis of several malignancies [14–17]. Beltran *et al.* [18] concluded that patients with a high RDW had a significantly poorer 5-year OS rate following R-CHOP (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone) treatment for de novo

DLBCL than patients with a normal RDW (51% vs. 79%,  $P=0.001$ ), and a high RDW appears to be a bad prognostic factor. The predictive power of IPI and NCCN-IPI for the prognosis of DLBCL patients was reportedly improved when RDW and PLT parameters were included [6]. Periša *et al.* [14] discovered that a high RDW was a separate risk factor for OS and PFS in DLBCL patients. Ai *et al.* [19] conducted a meta-analysis of seven research studies of the prognosis of RDW in hematologic malignancies' analysis. An elevated RDW predicted shorter OS, event-free survival, and PFS in patients with hematologic malignancies; moreover, similar results could be obtained in subgroup analyses of different tumors, including DLBCL.

In addition, studies have shown that platelets are an inflammation-related marker; however, the biological mechanism by which platelets influence the prognosis of DLBCL is unclear. Interestingly, early research indicated that thrombocytopenia negatively affects the survival of lymphoma patients if the bone marrow is involved [20, 21]. Moreover, a reduced PLT suggests a poor prognosis for DLBCL [6].

In recent years, a new inflammation composite index combining RDW and PLT count, namely RPR, can be used to predict the prognosis of different malignancies [9, 11]. In addition, Bilgin *et al.* [22] concluded that RPR can be utilized as a prognostic indicator for patients with colorectal cancer. However, no study of the effect of RPR on the prognosis of DLBCL has been reported to date. Our study showed that patients in the high RPR ( $\geq 0.0549$ ) group were more prone to bone marrow invasion. It also found that a high RPR is an independent influencing factors of OS in DLBCL patients by univariate and multifactorial prognostic analysis and that patients in the high RPR group had significantly shorter PFS and OS, suggesting that a higher RPR level is among the risk factors affecting the prognosis of DLBCL.

DLBCL is commonly classified clinically by the Hans system according to immunohistochemistry: GCB type and activated B-cell type (ABC) or non-GCB type. They differ in gene expression profiles and clinical presentations. Relevant studies reported that DLBCL of GCB origin has longer survival than the ABC (non-GCB) type and that better survival is achieved with CHOP/R-CHOP treatment [1, 23, 24], so the cell origin typing of DLBCL is of great significance for prognosis and treatment guidance in clinical practice. More

**Table 3.** Multifactorial analysis of predictors of overall survival (OS) and progression-free survival (PFS) time in patients with newly diagnosed DLBCL.

Factors	PFS		OS	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
B symptoms	1.505 (0.736–3.077)	0.262	1.058 (0.408–2.741)	0.908
LDH elevated	2.196 (1.049–4.594)	0.037	5.271 (1.608–17.282)	0.006
Extranodal sites $\geq 2$	0.898 (0.431–1.871)	0.773	1.193 (0.443–3.209)	0.727
Bone marrow involvement	3.644 (1.510–8.794)	0.004	2.585 (0.874–7.651)	0.086
RPR $\geq 0.0549$	1.923 (0.925–3.998)	0.080	8.542 (1.945–37.521)	0.004

Abbreviations: LDH, lactate dehydrogenase; PLT, platelet count; RDW, red blood cell distribution width; RPR, RDW to PLT ratio.



importantly, our study also found that, in the GCB group, compared to the low RPR group, the high RPR group's PFS and OS were shorter. In addition, in the ABC group, OS was significantly shorter in the high versus low RPR group. DLBCL predominates in older people, with a median age at onset of about 70 years [1]. The results of this study showed that patients in the high RPR group were older than those in the low RPR group, consistent with the above findings. In the subgroup analysis, among DLBCL patients aged  $\leq 60$  years, PFS and OS were significantly lower in the high versus low RPR group; among DLBCL patients aged  $> 60$  years, OS was shorter in the high versus low RPR group. The above findings suggest that high RPR levels are connected with bad prognosis in DLBCL patients. Therefore, this implies that RPR could further refine risk stratification.

RPR is a new inflammatory measure that can be used to assess a patient's DLBCL prognosis, but this study has certain restrictions due to its single-center retrospective design and limited sample size. Although we performed a multi-factorial analysis of the study results, the effect of confounding factors still cannot be completely excluded. Second, the biochemical mechanisms through which RDW and PLT affect the prognosis of patients with DLBCL remain unknown. Therefore, to further confirm the clinical application value of RPR levels in patients with DLBCL, large prospective multicenter studies are required to provide a simple and easy-to-use parameter for prognostic assessments of DLBCL patients.

The findings of this study indicate that RPR is an independent risk factor for OS in DLBCL patients and closely correlated with the prognosis of newly diagnosed DLBCL patients; therefore, RPR can be used as a simple and easy prognostic biomarker or be combined with immunohistochemistry for more accurate prognostic assessments of patients with DLBCL.

#### Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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