Pharmacogenomics and Personalized Medicine

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Construction and Validation of a Novel Nomogram for Predicting the Recurrence of Diffuse Large B Cell Lymphoma Treated with R-CHOP

Yuxi Gong[1], Haitao Yan[2], Yefan Yang[1], Boya Zhai[1], Zhendong Huang[1], Zhihong Zhang[1]

[1]Department of Pathology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, People's Republic of China; [2]Department of Interventional Radiology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, People's Republic of China

Correspondence: Zhihong Zhang, Department of Pathology, The First Affiliated Hospital of Nanjing Medical University, 300 Guangzhou Road, Nanjing, Jiangsu Province, 210029, People's Republic of China, Tel/Fax +86-25-68303709, Email zhangzh@njmu.edu.cn

Purpose: To explore recurrence-risk factors of diffuse large B cell lymphoma (DLBCL) and construct a risk nomogram for predicting recurrence.

Patients and Methods: A retrospective analysis was performed on 228 DLBCL patients who achieved complete remission after R-CHOP treatment between January 2015 and December 2019. Univariate and multivariate analyses were applied to identify recurrence-related risk factors from the pretreatment evaluation factors covering patients' demographic characteristics, clinical manifestations, serological indicators, pathological and immunohistochemical results. A nomogram was developed based on the above results and validated by the concordance index (C-index), the receiver operating characteristic (ROC) curve, and the calibration curve.

Results: The training and validation cohorts consisted of 160 and 68 patients (randomized by 7:3). Of the whole cohort, 50 of 228 (21.9%) cases recurred during follow-up. Three recurrence-risk factors including BCL2 expression (P = 0.027), CD10 expression (P = 0.021), LDH level (P = 0.004) were identified from multivariate analysis and entered the final nomogram. The C-index of the nomogram was 0.815 in training cohort and 0.797 in the validation cohort, higher than that of IPI system (0.699) and NCCN-IPI system (0.709). And the 1-year, 2-year, 3-year, and 4-year areas under ROC (AUC) were 0.812, 0.850, 0.837, and 0.801, respectively. The calibration curves also showed a good discrimination capability and accuracy.

Conclusion: The novel nomogram incorporating the three independent risk factors (BCL2 expression, CD10 expression and LDH level) provided a valuable tool for predicting DLBCL recurrence.

Keywords: diffuse large B cell lymphoma, DLBCL, recurrence, nomogram, risk factors

Introduction

Diffuse Large B cell Lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma, with significant biological and clinical heterogeneity. Most patients can benefit from the first-line treatment – R-CHOP and achieve complete remission (CR), but 30–40% of patients will experience relapse, progression or even death.[1] As the salvage regimen for these relapsed patients, high-dose cytarabine-based chemotherapy or ifosfamide-based chemotherapy combined with Auto Stem Cell Transplantation (ASCT) can only guarantee a 3-year progression-free survival rate of 55%.[2,3] And there are cases that failed in stem cell collection due to advanced age or complications. Therefore, early identification of DLBCL patients with high relapse risk is of great significance for formulating personalized treatment and improving prognosis.

Efforts have been made to find suitable prognostic markers. Since 1993, the International Prognostic Index (IPI), which is based on age, Ann Arbor stage, Eastern Cooperative Oncology Group (ECOG) performance status, number of

Received: 27 November 2022
Accepted: 21 March 2023
Published: 1 April 2023

extranodal sites, and serum lactate dehydrogenase (LDH) levels, has been widely used for risk stratification and prognosis prediction,[4] and further refined into Revised IPI (R-IPI) and National Comprehensive Cancer Network IPI (NCCN-IPI) in the rituximab era.[5,6] However, the IPI system only contains clinical indicators and cannot fully reveal the biological heterogeneity of DLBCL. Patients with same IPI scores still show different outcomes. Recent studies attempt to incorporate numerous biological markers into prognostic scores, including pathological markers such as cell-of-origin classification, CD5 expression and BCL2 expression, serological indicators such as β2 -microglobulin (β2-MG), hemoglobin.[7,8] However, the discriminative abilities of these prognostic risk markers for relapsed DLBCL patients still need further exploration.

The utilization of a simple and accurate recurrence-risk predictive model is important to identify high-risk patients. Nomogram, a statistical predictive tool, can be used to calculate the probability of a clinical event by integrating diverse risk factors.[9] We wish to develop a specific risk stratification nomogram incorporating clinical and pathological factors that can predict recurrence of DLBCL. In the present study, we performed a retrospective study on 228 DLBCL cases achieved CR after R-CHOP treatment, 50 of which experienced relapses. Clinical manifestations, pathological features, and laboratory indicators at the initial diagnosis were collected to explore recurrence-risk factors. We further conducted and validated a nomogram model predicting recurrence, which may provide insight for individualized clinical chemotherapy and targeted therapy.

Materials and Methods

The use of samples in this study was in accordance with the Declaration of Helsinki and approved by the Ethics Committee of The First Affiliated Hospital of Nanjing Medical University (2020-SR-097). All patients signed the consent form of remaining biological samples for scientific research before surgery.

Sample Selection and Follow Up

According to the WHO classification of Tumors of Hematopoietic and Lymphoid Tissue (2022), 573 patients were diagnosed with DLBCL, NOS (including consultation) by the Department of Pathology and received standard R-CHOP-like treatment in the Department of Hematology between January 2015 and December 2019 at the First Affiliated Hospital of Nanjing Medical University. The exclusion criteria were as follows: (1) transformed from indolent lymphoma or other lymphohematopoietic system diseases; (2) merged with other malignant tumors at the same time; (3) originated in the mediastinum or central nervous system; (4) with positive EBER expression; (5) DLBCL/high-grade B-cell lymphoma (HGBL)-MYC/BCL2 confirmed by FISH (with MYC rearrangement, BCL2 rearrangement, BCL6 rearrangement or germline configuration). In total, 228 patients achieved complete remission after initial treatment, and all patients did not receive any treatment at the time of initial diagnosis. All patients were randomly assigned to the training cohort and validation cohort in a 7:3 ratio. A flowchart of the enrolled patients is shown in Figure 1.

After achieving CR, patients were followed up through hematologic examination and Computed Tomography (CT) examination at the outpatient clinic. Telephone interviews were also used for later outcomes. According to the Lugano 2014 criteria, CR was defined as: (1) PET-CT: Deauville 5-point scale with scores 1–3, with or without a residual mass; no new lesions; no evidence of FDG-avid disease in marrow; or (2) CT: Target nodes/nodal masses regress to ≤1.5cm; no extralymphatic sites of disease; absent of nonmeasured lesion; enlarged organs regress to normal; no new lesions; normal bone marrow morphology. Relapse referred to disease reappearance after obtaining CR for more than one month. The deadline for follow-up was May 2021, and progression-free survival (PFS) was defined as the time interval from the date of diagnosis to the end of follow-up without progression or recurrence or death.

Clinical and Pathological Indicators

Pretreatment evaluation factors covered patients' demographic characteristics, clinical manifestations, serological indicators, pathological and immunohistochemical results, including age, sex, HBV infection, B symptoms (fever, night sweats, weight loss), primary site of origin, extranodal involvement, Ann Arbor stage, ECOG score, IPI score, NCCN-IPI score, total protein (abnormal: <65g/L), albumin (abnormal: <30g/L), hemoglobin (abnormal: <110g/L (female) or 120g/L (male)), LDH (abnormal: >271U/L), β2-MG (abnormal: >2.53mg/L), C-reaction protein (CRP, abnormal: >8mg/L),

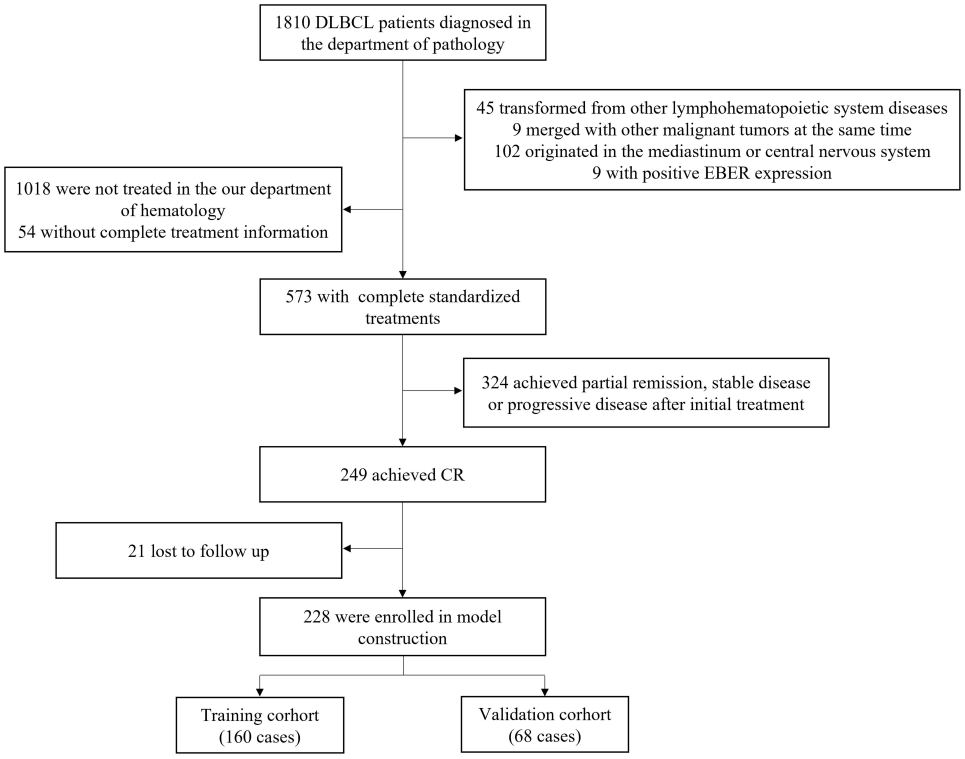

Figure 1 Patient selection.
Abbreviations: DLBCL, diffuse large B cell lymphoma; CR, complete remission.

cell of origin (COO) subtypes, the expressions of CD10, BCL6, MUM1, BCL2 and Ki-67 index. The cutoff value of 30% was used for CD10, BCL6 and MUM1 expression, and 50% for BCL2 expression. The response assessment was based on the Cheson (2014) classification.[10]

Nomogram Construction and Validation

Univariate analysis was applied to identify recurrence-related risk factors with P value <0.1, and then independent relapsed parameters were evaluated by multivariate Cox regression analysis for further constructing a nomogram for recurrence. The receiver operating characteristic (ROC) curve and the calibration curve constructed by means of 1000 bootstrap resamples were used for model internal validation. The area under ROC curve (AUROC) and the concordance index (C-index) could evaluate the discrimination of the model, and the calibration curve was a useful tool for showing the concordance between predicted and observed probabilities for recurrence.

Statistical Analysis

Statistical analysis was performed using the rms, survival, survival *ROC* package in R 4.0.5 software (http://www.r-project.org). Chi-square test was used to compare the differences in clinicopathological characteristics between the two cohorts. Kaplan–Meier curves were used for evaluation of PFS, and Log rank test was used for univariate analysis. Multivariate Cox regression analysis was performed to identify independent relapsed factors for risk nomogram construction, and calculate the hazard ratio and the 95% confidence interval (CI). $P < 0.05$ was considered significant.

Results

Baseline Characteristics of DLBCL Patients

In the whole cohort, the median age at diagnosis was 56 (15–84) years, and the median PFS was 36 (6–77) months, the average PFS was 37.2 months. Fifty patients relapsed during follow-up, accounting for 21.9%. The accumulative

recurrence rates of 1-year, 2-year, 3-year, and 4-year are 7.5% (17/228), 16.2% (37/228), 16.7% (38/228), and 19.3% (44/228), respectively. The majority of the relapses occurred within the first 2 years. The baseline characteristics of patients in the two cohorts are summarized in Table 1, and there was no statistical difference.

Table 1 The Clinical Characteristics, Laboratory Indicators and Pathological Features of 228 DLBCL Patients

Parameters	Total	Training Group	Validation Group	P value
Sex				0.083
Male	114 (50.0)	86 (53.8)	28 (41.2)	
Female	114 (50.0)	74 (46.2)	40 (58.8)	
Age				0.847
≤40	34 (14.9)	24 (15.0)	10 (14.7)	
41–60	95 (41.7)	66 (41.3)	29 (42.6)	
61–74	86 (37.7)	60 (37.5)	26 (38.2)	
≥75	13 (5.7)	10 (6.2)	3 (4.4)	
HBV				0.291
Present	54 (23.7)	41 (25.6)	13 (19.1)	
Absent	174 (76.3)	119 (74.4)	55 (81.9)	
Primary site				0.081
Nodal	124 (54.4)	81 (50.6)	43 (63.2)	
Extranodal	104 (45.6)	79 (49.4)	25 (36.8)	
Ann Arbor stage				0.183
I–II	126 (55.3)	93 (58.1)	33 (48.5)	
III–IV	102 (44.7)	67 (41.9)	35 (51.5)	
ECOG				0.475
0–1	199 (87.3)	138 (86.3)	61 (89.7)	
2–4	29 (12.7)	22 (14.7)	7 (10.3)	
Extranodal involvement				0.140
<2	163 (71.5)	119 (74.4)	44 (64.7)	
≥2	65 (28.5)	41 (25.6)	24 (35.3)	
IPI score				0.895
0–2	159 (69.7)	112 (70.0)	47 (69.1)	
3–5	69 (30.3)	48 (30.0)	21 (30.9)	
NCCN-IPI score				0.712
0–1	68 (29.8)	51 (31.9)	17 (25.0)	
2–3	96 (42.1)	65 (40.6)	31 (45.6)	
4–5	52 (22.8)	35 (21.9)	17 (25.0)	
6–8	12 (5.3)	9 (5.6)	3 (4.4)	
B symptoms				0.474
Present	61 (26.8)	45 (28.1)	16 (23.5)	
Absent	167 (73.2)	115 (71.9)	52 (76.5)	
Total protein				0.178
Normal	141 (61.8)	93 (58.1)	48 (70.6)	
Decreased	87 (38.2)	67 (41.9)	20 (29.4)	
Albumin				0.585
Normal	101 (44.3)	69 (43.1)	32 (47.1)	
Decreased	127 (55.7)	91 (56.9)	36 (52.9)	
Hemoglobin				0.796
Normal	112 (49.1)	77 (48.1)	35 (51.5)	
Decreased	116 (50.9)	83 (51.9)	33 (48.5)	
LDH ratio				0.825
<1× ULN	152 (66.7)	106 (66.2)	46 (67.6)	
1–3× ULN	65 (28.5)	46 (28.8)	19 (27.9)	

(*Continued*)

Table 1 (Continued).

Parameters	Total	Training Group	Validation Group	P value
>3× ULN	11 (4.8)	8 (5.0)	3 (4.4)	
β2-MG				0.610
Normal	146 (65.2)	104 (66.2)	42 (62.7)	
Elevated	78 (34.8)	53 (33.8)	25 (37.3)	
CRP				0.762
Normal	142 (65.7)	99 (65.6)	43 (66.2)	
Elevated	74 (34.3)	52 (34.4)	22 (33.8)	
COO subtype				0.539
GCB	83 (36.4)	61 (38.1)	22 (32.4)	
Non-GCB	145 (63.6)	99 (61.9)	46 (67.6)	
CD10				0.417
Negative	160 (70.2)	109 (68.1)	51 (75.0)	
Positive	68 (29.8)	51 (31.9)	17 (25.0)	
BCL6				0.170
Negative	33 (14.7)	20 (12.6)	13 (19.7)	
Positive	192 (85.3)	139 (87.4)	53 (80.3)	
MUM1				0.367
Negative	34 (15.0)	26 (16.5)	8 (11.8)	
Positive	192 (85.0)	132 (83.5)	60 (88.2)	
Ki67 index				0.707
<75%	63 (27.8)	46 (28.9)	17 (25.0)	
≥75%	164 (72.2)	113 (71.1)	51 (75.0)	
BCL2				0.984
Negative	77 (37.2)	54 (37.2)	23 (37.1)	
Positive	130 (62.8)	91 (62.8)	39 (62.9)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; NCCN-IPI, National comprehensive cancer network International Prognostic Index; LDH, lactate dehydrogenase; β2-MG, β2 -microglobulin; CRP, C-reaction protein; COO, cell of origin; GCB, germinal center B-cell.

Construction of Risk Nomogram for Recurrence and Validation

The univariate analysis revealed that primary site of origin, Ann Arbor stage, NCCN-IPI score, numbers of extranodal involvement, LDH level, β2-MG level, CRP level, COO subtype, CD10 expression, and BCL2 expression were factors affecting recurrence. The multivariate analysis indicated that negative CD10 expression (P = 0.021), positive BCL2 expression (P = 0.027) and elevated LDH level (P = 0.004) were independent risk factors associated with recurrence (Table 2).

Table 2 Univariate and Multivariate Analysis of 160 DLBCL Patients in the Training Cohort

Parameters		Average PFS (m)	Univariate		Multivariate	
			HR (95% CI)	P value	HR (95% CI)	P value
Sex	Female	38.9	Ref.			
	Male	38.5	0.629 (0.311–1.271)	0.196		
Age	≤40	37.7	Ref.			
	41–60	40.2	1.155 (0.751–1.777)	0.511		
	61–74	38.5				
	≥75	32.8				
HBV	Absent	40.1	Ref.			
	Present	34.6	0.889 (0.384–2.060)	0.784		

(*Continued*)

Table 2 (Continued).

Parameters		Average PFS (m)	Univariate		Multivariate	
			HR (95% CI)	P value	HR (95% CI)	P value
Primary site	Nodal	35.4	Ref.			
	Extranodal	42.1	0.272 (0.123–0.602)	**0.001***	0.589 (0.186–1.872)	0.370
Ann Arbor stage	I–II	42.8	Ref.			
	III–IV	33.0	5.502 (2.485–12.180)	**0.000***	1.985 (0.521–7.558)	0.315
ECOG	0–1	39.1	Ref.			
	2–4	36.5	1.129 (0.454–2.803)	0.794		
Extranodal involvement	<2	41.1	Ref.			
	≥2	31.9	3.778 (1.913–7.461)	**0.000***	1.112 (0.390–3.175)	0.842
NCCN-IPI score	0–1	42.5	Ref.			
	2–3	41.5	4.087 (2.327–7.181)	**0.000***	0.710 (0.293–1.718)	0.448
	4–5	33.5				
	6–8	17.4				
B symptoms	Absent	39.3	Ref.			
	Present	37.3	1.219 (0.591–2.516)	0.592		
Total protein	Normal	38.5	Ref.			
	Decreased	38.9	0.928 (0.457–1.882)	0.836		
Albumin	Normal	39.8	Ref.			
	Decreased	37.9	1.005 (0.500–2.021)	0.989		
Hemoglobin	Normal	40.2	Ref.			
	Decreased	37.3	0.983 (0.491–1.967)	0.961		
LDH ratio	<1× ULN	43.0	Ref.			
	1–3× ULN	32.6	3.696 (2.228–6.132)	**0.000***	3.717 (1.518–9.101)	**0.004***
	>3× ULN	16.9				
β2-MG	Normal	41.2	Ref.			
	Elevated	33.1	2.085 (1.037–4.194)	**0.039***	0.967 (0.408–2.289)	0.938
CRP	Normal	40.0	Ref.			
	Elevated	34.3	3.137 (1.548–6.359)	**0.002***	1.933 (0.781–4.785)	0.154
COO subtype	GCB	41.2	Ref.			
	Non-GCB	37.2	2.680 (1.166–6.159)	**0.020***	0.489 (0.126–1.892)	0.300
CD10	Negative	37.9	Ref.			
	Positive	40.4	0.254 (0.089–0.723)	**0.010***	0.108 (0.016–0.713)	**0.021***
BCL6	Negative	37.9	Ref.			
	Positive	38.7	0.459 (0.209–1.006)	0.052	0.874 (0.336–2.278)	0.783
MUM1	Negative	40.7	Ref.			
	Positive	38.2	1.855 (0.642–5.360)	0.254		
Ki67 index	<75%	46.4	Ref.			
	≥75%	35.6	1.507 (0.673–3.379)	0.319		
BCL2	Negative	38.0	Ref.			
	Positive	36.1	2.351 (1.015–5.442)	**0.046***	3.181 (1.144–8.841)	**0.027***

Notes: Bold text with. *Label: P value is statistically significant.

Abbreviations: PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; NCCN-IPI, National comprehensive cancer network International Prognostic Index; LDH, lactate dehydrogenase; β2-MG, β2-microglobulin; CRP, C-reaction protein; COO, cell of origin; GCB, germinal center B-cell.

We then developed a new nomogram model (Figure 2), including the three independent factors to predict 1-, 2-, 3-, 4-recurrence based on the results of the multivariate analysis. In this nomogram, a DLBCL patient with positive BCL2 expression, negative CD expression, elevated LDH level (1–3× ULN) or elevated LDH level (>3× ULN) could obtain 40 points, 61 points, 47 points and 100 points, respectively.

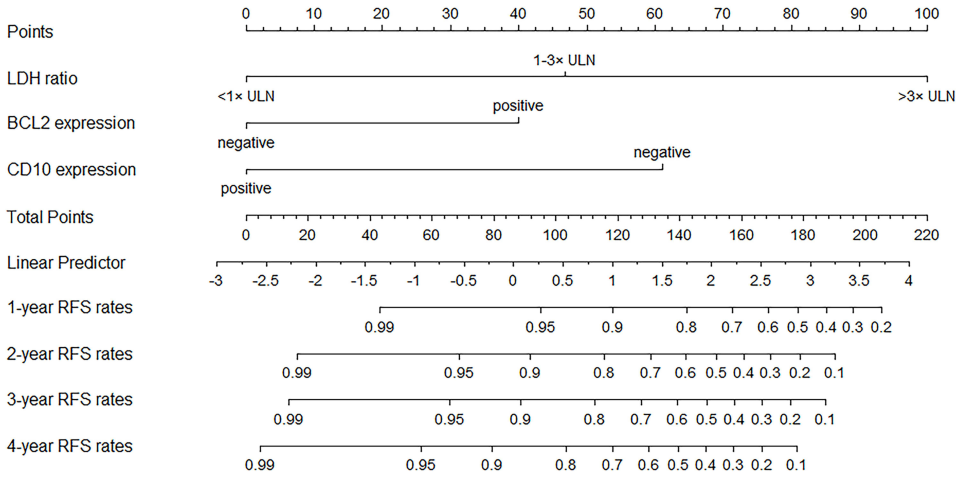

Figure 2 The novel nomogram incorporating LDH level with BCL2 expression and CD10 expression for DLBCL. A DLBCL patient with positive BCL2 expression, negative CD expression, elevated LDH level (1–3× ULN) or elevated LDH level (>3× ULN) could obtain 40 points, 61 points, 47 points and 100 points, respectively.
Abbreviations: LDH, serum lactate dehydrogenase; ULN, Upper Limit of Normal; RFS, recurrence-free survival.

The nomogram had a C-index of 0.815 (95% CI, 0.777–0.853). The calibration plots showed a significant correlation between predicted and observed probabilities for recurrence (Figure 3A). The time-dependent ROC curves and the corresponding 1-year, 2-year, 3-year and 4-year AUROC are shown in Figure 4A. We further validated the nomogram externally. The C-index of 0.797 and the calibration plots of the validation cohort (Figure 3B) also demonstrated that this nomogram had advantages in predicting recurrence, especially in predicting 2- and 3-recurrence rates.

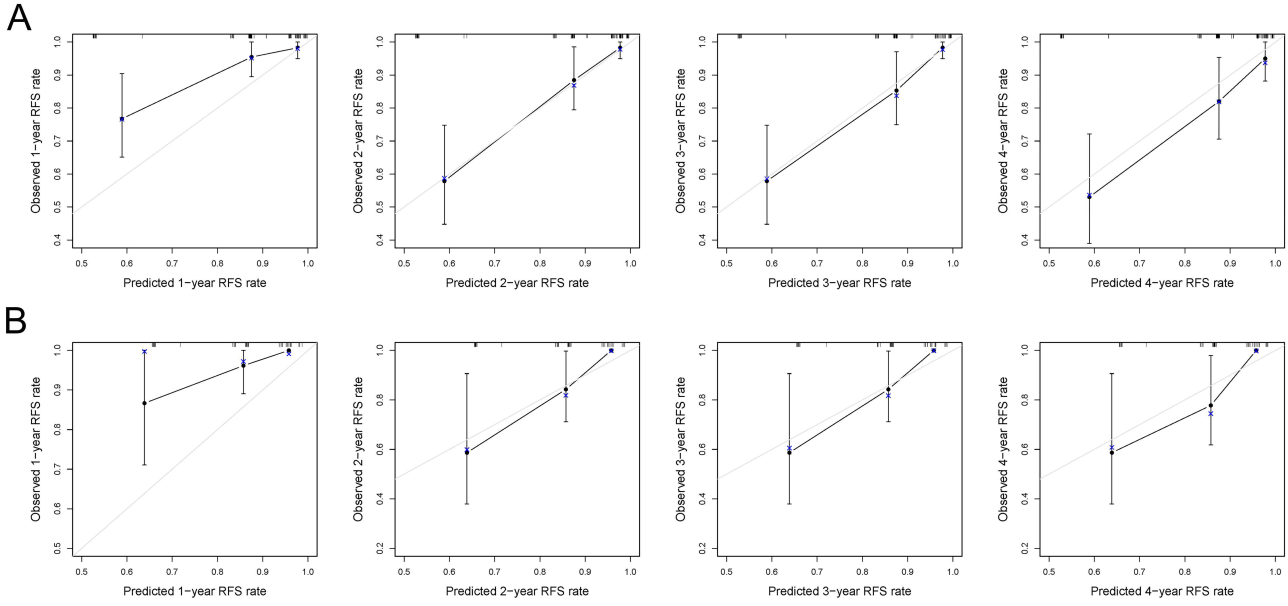

Figure 3 The calibration plots of nomogram in training cohort (**A**) and validation cohort (**B**) showed the predicted RFS rate on the x axis and the observed RFS on the y axis.
Abbreviation: RFS, recurrence-free survival.

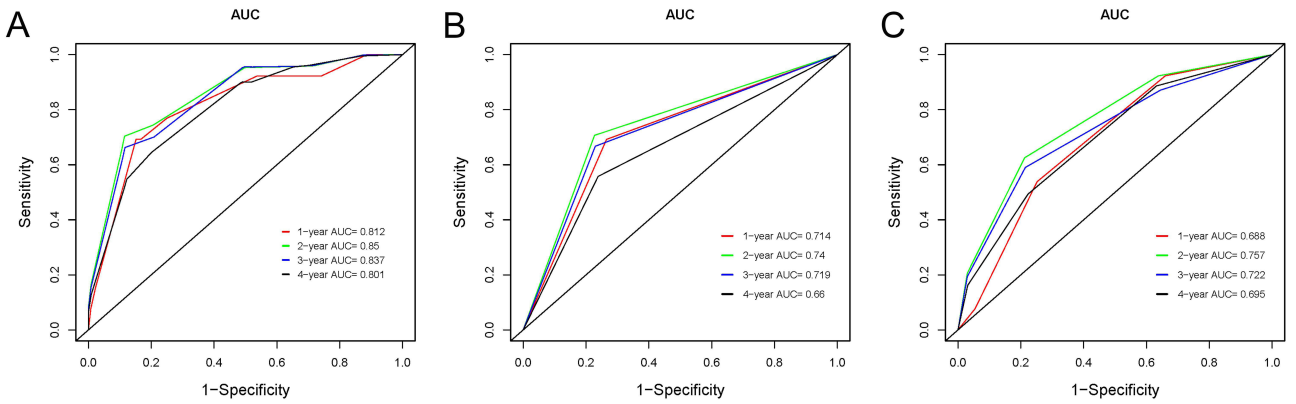

Figure 4 The predictive effectiveness of the novel nomogram, IPI system and NCCN-IPI system. (**A**) The 1-year, 2-year, 3-year and 4-year AUC of the novel nomogram was 0.812, 0.85, 0.837, and 0.801, respectively. (**B**) The 1-year, 2-year, 3-year and 4-year AUC of IPI system was 0.714, 0.74, 0.719, and 0.66, respectively. (**C**) The 1-year, 2-year, 3-year and 4-year AUC of NCCN-IPI system was 0.688, 0.757, 0.722, and 0.695, respectively.
Abbreviations: RFS, recurrence-free survival; AUC, area under receiver operating characteristic curve.

Comparison of the Predictive Accuracy for Recurrence Among the Nomogram, IPI System and NCCN-IPI System

The current IPI system was widely applied for prognostic evaluation, and the enhanced IPI score (NCCN-IPI) was developed for newly diagnosed patients with DLBCL and treated with R-CHOP. Univariate analysis suggested that both IPI score and NCCN-IPI score could affect recurrence and clearly distinguish low-risk and high-risk patients. We wondered if IPI score and NCCN-IPI score had the same ability to predict recurrence as the new nomogram? The time-dependent ROC curves and the corresponding 1-year, 2-year, 3-year and 4-year AUROC of IPI system and NCCN-IPI system are shown in Figure 4B and C. While all AUROC of the two classic predicting systems were significantly less than that of the constructed nomogram. The nomogram also had a higher C-index of 0.815 than that of IPI system (0.699, 95% CI, 0.657–0.741) and NCCN-IPI system (0.709, 95% CI, 0.666–0.752). It indicated that the new nomogram was more satisfactory for recurrence risk assessment than the IPI system and NCCN-IPI system.

Discussion

Some DLBCL patients would relapse within the first two or three years after diagnosis, and late relapse that occurred after five years was less common.[11] To screen out patients prone to relapse at the first diagnosis was a hot spot in clinical research. Although significant achievements had been made in studying prognostic markers of novel DLBCL, and the nomogram had been validated as a useful tool for predicting overall survival (OS) with higher sensitivity and accuracy than IPI system[7]. The recurrence-related risk factors of DLBCL and the nomogram models for recurrence risk assessment needed to be further explored.

In this study, to avoid the effect of different treatment regimens on prognosis, 228 patients who had already achieved complete response to R-CHOP were enrolled as objects. We focused on those widely concerning parameters in daily clinical and pathological work and found three independent predictors: positive BCL2 expression, negative CD10 expression and elevated LDH level.

As a key regulator in cell apoptosis, dysregulation of BCL2 caused by chromosome translocation, gene amplification, or activation of the NF-κB signal pathway could promote the occurrence and development of B-cell lymphoma.[12] BCL2 overexpression was associated with drug resistance and poor prognosis,[13] and could be inhibited by Venetoclax in many hematological cancers.[14] Naoko Tsuyama et al[15] found that DLBCL patients with BCL2 overexpression had a lower rate to obtain CR, a higher probability of recurrence after CR, and a worse 3-year PFS rate. What is more, DLBCL with coexpression of MYC and BCL2 protein (so-called double-expressor lymphoma, DEL) was considered to have adverse outcomes and increased risk of CNS recurrence.[16] Since there was little information regarding the MYC protein expression in consultation cases in our study, the relationship between the co-expression of BCL2 and MYC and the

recurrence of DLBCL was unknown. But we did find that positive BCL2 expression was a significant independent risk factor for DLBCL recurrence, which was consistent with that in previous studies.

Since CD10 protein was used as a marker for Han's classification, lots of research on its prognostic significance had been conducted. Although most studies suggested that positive CD10 expression was correlated with improved survival,[17] Fabiani 's review found that both OS and PFS of DLBCL were not different according to CD10 expression.[18] But in our study, a patient with positive CD10 expression had a lower risk of recurrence, and CD10 expression could be used as a good indicator to assess the risk of recurrence in DLBCL. Fan et al[19] also found CD10 was a significant factor predicting 3-year recurrence rate of patients with DLBCL, and they constructed a risk model based on CD10 and other five factors with good discrimination and calibration ability.

The elevated LDH level could also promote the relapse of DLBCL in this study. LDH, a valuable biomarker, could be easily measured in clinical and hospital laboratories. As its elevation was mostly associated with high tumor burden and adverse clinical behavior, LDH level was of great prognostic effect on solid tumors, in particular melanoma, prostate and renal cell carcinomas,[20] and was also widely used as one of the independent prognostic factors in IPI system and other prognostic nomogram models in aggressive B-cell lymphomas.[7,21,22] In terms of DLBCL, elevated LDH level at initial diagnosis was found to be related to the increased risks of CNS relapse.[23,24] Compared with patients with late relapses, patients with early relapses were more likely to have a higher LDH level, higher IPI score and adverse stage (III–IV).[25] In Huang's study, univariate analysis also indicated that LDH >1000U/L was one of the relapse risk factors of pediatric mature B cell lymphoma.[26]

Among these three independent recurrence-related predictors, except LDH level, both BCL2 expression and CD10 expression were not commonly used for prognosis. We considered the reasons for different results from previous studies including: 1) different research purposes: This study was aimed to explore recurrence-related risk factors, but the prognosis that was concerned in previous studies included not only relapse, but also death, progression, etc. 2) strict inclusion criteria in our study: To study the recurrence risk of DLBCL, only patients sensitive to R-CHOP and able to obtain CR were enrolled. The baseline characteristics of these patients may be different from those of large samples in other studies. 3) different explored factors: To identify DLBCL with high risk of relapse before treatment, we only focused on pretreatment factors, while previous studies may cover both in-treatment and post-treatment factors.

The final nomogram consisted of 3 predictors: CD10 expression, BCL2 expression, and LDH level. Based on the data in our study, this newly recurrence-risk predicted nomogram had a higher C-index than IPI system and NCCN-IPI system. The ROC curves and calibration plots also demonstrated its advantaged discriminative ability and accuracy. This nomogram also achieved a C-index of 0.797 in external validation cohort. It could be a valuable tool for clinicians to assess individual recurrence risk before treatment at certain time intervals, so as to formulate personalized treatment to improve the prognosis.

However, this study had some limits. Firstly, as a retrospective study, there was a certain bias in patients' selection and a sample size limitation. Secondly, although patients received R-CHOP-like chemotherapy, the effects of dosage and other adjuvant treatments on the prognosis were not explored. Lastly, this model had not yet included molecular factors. We would try to realize multi-center prospective research to expand the sample size and control confounding factors, and incorporate more novel biomarkers for further improving this nomogram model and verifying its feasibility in future studies.

Conclusion

In summary, our study explored three independent recurrence-risk factors of DLBCL, and constructed a new nomogram incorporating LDH level with BCL2 and CD10 expression, which provided a valuable tool for predicting DLBCL recurrence.

Abbreviations

DLBCL, diffuse large B cell lymphoma; CR, complete remission; ASCT, Auto Stem Cell Transplantation; IPI, International Prognostic Index; ECOG, Eastern Cooperative Oncology Group; LDH, serum lactate dehydrogenase; β2-MG, β2 -microglobulin; PFS, progression-free survival; ROC curve, the receiver operating characteristic curve;

AUROC, the area under ROC curve; C-index, the concordance index; CI, confidence interval; HR, hazard ratio; ECOG, Eastern Cooperative Oncology Group; NCCN-IPI, National comprehensive cancer network International Prognostic Index; CRP, C-reaction protein; COO, cell of origin; GCB, germinal center B-cell.

Data Sharing Statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Acknowledgments

We are very grateful to all the haematologists and pathologists who assisted in the collection of clinical data. We thank G. Song and J. Tang for immunohistochemical staining.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Li S, Young KH, Medeiros LJ. Diffuse large B-cell lymphoma. *Pathology*. 2018;50:74–87. doi:10.1016/j.pathol.2017.09.006
2. Lignon J, Sibon D, Madelaine I, et al. Rituximab, dexamethasone, cytarabine, and oxaliplatin (R-DHAX) is an effective and safe salvage regimen in relapsed/refractory B-cell non-Hodgkin lymphoma. *Clin Lymphoma Myeloma Leuk*. 2010;10:262–269. doi:10.3816/CLML.2010.n.055
3. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. *J Clin Oncol*. 2010;28:4184–4190. doi:10.1200/JCO.2010.28.1618
4. Ng EH, Miao B, Cheung W, et al. A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med*. 1993;329:987–994. doi:10.1056/NEJM199309303291402
5. Sehn LH, Berry B, Chhanabhai M, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. *Blood*. 2007;109:1857–1861. doi:10.1182/blood-2006-08-038257
6. Zhou Z, Sehn LH, Rademaker AW, et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. *Blood*. 2014;123:837–842. doi:10.1182/blood-2013-09-524108
7. Han Y, Yang J, Liu P, et al. Prognostic nomogram for overall survival in patients with diffuse large B-cell lymphoma. *Oncologist*. 2019;24:e1251–e1261. doi:10.1634/theoncologist.2018-0361
8. Jelicic J, Larsen TS, Frederiksen H, et al. Statistical challenges in development of prognostic models in diffuse large B-cell lymphoma: comparison between existing models - a systematic review. *Clin Epidemiol*. 2020;12:537–555. doi:10.2147/CLEP.S244294
9. Balachandran VP, Gonen M, Smith JJ, et al. Nomograms in oncology: more than meets the eye. *Lancet Oncol*. 2015;16:e173–e180. doi:10.1016/S1470-2045(14)71116-7
10. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol*. 2014;32:3059–3068. doi:10.1200/JCO.2013.54.8800
11. Friedberg JW. Relapsed/refractory diffuse large B-cell lymphoma. *Hematology Am Soc Hematol Educ Program*. 2011;2011:498–505. doi:10.1182/asheducation-2011.1.498
12. Warren C, Wong-Brown MW, Bowden NA. BCL-2 family isoforms in apoptosis and cancer. *Cell Death Dis*. 2019;10:177. doi:10.1038/s41419-019-1407-6
13. Delbridge AR, Grabow S, Strasser A, et al. Thirty years of BCL-2: translating cell death discoveries into novel cancer therapies. *Nat Rev Cancer*. 2016;16:99–109. doi:10.1038/nrc.2015.17
14. Roberts AW, Davids MS, Pagel JM, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2016;374:311–322. doi:10.1056/NEJMoa1513257
15. Tsuyama N, Sakata S, Baba S, et al. BCL2 expression in DLBCL: reappraisal of immunohistochemistry with new criteria for therapeutic biomarker evaluation. *Blood*. 2017;130:489–500. doi:10.1182/blood-2016-12-759621
16. Qualls D, Abramson JS. Advances in risk assessment and prophylaxis for central nervous system relapse in diffuse large B-cell lymphoma. *Haematologica*. 2019;104:25–34. doi:10.3324/haematol.2018.195834
17. Ohshima K, Kawasaki C, Muta H, et al. CD10 and Bcl10 expression in diffuse large B-cell lymphoma: CD10 is a marker of improved prognosis. *Histopathology*. 2001;39:156–162. doi:10.1046/j.1365-2559.2001.01196.x
18. Fabiani B, Delmer A, Lepage E, et al. CD10 expression in diffuse large B-cell lymphomas does not influence survival. *Virchows Arch*. 2004;445:545–551. doi:10.1007/s00428-004-1129-7
19. Fan S, Zhao Z, Zhang Y, et al. Probability calibration-based prediction of recurrence rate in patients with diffuse large B-cell lymphoma. *Biodata Min*. 2021;14:38. doi:10.1186/s13040-021-00272-9
20. Petrelli F, Cabiddu M, Coinu A, et al. Prognostic role of lactate dehydrogenase in solid tumors: a systematic review and meta-analysis of 76 studies. *Acta Oncol*. 2015;54:961–970. doi:10.3109/0284186X.2015.1043026

21. Jurisic V, Radenkovic S, Konjevic G. The actual role of LDH as tumor marker, biochemical and clinical aspects. *Adv Exp Med Biol*. 2015;867:115–124.
22. Zhong H, Chen J, Cheng S, et al. Prognostic nomogram incorporating inflammatory cytokines for overall survival in patients with aggressive non-Hodgkin's lymphoma. *Ebiomedicine*. 2019;41:167–174. doi:10.1016/j.ebiom.2019.02.048
23. Zhang J, Chen B, Xu X. Impact of rituximab on incidence of and risk factors for central nervous system relapse in patients with diffuse large B-cell lymphoma: a systematic review and meta-analysis. *Leuk Lymphoma*. 2014;55:509–514. doi:10.3109/10428194.2013.811239
24. Nazir A, Fawad SN, Hameed A. CNS relapse of diffuse large B cell Lymphoma A single centre experience. *Pak J Med Sci*. 2017;33:1454–1458. doi:10.12669/pjms.336.13812
25. Kang J, Chae H, Hong JY, et al. Distinct clinical characteristics at diagnosis in patients with late relapses compared with early relapses of diffuse large B-cell lymphoma treated with R-CHOP. *Leuk Lymphoma*. 2020;61:1119–1125. doi:10.1080/10428194.2019.1709831
26. Huang S, Jin L, Yang J, et al. 复发儿童B细胞淋巴瘤19例临床病理特征及治疗预后分析 [Clinical pathologic characteristics and treatment outcomes of 19 relapsed pediatric B-cell lymphoma]. *Zhonghua Er Ke Za Zhi*. 2017;55:748–753. Chinese. doi:10.3760/cma.j.issn.0578-1310.2017.10.007