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Original Article

Prognostic value of multiple immune inflammatory markers in diffuse large B-cell lymphoma

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Abstract: Objective: To explore the prognostic value of multiple immune inflammatory indicators for diffuse large B-cell lymphoma (DLBCL). Methods: The clinical data of 175 patients with DLBCL who were diagnosed and received Immunochemotherapy in The Qinzhou First People's Hospital between January 2015 and December 2021 were retrospectively analyzed for this study. Patients were classified into a death group (n = 54) and a survival group (n = 121) depending on their prognosis. The clinical data of the patients with lymphocytes-to-beads (LMR), neutrophils-to-lymphocytes (NLR), and platelets-to-lymphocytes (PLR) were collected. The receiver operator characteristic curve (ROC) was used to determine the optimal critical value of the immune index. The Kaplan-Meier was used to draw the survival curve. The Cox regression model was used to analyze the factors affecting the prognosis of DLBCL. A nomogram risk prediction model was constructed to verify its effectiveness. Results: By the ROC curve analysis, the optimal cut-off value was 3.93 × 10^9/L for neutrophil count, 2.42 for LMR, 23.6 mg/L for C-reactive protein (CPR), 2.44 for NLR, 0.67 × 10^9/L for Monocyte, and 195.89 for PLR. The survival rate of patients with neutrophil number ≤ 3.93 × 10^9/L, LMR > 2.42, CRP ≤ 23.6 mg/L, NLR ≤ 2.44, Monocyte ≤ 0.67 × 10^9/L, PLR ≤ 195.89 was higher than that of patients with neutrophil number > 3.93 × 10^9/L, LMR ≤ 2.42, CRP > 23.6 mg/L, NLR > 2.44, and Monocyte > 0.67 × 10^9/L, PLR > 195.89. The nomogram was constructed based on the results of the multivariate analysis. The AUC of the nomogram was 0.962 (95% CI: 0.931-0.993) and 0.952 (95% CI: 0.883-1) in the training set and the test set, respectively. The calibration curve showed that the predicted value of the nomogram was in good agreement with the actual observed value. Conclusion: IPI score, neutrophil count, NLR, and PLR are risk factors impacting the prognosis of DLBCL. The combined prediction of IPI score, neutrophil count, NLR, and PLR can better reflect the prognosis of DLBCL. It can be used as a clinical index to predict the prognosis of diffuse large B-cell lymphoma, and provide clinical basis for improving the prognosis of patients.

Keywords: DLBCL, NLR, PLR, LMR

Introduction

DLBCL is a common non-Hodgkin's lymphoma [1]. Patients with this disease are treated in combination with chemotherapy, immunotherapy, and targeted drug therapy. These help to improve the survival rate of patients. Individuals are heterogenous in clinical manifestations. There will be different therapeutic responses during treatment [2], leading to different prognosis. There are many clinical indicators used to evaluate the prognosis of DLBCL, like the International Prognostic Index (IPI) and BCL-2 [3]. With the wide application of rituximab, the prediction efficiency of IPI for DLBCL has been reduced. It has been unable to effectively guide the clinical prognosis of patients [4]. It is necessary to explore feasible and effective prognostic indicators to provide a reference for future treatment of DLBCL. There are many pieces of research to explore related indicators for predicting tumor prognosis [5]. Han Ying [6] pointed out that inflammation affects the development of tumor diseases. Several studies [7, 8] showed that peripheral blood neutrophil/lymphocyte ratio (NLR) can be used to evaluate the prognosis of various tumors. Several studies [6, 9] used these indicators as prognostic indicators for DLBCL. The sample size selected in the above study was small. The regions of the

included research objects were different. The heterogeneity between individuals is large, resulting in different research results. This study analyzed the relationship between peripheral blood neutrophil count, monocyte count, LMR, NLR, and PLR immune inflammatory indicators and prognosis of DLBCL patients in Qinzhou City. By constructing a nomogram risk prediction model, the predictive value of immune inflammation indicators for the prognosis of patients with DLBCL was explored to provide a clinical basis for improving the prognosis of patients.

Materials and methods

General information

In this retrospective analysis, 175 patients with DLBCL who were diagnosed and received Immunochemotherapy in Qinzhou First People's Hospital between January 2015 to December 2021 were selected as research objects. Inclusion criteria: (1) The patients were pathologically diagnosed as DLBCL; (2) The patient's clinical data, laboratory test data, and follow-up data were completed. Exclusion criteria: (1) Severe diseases of the heart and liver; (2) The patient had other malignancies. This research was approved by Qinzhou First People's Hospital ethics.

Information collection

The clinical data of patients before Immunochemotherapy were collected. This included the gender, age, B symptoms, clinical stage, International Prognostic Index (IPI) grading (0-1 = low risk, 2 = low-moderate risk, 3 = medium-high risk, 4-5 = high risk), extranodal involvement site, and ECOG behavior score (0-5 points, 0 being normal and 5 being dead. The lower the score was, the healthier the patient's physical function). The IPI score included age, clinical stage, extranodal involvement, ECOG behavior score, and LDH level. The hospital laboratory indicators: peripheral blood neutrophil count, monocyte count, C-reactive protein (CPR), lymphocyte count, platelet count, and calculate the ratio of lymphocytes-to-monocytes (LMR), neutrophils-to-lymphocytes (NLR), platelets-to-lymphocytes (PLR) were also included.

Research objective: To analyze the risk factors affecting the prognosis of DLBCL, and to construct the risk prediction model of line graph using R software. To explore the predictive value of LMR, NLR, and PLR immune indicators for the prognosis of DLBCL. This helped to provide a clinical basis for the improvement of the prognosis of patients.

Observation endpoint and grouping

The total survival time (OS) was measured from the time when diagnosis was confirmed until death. The date of treatment initiation was taken as the start date of follow-up. Follow-up was conducted through outpatient review and telephone interview. The deadline for follow-up was August 31, 2022. Depending on the prognosis of the patients, they were divided into a death group (n = 54) and a survival group (n = 121).

Statistical methods

The spss23.0 program was employed for analysis and processing. Count data were indicated by the number of instances (%). The chi-square test was applied for between-group comparisons. Quantitative data conforming to normal distribution were expressed as $\bar{x} \pm s$ and compared using t-test. The survival curve was drawn by Kaplan-Meier. The Log-rank test was used for comparison. The Cox proportional hazard model was used for univariate and multivariate regression analysis of prognostic factors. The nomogram risk prediction model was constructed by R software. The ROC curve was used to evaluate the discrimination of the model. The fitting of the model was expressed by the calibration curve. $P < 0.05$ was considered a significant difference.

Results and discussion

Comparison of general data

A comparison of general data between the two groups showed significant gender differences, B symptoms, clinical stage, IPI, ECOG behavior score, extranodal involvement, peripheral neutrophil count, monocyte count, CRP, LMR, NLR, and PLR (all $P < 0.05$), as shown in **Table 1**.

Calculation of optimal cut-off values of different indexes

The results of the ROC curve showed that the optimal cut-off value of LMR was 2.42, CRP was

Table 1. Comparison of clinical data between the two groups of patients

Influencing factors	Group of Death (n = 54)	Survival group (n = 121)	X^2/t value	*P* value
Gender [n (%)]				
male	41 (75.93)	70 (57.85)	5.258	0.022
female	13 (24.07)	51 (42.15)		
Age ($\bar{x}$±s)	59.06±12.69	56.76±14.05	1.027	0.306
Clinical stage [n (%)]				
I-II period	8 (14.81)	67 (55.37)	25.078	< 0.001
III-IV period	46 (85.19)	54 (44.63)		
B Symptoms [n (%)]				
yes	30 (55.56)	32 (26.45)	13.830	< 0.001
no	24 (44.44)	89 (73.55)		
Extranodal involved site [n (%)]				
0	10 (18.52)	70 (57.85)	23.417	< 0.001
1	35 (64.81)	42 (34.71)		
≥2	9 (16.67)	9 (7.44)		
ECOG [n (%)]				
0-1	41 (75.93)	115 (95.04)	14.096	< 0.001
2-5	13 (24.07)	6 (4.96)		
LDH ($\bar{x}$±s, U/L)	385.65±300.48	305.60±298.43	1.636	0.104
IPI ($\bar{x}$±s, points)	2.32±1.11	1.40±1.16	4.902	< 0.001
Neutrophil count ($\bar{x}$±s, × 10^9/L)	5.81±3.27	3.05±1.92	5.779	< 0.001
Monocyte count ($\bar{x}$±s, × 10^9/L)	1.84±3.73	0.78±0.94	2.058	0.044
NLR ($\bar{x}$±s)	6.22±6.82	3.10±8.04	2.478	0.014
PLR ($\bar{x}$±s)	328.42±262.95	176.88±346.43	2.865	0.005
LMR ($\bar{x}$±s)	2.00±1.71	3.46±3.80	2.693	0.008
CRP ($\bar{x}$±s, mg/L)	34.75±46.48	17.47±15.00	2.669	0.010

IPI, International Prognostic Index; LMR, lymphocytes-to-beads; NLR, neutrophils-to-lymphocytes; PLR, platelets-to-lymphocytes.

23.6 mg/L, neutrophil count was 3.93 × 10^9/L, NLR was 2.44, Monocyte was 0.67 × 10^9/L, and PLR was 195.89 (**Table 2**). The comparison of AUC, sensitivity and specificity of each index is shown in **Table 3**.

Comparison of survival rate of patients with different index levels

The Kaplan-Meier analysis yielded a higher survival rate for female patients than male patients. The survival rate of patients in I-II period was higher than that in III-IV period. The survival rate of patients with B symptoms was low. The more extranodal sites involved, the lower the survival rate of patients (**Figure 1**).

Patients with low ECOG and IPI scores had higher survival rates. Survival rates were higher in patients with neutrophil counts ≤ 3.93 × 10^9/L than in those with neutrophil counts > 3.93 × 10^9/L. Survival rates were higher in patients with Monocyte counts ≤ 0.67 × 10^9/L than in those with Monocyte counts > 0.67 × 10^9/L (**Figure 2**).

Patients with NLR ≤ 2.44 had a higher survival rate than those with NLR > 2.44. The patients with PLR ≤ 195.89 had a higher survival rate than those with PLR > 195.89. Patients with LMR > 2.42 had a higher survival rate than those with LMR ≤ 2.42. The survival rate of patients with CRP ≤ 23.6 mg/L was higher than that of CRP > 23.6 mg/L (**Figure 3**).

Single factor analysis of prognosis of patients with DLBCL

The univariate COX regression analysis showed that gender, B symptoms, clinical stage, IPI, ECOG, extranodal involvement, neutrophil

Table 2. ROC curve analysis

Influencing factors	Optimal sectional value	Specificity (%)	Sensitivity (%)	AUC	95% CI	*P* value
LMR	2.42	59.50	75.93	0.676	0.602-0.745	< 0.001
CRP	23.6	83.47	40.74	0.604	0.527-0.677	0.037
Neutrophil count	3.93	87.60	85.19	0.877	0.819-0.922	< 0.001
NLR	2.44	78.51	96.30	0.860	0.799-0.907	< 0.001
Monocyte	0.67	64.46	68.52	0.663	0.588-0.733	< 0.001
PLR	195.89	81.82	77.78	0.803	0.736-0.859	< 0.001

LMR, lymphocytes-to-beads; NLR, neutrophils-to-lymphocytes; PLR, platelets-to-lymphocytes.

Table 3. Comparison of specificity, sensitivity, and AUC of each index

	Specificity (%)	Sensitivity (%)	AUC
LMR vs CRP	$P < 0.001$	$P < 0.001$	$P > 0.05$
LMR vs Neutrophil count	$P < 0.001$	$P < 0.05$	$P < 0.001$
LMR vs NLR	$P < 0.001$	$P < 0.001$	$P < 0.001$
LMR vs Monocyte	$P > 0.05$	$P < 0.05$	$P > 0.05$
LMR vs PLR	$P < 0.001$	$P > 0.05$	$P < 0.001$
CRP vs Neutrophil count	$P > 0.05$	$P < 0.001$	$P < 0.001$
CRP vs NLR	$P < 0.05$	$P < 0.001$	$P < 0.001$
CRP vs Monocyte	$P < 0.001$	$P < 0.001$	$P > 0.05$
CRP vs PLR	$P > 0.05$	$P < 0.001$	$P < 0.001$
Neutrophil count vs NLR	$P < 0.05$	$P < 0.05$	$P > 0.05$
Neutrophil count vs Monocyte	$P < 0.001$	$P < 0.05$	$P < 0.001$
Neutrophil count vs PLR	$P > 0.05$	$P < 0.05$	$P > 0.05$
NLR vs Monocyte	$P < 0.05$	$P < 0.05$	$P < 0.001$
NLR vs PLR	$P > 0.05$	$P < 0.05$	$P > 0.05$
Monocyte vs PLR	$P < 0.001$	$P < 0.05$	$P < 0.001$

LMR, lymphocytes-to-beads; NLR, neutrophils-to-lymphocytes; PLR, platelets-to-lymphocytes.

count, monocyte count, CRP, LMR, NLR, and PLR were all related to DLBCL, as shown in **Table 4**.

Multivariate analysis of prognosis in patients with DLBCL

Significant variables from the univariate analysis were entered into a multi-factor regression analysis and the assignment is shown in **Table 5**. The multi-factor Cox regression analysis concluded that a higher IPI score, higher neutrophil count, and higher NLR and PLR were prognostic risk factors ($P < 0.05$), as shown in **Table 6**.

Construct a nomogram risk prediction model for DLBCL prognosis

Taking 127 patients in the training set as samples, the above four risk factors affecting the prognosis of DLBCL were included in the risk assessment. A nomogram risk model was established (**Figure 4**). To verify the prediction efficiency of the model, the ROC curves of the training set and the test set were drawn respectively (**Figure 5**). The prediction accuracy of the model was high in the training set and the test set. The ACU was 0.962 (95% CI: 0.931-0.993) and 0.952 (95% CI: 0.883-1), respectively. The calibration curve (**Figure 6**) shows that the nomogram prediction probability has good consistency in the training set and the test set.

Discussion

Clinical studies have shown that [10] malignant tumors often occur at the site of repeated infection or inflammation. The tumor microenvironment is composed of tumor cells, surrounding stromal cells, and infiltrating inflammatory cells. These evade immune surveillance for tumor cells. Diffuse large B-cell lymphoma is a hematological malignancy with rapid progression [11]. Related literature [12] reported that inflammatory factors in the tumor microenvironment are related to the occurrence, development, and metastasis of tumors, such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). DLBCL is a rapidly progressing hematologic malignancy. Targeted drug therapy currently used can improve the prognosis of patients. Complete remission can reach 40% [13]. Dotto [16] and other researchers have shown that inflammatory reactions can induce excessive cell proliferation, lead to immunosuppression, and stimulate the development of tumor cells. The

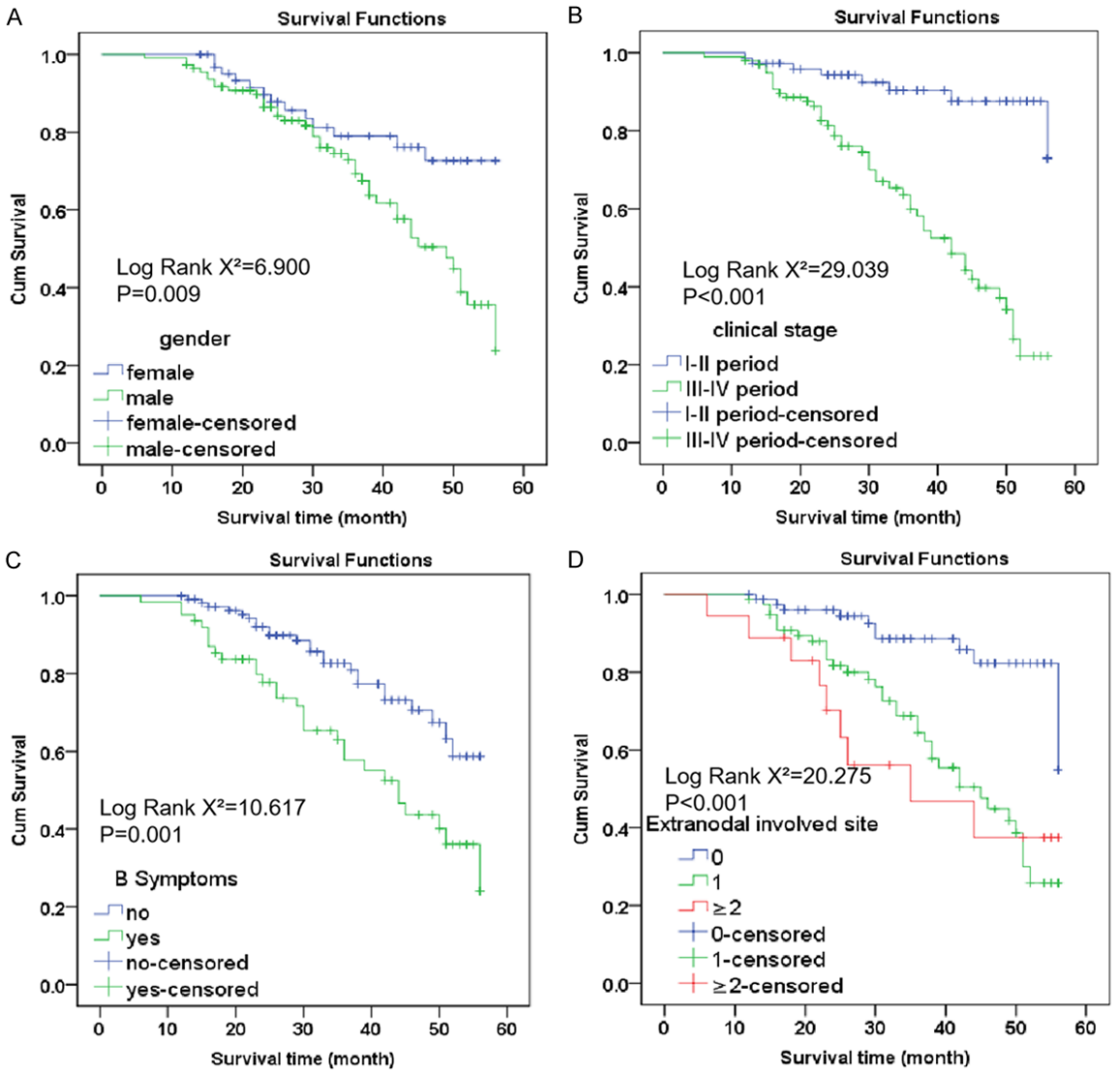

Figure 1. Survival curve of patients with different index levels. Note: A. The survival curve of patients with different gender; B. The survival curve of patients with different clinical stage; C. The survival curve of patients with different B symptoms; D. The survival curve of patients with different extranodal involved site.

immune inflammatory reaction may be the cause of tumor development. Relevant studies [14, 15] pointed out that the number of peripheral blood neutrophils and lymphocytes showed different expressions in the immune system and tumor environment. They played a great role in related tumor diseases and immune responses, which can predict tumor prognosis. Peripheral blood NLR and PLR are common immune inflammatory indicators, which played an influential role in the prognosis of many tumor diseases [16]. This study explored the predictive value of various immune inflammatory indicators such as NLR and PLR in the prognosis of DLBCL. In this study, the effects of immune indexes such as NLR and PLR on survival and prognosis of 175 DLBCL patients before treatment were analyzed. The results showed that the survival rate of patients with neutrophil count > 3.93 × 10^9/L, NLR > 2.44 and PLR > 195.89 was significantly lower. It was suggested that the higher the levels of neutrophils, NLR, and PLR in DLBCL patients, the more prone to the invasion and metastasis of tumor cells. This leads to the occurrence of poor prognosis in DLBCL patients.

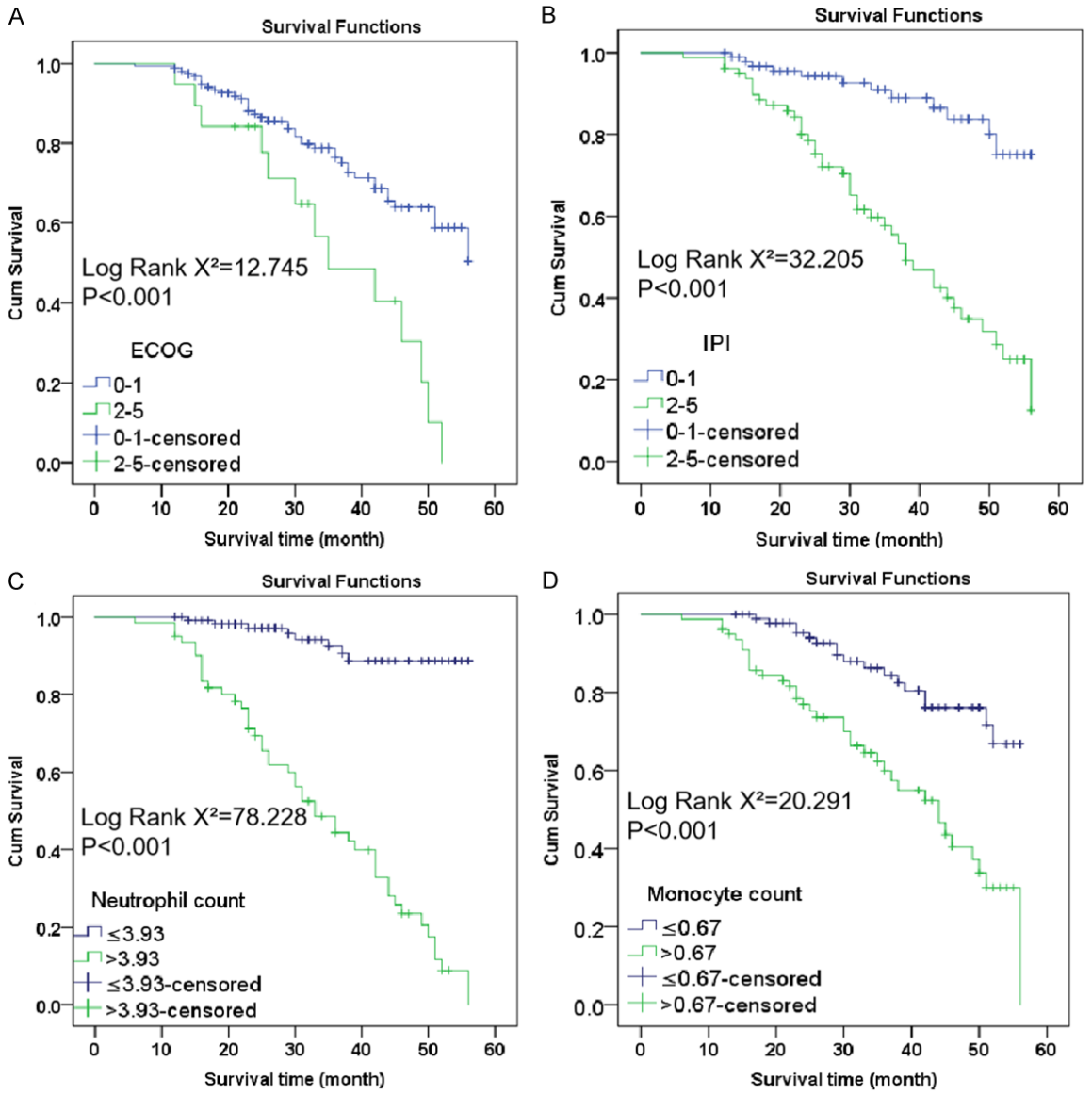

Figure 2. Survival curve of patients with different index levels. Note: A. The survival curve of patients with different ECOG; B. The survival curve of patients with different IPI; C. The survival curve of patients with different neutrophil counts; D. The survival curve of patients with different monocyte counts. IPI, International Prognostic Index.

During recent years, many studies [17-21] have predicted the prognosis of various malignant tumors with NLR. This was one of the prognostic factors affecting tumor diseases. The present research indicated that patients with reduced neutrophil counts and reduced NLR ratios had significantly higher survival rates. The results are like those of studies such as KETM [22]. This result implied that elevated NLR was relevant to poor patient prognosis. Neutrophils are inflammatory cells, which can secrete angiogenic factors [23], including VEGF, IL-8, and matrix metalloproteinase. These cytokines play an important role in tumor invasion and metastasis. It affects the progress of the tumor and can promote the proliferation of the tumor cells [24]. Lymphocytes are a major constituent of the immune system. In the case of tumor cells, lymphocytes can suppress their proliferation and differentiation. When lymphocytes are diminished, it will lead to the release of immune mediators and promote the proliferation of tumor cells [25, 26]. When NLR is increased, it means that neutrophils are in-

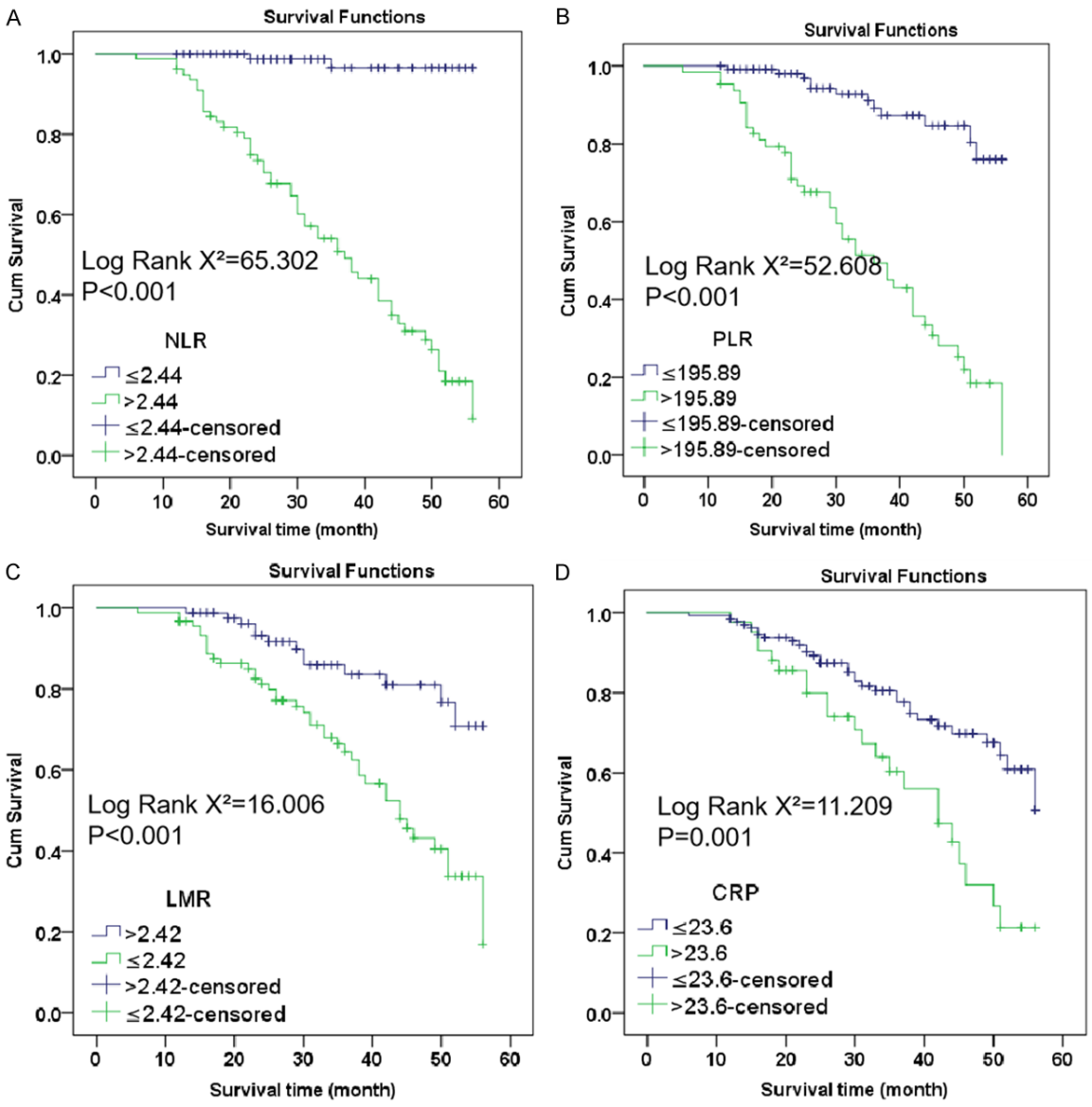

Figure 3. Survival curve of patients with different index levels. Note: A. The survival curve of patients with different NLR levels; B. The survival curve of patients with different PLR levels; C. The survival curve of patients with different LMR levels; D. The survival curve of patients with different CRP levels. lymphocytes-to-beads (LMR), neutrophils-to-lymphocytes (NLR), and platelets-to-lymphocytes (PLR).

creased or lymphocytes are decreased. This leads to the decline of body immunity and the deficiency of immune system function, leading to poor prognosis of patients. ZHAO [27] and other studies have pointed out that PLR can predict ovarian borderline tumors and have clarified the value of PLR in tumor prognosis. The present findings indicated that patients with high PLR had a lower survival rate. This demonstrated that the prognosis of patients with high PLR may be poor. Platelets can promote the proliferation and growth of inflammatory factors in the blood [28]. The possible causes of elevated PLR are higher platelets due to immune system dysfunction or decreased lymphocytes. This accelerates the development of the disease and has a poor prognosis. The results showed that IPI was part of the risk factors affecting the prognosis. The higher the IPI scores, the faster the tumor cells spread and the wider the range, causing poor prognosis. There are many factors influencing

Table 4. Univariate analysis of factors affecting DLBCL

Influencing factors	B value	SE value	Wald value	*P* value	HR (95% CI)
Gender [n (%)]	0.813	0.320	6.465	0.011	2.255 (1.205-4.22)
Clinical stage [n (%)]	1.834	0.388	22.292	< 0.001	6.26 (2.923-13.404)
B Symptoms [n (%)]	0.861	0.274	9.869	0.002	2.366 (1.382-4.048)
Extranodal involved site [n (%)]	0.800	0.193	17.198	< 0.001	2.226 (1.525-3.25)
ECOG [n (%)]	1.084	0.321	11.438	0.001	2.957 (1.578-5.544)
IPI ($\bar{x}$±s, points)	0.489	0.103	22.612	< 0.001	1.631 (1.333-1.995)
Neutrophil count ($\bar{x}$±s, × 10^9/L)	0.173	0.032	28.859	< 0.001	1.189 (1.116-1.266)
Monocyte count ($\bar{x}$±s, × 10^9/L)	0.122	0.039	9.766	0.002	1.13 (1.046-1.219)
NLR ($\bar{x}$±s)	0.030	0.011	7.473	0.006	1.030 (1.008-1.053)
PLR ($\bar{x}$±s)	0.001	0.000	11.798	0.001	1.001 (1.000-1.001)
LMR ($\bar{x}$±s)	-0.286	0.090	10.045	0.002	0.751 (0.629-0.896)
CRP ($\bar{x}$±s, mg/L)	0.008	0.003	7.657	0.006	1.008 (1.002-1.013)

IPI, International Prognostic Index; LMR, lymphocytes-to-beads; NLR, neutrophils-to-lymphocytes; PLR, platelets-to-lymphocytes.

Table 5. Assignment of prognostic factors affecting DLBCL

Influencing factors	Assignment of factors
gender	0 = female, 1 = male
clinical stage	0 = I-II period, 1 = III-IV period
B Symptoms	0 = no, 1 = yes
Extranodal involved site	0 = 0, 1 = 1, ≥2 = 2
LDH	Original value input
ECOG	0 = 0-1, 1 = 2-5
IPI	Original value input
Neutrophil count	Original value input
Monocyte count	Original value input
NLR	Original value input
PLR	Original value input
LMR	Original value input
CRP	Original value input

IPI, International Prognostic Index; LMR, lymphocytes-to-beads; NLR, neutrophils-to-lymphocytes; PLR, platelets-to-lymphocytes.

the prognosis of DLBCL. The findings of the univariate analysis showed that gender, B-symptom, clinical stage, IPI, extranodal involvement, ECOG, peripheral blood neutrophil count, monocyte count, CRP, LMR, NLR, and PLR were all related factors impacting the prognosis of DLBCL patients ($P < 0.05$). The multivariate Cox regression analysis showed that higher IPI scores, higher neutrophil counts, higher PLR, and higher NLR were risk factors for the prognosis of DLBCL.

This study constructed a nomogram risk prediction model based on independent risk factors. Risk prediction was performed by nomogram. The ROC curve was drawn to evaluate the discrimination of the model. The nomogram is composed of IPI score, neutrophil count, NLR, and PLR, which has high reliability and clinical practicability. The nomogram emphasizes the relative importance of each index, suggesting that IPI score, neutrophil count, NLR, and PLR can accurately predict the prognosis of DLBCL patients, with good discrimination, calibration, and accuracy. In recent years, studies have shown that [29], NLR, and PLR have become a hot topic in biomedical research. Accurate and unique optimal cutoff values have not been found. It has been recognized as a marker of immune system homeostasis and has good prognostic value. By studying the prognostic effects of NLR and PLR alone and in combination to predict the prognosis of DLBCL, the degree of pathological damage of patients can be analyzed more accurately. This assists in determining the prognosis of patients in a timely and effective manner.

This study had some limitations. This study was a retrospective analysis of case data. Some indicators were not perfect. The samples came from the same area. The number of samples was small. There may be some bias in the analysis results. In subsequent studies, multicenter, prospective studies are needed to obtain more complete clinical indicators to confirm the predictive value of immune inflammation indicators for DLBCL and the confirmation of the best cut-off value and expand the applicability.

Table 6. Multivariate analysis of factors affecting the prognosis of DLBCL

Influencing factors	B	SE	Wald	*P*	HR (95% CI)
gender	0.615	0.379	2.634	0.105	1.851 (0.880-3.891)
clinical stage	0.842	0.492	2.929	0.087	2.321 (0.885-6.088)
B Symptoms	0.038	0.311	0.015	0.902	1.039 (0.565-1.912)
Extranodal involved site	0.132	0.309	0.183	0.669	1.141 (0.623-2.091)
LDH	0.000	0.001	0.516	0.472	1.000 (0.999-1.001)
ECOG	-0.112	0.380	0.086	0.769	0.894 (0.424-1.885)
IPI	0.394	0.189	4.359	0.037	1.483 (1.024-2.147)
Neutrophil count	0.345	0.079	18.834	< 0.001	1.411 (1.208-1.649)
Monocyte count	0.022	0.055	0.157	0.692	1.022 (0.918-1.137)
NLR	-0.190	0.051	13.613	< 0.001	0.827 (0.748-0.915)
PLR	0.003	0.001	11.491	0.001	1.003 (1.001-1.005)
LMR	-0.059	0.088	0.454	0.501	0.942 (0.793-1.120)
CRP	-0.005	0.004	1.187	0.276	0.995 (0.987-1.004)

IPI, International Prognostic Index; LMR, lymphocytes-to-beads; NLR, neutrophils-to-lymphocytes; PLR, platelets-to-lymphocytes.

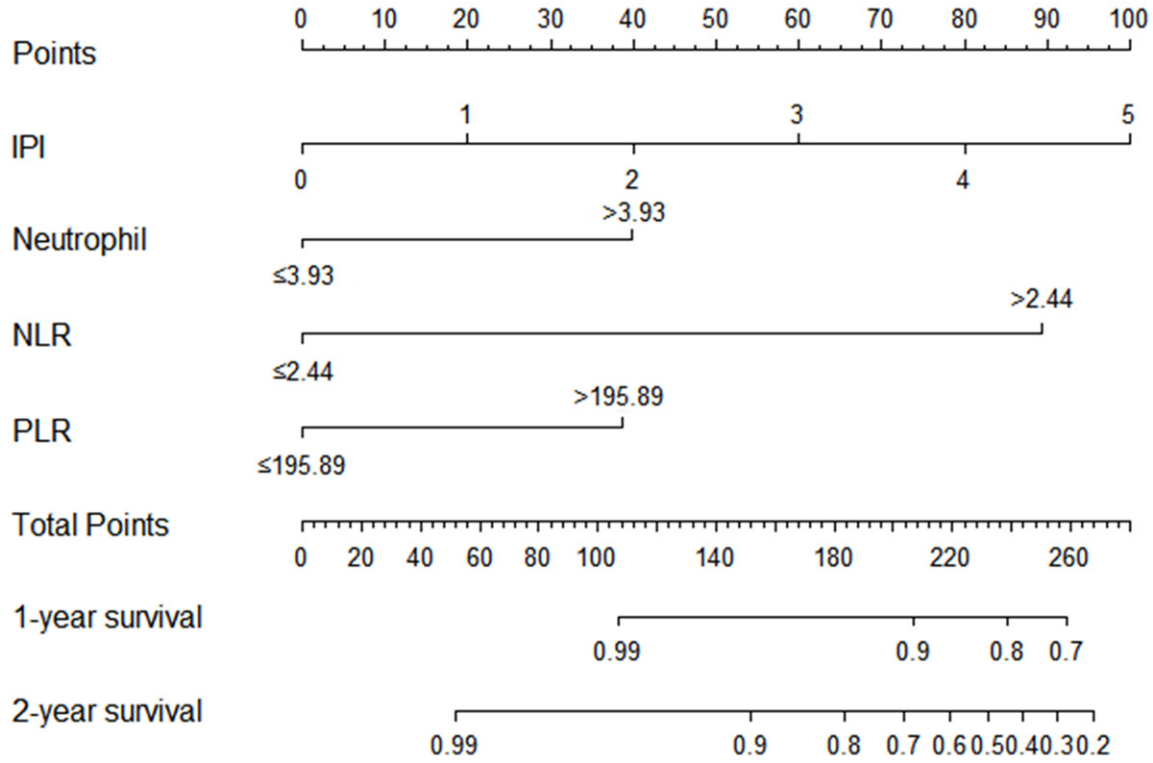

Figure 4. Nomogram for predicting the prognostic risk of DLBCL. IPI, International Prognostic Index; lymphocytes-to-beads (LMR), neutrophils-to-lymphocytes (NLR), and platelets-to-lymphocytes (PLR).

IPI, neutrophil count, NLR, and PLR are factors impacting the prognosis of DLBCL. The higher IPI, neutrophil number, NLR, and PLR indicate a poor prognosis. The nomogram risk prediction model has good diagnostic efficacy and application value and provides a reference for clinical decision-making of DBLCL patients.

Disclosure of conflict of interest

None.

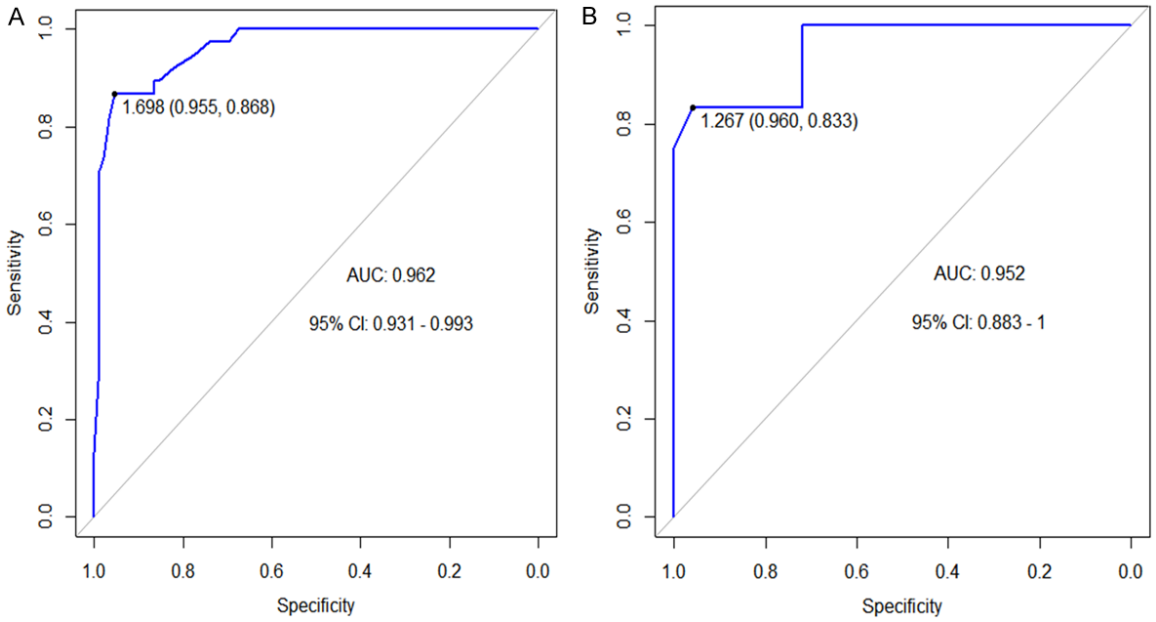

Figure 5. Predictive value of nomogram for prognosis of DLBCL. Note: A. ROC curve of training set nomogram; B. ROC curve of test set nomogram.

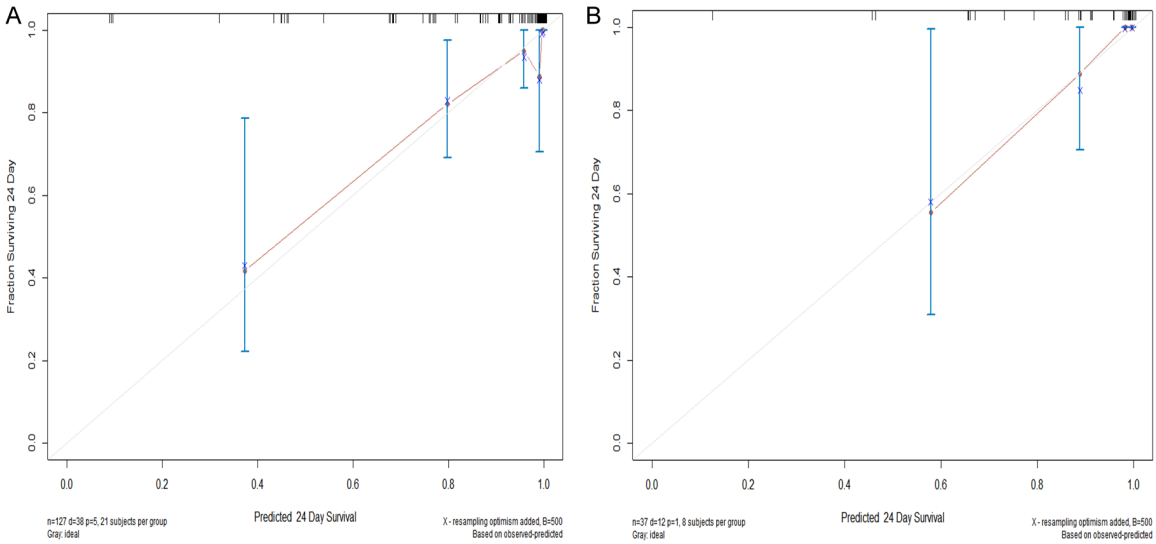

Figure 6. Calibration curve. Note: A. Calibration curve of training set nomogram; B. Calibration curve of test set line graph.

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