Original Article

Establishment and evaluation of a nomogram for predicting the survival outcomes of patients with diffuse large B-cell lymphoma based on International Prognostic Index scores and clinical indicators

Yao Chen[1#], Jiaqin Xu[2#], Jiao Meng[1], Mingshuang Ding[1], Yiwei Guo[1], Dongwei Fu[3], Aichun Liu[1]

[1]Hemolymph Department, Harbin Medical University Cancer Hospital, Harbin, China; [2]Department of Epidemiology and Biostatistics, School of Public Health, Harbin Medical University, Harbin, China; [3]Oncology Department, Heilongjiang Provincial Hospital of General Bureau of Agriculture, Harbin, China

Contributions: (I) Conception and design: Y Chen, A Liu; (II) Administrative support: A Liu; (III) Provision of study materials or patients: J Meng, M Ding; (IV) Collection and assembly of data: Y Chen, J Xu, Y Guo; (V) Data analysis and interpretation: Y Chen, D Fu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Aichun Liu. Hemolymph Department, Harbin Medical University Cancer Hospital, No. 150 Haping Road, Harbin 150086, China. Email: aichun2002@hotmail.com.

Background: Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive lymphoma, treatment outcomes of patients vary greatly. The current International Prognostic Index (IPI) is not enough to distinguish patients with poor prognosis, and genetic testing is very expensive, so a inexpensive risk prediction tool should be developed for clinicians to quickly identify the poor prognosis of DLBCL patients.

Methods: DLBCL patients (n=420; 18–80 years old) who received a combination of cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP) with or without rituximab (R-CHOP) at our hospital between 2008 and 2017 were included in the study. Potential predictors of survival were determined by univariate and multivariate Cox regression analyses, and significant variables were used to construct predictive nomograms. The new prediction models were assessed using concordance indexes (C-indexes), calibration curves, and their clinical utility was assessed by decision curve analyses (DCAs).

Results: The 5-year overall survival (OS) rate was 70.62% and the 5-year progression-free survival (PFS) rate was 59.02%. The multivariate Cox analysis indicated that IPI, Ki-67, the lymphocyte/monocyte ratio, and first-line treatment with rituximab were significantly associated with survival. The C-index results indicated that a predictive model that included these variables had better discriminability for OS (0.73 *vs.* 0.67) and PFS (0.68 *vs.* 0.63) than the IPI-based model. The calibration plots showed good agreement with observations and nomogram predictions. The DCAs demonstrated the clinical value of the nomograms.

Conclusions: Our study identified prognostic factors in patients who were newly diagnosed with DLBCL to construct an individualized risk prediction model, combined IPI with common clinical indicators. Our model might be a valuable tool that could be used to predict the prognosis of DLBCL patients who receive standard first-line treatment regimens. It enables clinicians to quickly identify some patients with possible poor prognosis and choose more active treatment for patients, such as chimeric antigen receptor T-cell (CART) Immunotherapy and other new drugs therapy, so as to prolong the PFS and OS of patients.

Keywords: Diffuse large B-cell lymphoma (DLBCL); clinical indexes; the international prognostic index; prognosis; nomogram

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL) and accounts for 30–40% of all new diagnoses of NHL (1). Patients with DLBCL differ in terms of their morphologic, immunophenotypic, clinical, and genetic features, and this heterogeneity underlies their different responses to chemotherapy regimens (2). Previously, the standard first-line treatment was cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP), but more recent studies have shown that the addition of rituximab to CHOP (R-CHOP) decreases the risk of early and late recurrence (3,4). Subsequent clinical study reported that R-CHOP cures >50% of DLBCL patients, and this regimen is now accepted as a standard first-line treatment for DLBCL (5). However, some patients cannot receive rituximab treatment for various reasons, such as economic limitations and/or disease status, which may affect the effectiveness of treatments and patient prognosis. Thus, the use of rituximab should be considered when assessing the prognosis of patients with DLBCL.

The precise prognostic evaluation of patients with DLBCL is important for developing intervention and management strategies. Previous studies have used the International Prognostic Index (IPI) for the prognostic stratification of DLBCL patients. The IPI considers age, Ann Arbor stage, Eastern Cooperative Oncology Group Performance Status (ECOG PS), extra-nodal disease sites, and the serum level of lactate dehydrogenase (LDH). Subsequent studies have attempted to improve predictions of survival by revising this scale. For example, in 2007 Sehn *et al.* (6) established a revised-IPI (R-IPI) score system for patients who received the R-CHOP regimen. This new system categorized patients into 3 groups, was easier to use, and performed slightly better than the original IPI system. In 2014, Zhou *et al.* (7) established the National Comprehensive Cancer Network IPI (NCCN-IPI) score system. This new system assigned different weights to variables of age and LDH and had high sensitivity in the identification of patients with a 5-year survival probability rate <50%. However, these IPI-based scoring systems remain controversial, as some studies have found their predictive ability is not optimal for DLBCL patients who were identified as having a poor risk of survival (8,9).

With the continued development of new therapeutic methods and testing techniques, the choice of treatment regimens and potential clinical indexes should be reconsidered, as these differences may be responsible for the heterogeneity in the prognoses of patients with DLBCL. In an effort to improve the predictive performance of the IPI scoring system, we established and validated prognostic models that integrate specific clinical variables with the IPI to provide individualized survival risk assessments for patients with DLBCL. We present the following article in accordance with the TRIPOD reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-6023/rc).

Highlight box

Key findings

- A nomogram for predicting survival outcomes in patients with diffuse large B-cell lymphoma based on IPI score and clinical indicators was established.

What is known and what is new?

- Current prognostic models do not work well. Although there are prognostic models based on genetic testing in the past two years, they are expensive and have poor clinical popularity.
- Our predictive model only needs to combine commonly used clinical indicators and IPI scoring system to improve the accuracy of predicting prognosis.

What is the implication, and what should change now?

- Our prediction model showed some improvement over IPI score in distinguishing patients with high-risk factors. Subsequently, multi-center data will be included to expand the sample size, so as to further verify this prediction model.

Methods

Study population and data source

Patients diagnosed with DLBCL between January 2008 and December 2017 at the Harbin Medical University (HMU) Cancer Hospital (Heilongjiang, China) were enrolled in this study, the follow-up cut-off date was 31 August 2020. All the patients were classified using the 2008 World Health Organization's Classification of Tumors of Hematopoietic and Lymphoid Tissue. Patients were excluded if they were aged <18 or >80 years old, did not have complete clinical information, had a primary central nervous system (CNS) lymphoma, had positive serological status for human immunodeficiency virus (HIV), or received first-line immunochemotherapy without a CHOP-like or R-CHOP-like regimen. *Table 1* shows the rationales for these exclusion criteria. The study was conducted in accordance with the

Table 1 Exclusion criteria and their rationales

Criterion	Rationale
Patients without complete clinical information and histologic type	These patients did not have complete information on treatment, and some had missing immunohistochemistry data, which prevented classification into clear categories
Patients who were aged <18 or >80 years	Childhood DLBCL is rare, and young patients differ from adult patients in terms of demographics, treatments, and outcomes. Older patients are assessed differently in efforts to prolong survival, reduce toxicities, and improve quality of life
Patients diagnosed with CNS lymphoma, and those who did not receive a CHOP-like or R-CHOP-like regimen	CNS lymphoma has unique clinical characteristics, treatments, and prognoses. CHOP-like or R-CHOP-like regimens are not applicable to patients who have serious complications or poor physical status (e.g., HIV patients)
Patients without follow-up data	A lack of a phone numbers and addresses prevented the collection of follow-up data

DLBCL, diffuse large B-cell lymphoma; CNS, central nervous system; R-CHOP, rituximab plus cyclophosphamide, adriamycin, vincristine, and prednisone.

Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of the HMU Cancer Hospital (approval No. GZR2014-069). The individuals in our study signed informed consent forms.

Definition of variables

The primary event for the overall survival (OS) analysis was death. The time of OS and other outcome measures were defined as the time from the day of the DLBCL diagnosis until the event of interest. Progression-free survival (PFS) was defined as the time from the beginning of treatment until disease progression, recurrence, or death. As of the last follow-up, there were 150 deaths and 270 survivors. The following baseline demographic and clinical variables were recorded: age (18–59 or ≥60 years), gender (male or female), B symptoms (absent or present), pathological subtype [germinal center B (GCB) or non-GCB], IPI risk stratification group (low, low-intermediate, high-intermediate, or high), first-line treatment regimen (CHOP-like or R-CHOP-like), lymphocyte-monocyte ratio (LMR; ≤3 or >3), neutrophil-lymphocyte ratio (NLR; ≤2.5 or >2.5), and Ki-67 index (≤70% or >70%). The IPI score system considers age, Ann Arbor stage, extra-nodal disease sites, and ECOG PS.

Statistical analysis

The optimal cut-off values for the LMR (3) and NLR (2.5) were obtained by analyzing the significance of the log-rank results using a minimal P value approach with Cutoff Finder (10). The Kaplan-Meier method was used to analyze OS, and survival differences among the groups were compared using the log-rank test. The multivariate survival analysis included all the variables that were significant in the univariate analysis, and Cox proportional hazards regression was used to calculate hazard ratios (HRs) and 95% confidence interval (CIs). The nomogram for outcomes at 3 years and 5 years were constructed using significant risk factors from the multivariate Cox regression model. The Harrell concordance index (C-index) was used to assess the accuracy of the nomogram from 1000 bootstrap re-samples. The c-index is considered acceptable between 0.7 and 0.8, is considered excellent 0.8 and 0.9, and more than 0.9 is considered outstanding. Calibration curves were applied for the model validation, and points closer to the diagonal line (i.e., predictions matching observations) indicated a more accurate model. A decision curve analysis (DCA) was used to estimate the clinical usefulness and net benefit of the nomograms. All the statistical tests were 2-sided, and a P value <0.05 was considered significant. The statistical analysis was performed using R software version 3.6.1 (R Foundation, Vienna, Austria). The R package survminer function ggsurvplot was used to draw the survival curves.

Results

Patient characteristics and survival

We retrospectively examined the records of 420 DLBCL patients for whom active follow-up data were available (*Table 2*). The patients had a median age of 55 years, and were approximately equal in terms of the number of males and females (209 males, 211 females). A total of 100 patients (23.8%) had B symptoms and 291 (69.3%) had the non-

Table 2 Demographic and clinical characteristics of the enrolled DLBCL patients (n=420)

Variable	Number	Percentage
Age at diagnosis, years		
18–59	264	62.86
≥60	156	37.14
Gender		
Male	209	49.76
Female	211	50.24
B symptoms		
Absent	320	76.19
Present	100	23.81
Subtype		
GCB	129	30.71
Non-GCB	291	69.29
IPI risk		
Low [0–1]	234	55.71
Low-intermediate [2]	85	20.23
High-intermediate [3]	58	13.82
High [4–5]	43	10.24
First-line treatment		
CHOP-like	234	55.71
R-CHOP-like	186	44.29
LMR		
≤3	178	42.38
>3	242	57.62
NLR		
≤2.5	219	52.14
>2.5	201	47.86
Ki-67		
≤70%	150	35.71
>70%	270	64.29

DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell-like; IPI, International Prognostic Index; R-CHOP, rituximab plus cyclophosphamide, adriamycin, vincristine, and prednisone; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio.

GCB pathological subtype. The IPI classification indicated that 234 (55.7%) had a low risk, 85 (20.2%) had a low-intermediate risk, 58 (13.8%) had a high-intermediate risk, and 43 (10.2%) had a high risk. The first-line treatment was CHOP-like in 234 patients (55.7%) and R-CHOP-like in 186 patients (44.3%). A total of 242 patients (57.6%) had a LMR >3, 270 (64.3%) had a Ki-67 value >70%, and 201 (47.9%) had a NLR >2.5. The median PFS time was 110 months, and the median OS time was not reached; the 3- and 5-year OS rates were 76.18% and 70.62%, respectively, and the 3- and 5-year PFS rates were 63% and 59.02%, respectively.

Univariate and multivariate analyses

We performed univariate and multivariate Cox proportional hazards regression analyses to identify the potential prognostic factors for OS (*Figure 1* and *Table 3*) and PFS (*Figure 2* and *Table 4*). The univariate Cox regression analysis indicated that age at the time of diagnosis (*Figure 1A*, P=0.008), B symptoms (*Figure 1B*, P<0.001), the LMR (*Figure 1C*, P<0.001), the NLR (*Figure 1D*, P=0.002), the IPI (*Figure 1E*, P<0.001), the use of a first-line regimen with rituximab (*Figure 1F*, P=0.04), and Ki-67 (*Figure 1G*, P=0.002) were significantly associated with OS. Similarly, pathological subtype (*Figure 2A*, P=0.006), B symptoms (*Figure 2B*, P<0.001), the LMR (*Figure 2C*, P<0.001), the NLR (*Figure 2D*, P=0.002), the IPI (*Figure 2E*, P<0.001), the use of a first-line regimen with rituximab (*Figure 2F*, P=0.04), and Ki-67 (*Figure 2G*, P=0.002) were associated with PFS. The multivariate Cox regression model, which included the aforementioned significant factors, showed that a low IPI score, the use of a first-line regimen with rituximab, a high LMR, and a Ki-67 <70% were significantly associated with improved OS and PFS (all P<0.01).

Survival prediction model

We used the results of the multivariate analyses to construct nomograms for OS (*Figure 3A*) and PFS (*Figure 3B*) based on the 4 factors that were significantly associated with the outcomes in the multivariate analysis. These nomograms had good accuracy for predicting OS (C-index =0.73) and PFS (C-index =0.68), and slightly outperformed the IPI

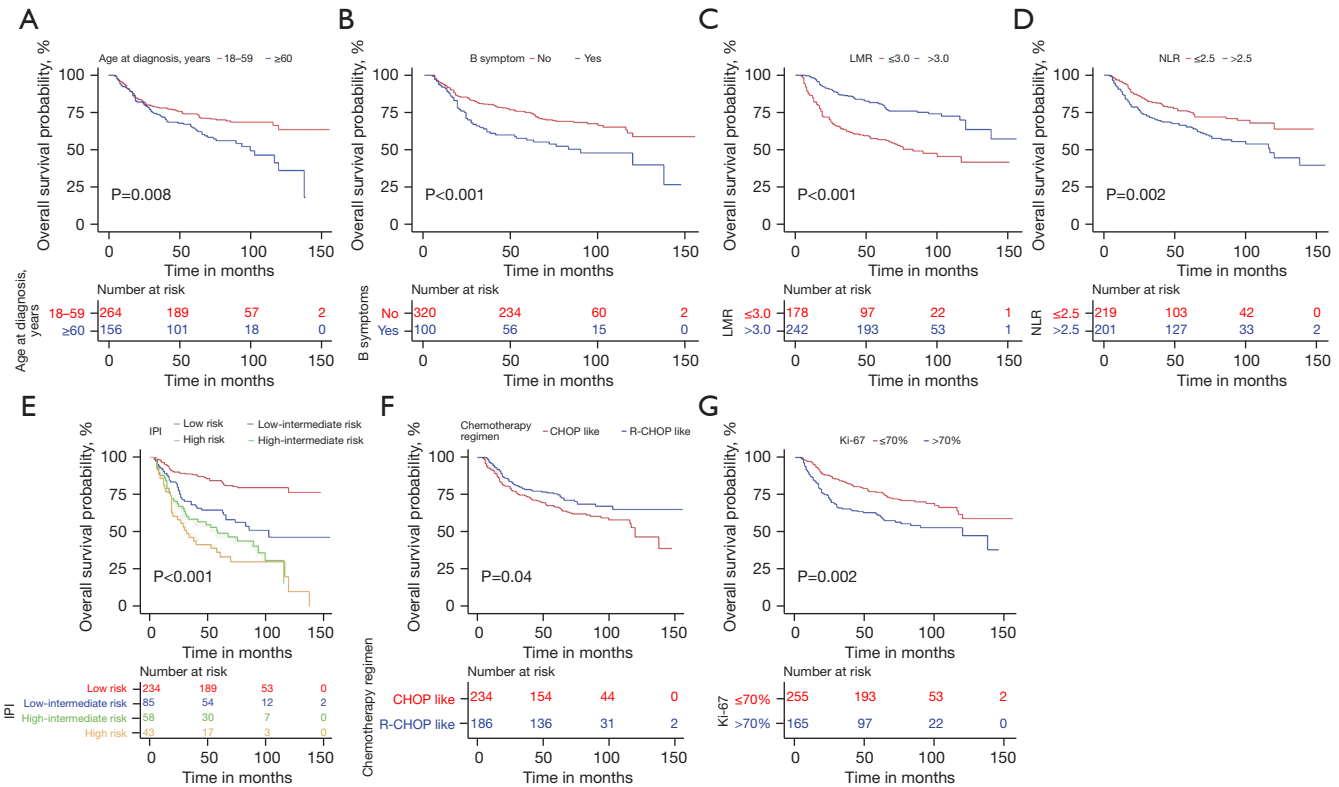

Figure 1 Kaplan-Meier curves of OS in patients with stratification by age (A), B symptoms (B), LMR (C), NLR (D), IPI (E), chemotherapy regimen (F), and Ki-67 (G). OS, overall survival; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; IPI, International Prognostic Index; R-CHOP, rituximab plus cyclophosphamide, adriamycin, vincristine, and prednisone.

(OS: C-index =0.67; PFS: C-index =0.63). The survival probability calibration curves for OS and PFS showed good agreement between the actual survival probability and nomogram-predicted survival probability (*Figure 3C-3F*). The DCA results showed that the net benefit of our model was greater than the screening using the original IPI system across a wide range of thresholds (0.01–0.86; *Figure 3G,3H*).

The Kaplan-Meier survival curves based on risk stratification using the modified IPI (*Figure 4A,4B*) were better able to discriminate among patients with different prognoses than survival curves using the IPI (*Figure 1E,2E*).

Discussion

We developed and validated nomograms that combined clinical prognostic factors with the IPI to predict the 3-year and 5-year OS and PFS of DLBCL patients who received standard first-line treatment regimens. The study has reported that the IPI showed consistently good performance in risk stratification and prognostic prediction, and that the R-IPI and age-adjusted (aa)-IPI provided no substantial improvements (11). Following the clinical introduction of rituximab, the original intent of the NCCN-IPI was to identify the subgroup of high-risk patients with poor survival by stratification using risk factors based on the IPI, and to re-assign scores based on different prognostic risk factors. The results showed that the NCCN-IPI discriminated among patients at poor risk using PFS instead of OS as the end point, but failed to identify the prognosis of patients with poor outcomes (12). Because the results of the IPI and NCCN-IPI did not differ significantly in terms of treatment decisions, and the IPI was simpler and easier to use, we based our prediction model on the IPI score system.

The previous IPI and NCCN-IPI risk scoring systems did not consider the effects of rituximab treatment. In our study, we enrolled patients receiving standard first-line treatment either with or without rituximab. Our results showed that the use of rituximab provided a significant survival advantage. The initial combination of rituximab with chemotherapy has been shown to reduce the risk of

Table 3 Univariate and multivariate Cox analysis of OS in DLBCL patients

Characteristic	3-year OS (%), median (IQR)	5-year OS (%), median (IQR)	Univariate		Multivariate	
			HR (95% CI)	P value	HR (95% CI)	P value
Age at diagnosis, years						
18–59	78.03 (73.19–83.19)	74.05 (68.92–79.56)	Reference	1.00	Reference	1.00
≥60	73.07 (66.42–80.37)	64.68 (57.48–72.78)	1.63 (1.18–2.25)	0.008	1.08 (0.74–1.58)	0.69
B symptoms						
Absent	80.62 (76.41–85.07)	75.03 (70.40–79.96)	Reference	1.00	Reference	1.00
Present	61.95 (53.12–72.25)	56.50 (47.49–67.23)	1.84 (1.31–2.59)	<0.001	1.11 (0.77–1.60)	0.97
Pathological subtype						
GCB	84.50 (78.48–90.98)	76.02 (68.86–83.93)	Reference	1.00	Reference	1.00
Non-GCB	72.50 (67.54–77.81)	68.23 (63.06–73.81)	1.70 (1.16–2.50)	0.007	1.32 (0.88–1.97)	0.18
IPI						
Low risk	88.46 (84.46–92.65)	84.41 (79.85–89.23)	Reference	1.00	Reference	1.00
Low-intermediate risk	68.24 (59.02–78.89)	64.71 (55.30–75.71)	2.83 (1.83–4.35)	<0.001	2.31 (1.37–3.86)	<0.001
High-intermediate risk	58.62 (47.22–72.77)	49.18 (37.70–64.15)	4.35 (2.79–6.79)	<0.001	3.43 (1.97–5.94)	<0.001
High risk	46.40 (33.62–64.02)	36.28 (24.24–54.31)	6.04 (3.83–9.54)	<0.001	4.39 (2.36–8.15)	<0.001
First-line treatment						
CHOP-like	74.36 (68.97–80.17)	66.69 (60.87–73.08)	Reference	1.00	Reference	1.00
R-CHOP-like	78.48 (72.79–84.62)	75.59 (69.63–82.07)	0.71(0.51–0.98)	0.04	0.64 (0.46–0.93)	<0.001
LMR						
≤3	62.33 (55.60–69.88)	56.80 (49.90–64.65)	Reference	1.00	Reference	1.00
>3	85.95 (81.68–90.44)	80.74 (75.88–85.91)	0.40 (0.29–0.55)	<0.001	0.49 (0.33–0.72)	<0.001
NLR						
≤2.5	81.27 (76.27–86.61)	75.56 (70.03–81.51)	Reference	1.00	Reference	1.00
>2.5	70.14 (64.09–76.76)	65.25 (58.92–72.25)	1.66 (1.2–2.3)	0.002	0.82 (0.56–1.19)	0.29
Ki-67						
<70%	83.13 (78.66–87.86)	76.58 (71.52–82.00)	Reference	1.00	Reference	1.00
≥70%	65.45 (58.58–73.12)	61.31 (54.22–69.32)	1.79 (1.30–2.47)	0.002	1.84 (1.32–2.58)	<0.001

B symptoms: unexplained fever above 38 ℃, night sweats, or weight loss of >10% within 6 months. OS, overall survival; DLBCL, diffuse large B-cell lymphoma; IQR, interquartile range; GCB, germinal center B-cell-like; IPI, International Prognostic Index; R-CHOP, rituximab plus cyclophosphamide, adriamycin, vincristine, and prednisone; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio.

relapse and improve PFS and long-term OS, rituximab has also been shown to be more effective in younger patients with a good prognosis than elderly patients (13). The selection of treatment regimen relies on a physician's discretion considering the specific status of each patient. The study reported that standard-dose rituximab (375 mg/m^2) significantly increased the risk of HBV reactivation compared with reduced-dose rituximab (200 mg/body) and no rituximab (14). The research also has found that rituximab is implicated in precipitating tumor lysis syndrome (TLS) in patients with high tumor burden (15). Clinicians recommend rituximab to patients who are in

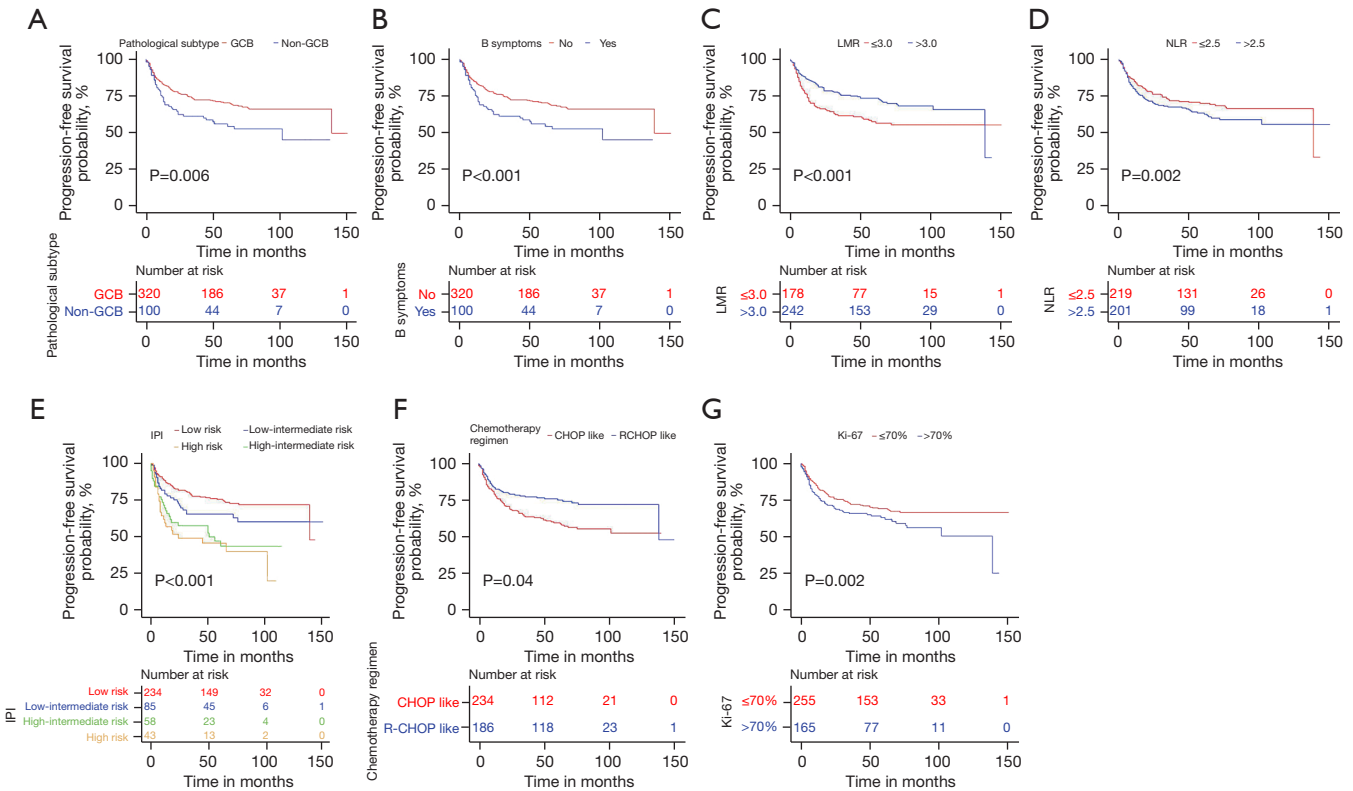

Figure 2 Kaplan-Meier curves of PFS in patients with stratification by pathological subtypes (A), B symptoms (B), LMR (C), NLR (D), IPI (E), chemotherapy regimen (F), and Ki-67 (G). PFS, progression-free survival; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio; IPI, International Prognostic Index; R-CHOP, rituximab plus cyclophosphamide, adriamycin, vincristine, and prednisone.

remission for comorbid conditions and who have clinical indication for rituximab therapy. Thus, some patients will not receive a regimen with rituximab for a variety of reasons as the first-line therapy. The nomograms presented in this study provide a visualization of the survival benefit of using rituximab and could be used to guide patient stratification and assist in the making of reasonable therapeutic decisions. In the absence of rituximab therapy, the follow-up strategies and management must be reconsidered; for example, adjusting the dosage and/or intensity of the chemotherapy regimen may improve efficacy (16).

Numerous factors affect oncogenesis, tumor progression, response to therapy, and the outcome of patients with lymphoma, including the tumor microenvironment, host immunity, and inflammatory responses (17). The LMR prior to the initiation of the first-line treatment is an important indicator of DLBCL prognosis, and a lower LMR is associated with a poor prognosis because it indicates poor host immunity, a factor that contributes to lymphoma progression (18). This is consistent with our results, which indicated that an LMR <3 is significantly associated with a reduced OS and PFS. Lymphocytes are important mediators of antibody-dependent cell-mediated cytotoxicity, and lymphopenia is an indicator of poor prognosis in DLBCL due to the reduced tumor clearance and surveillance ability of the host (19). An increased level of monocytes in the peripheral blood can promote tumor progression by increasing angiogenesis, inhibit anti-tumor immunity, and increase the proliferation of malignant cells (20). A low LMR favors tumorigenesis and progression by increasing the levels of cytokines released by tumor cells, such as granulocyte colony-stimulating factor. These cytokines promote the proliferation and differentiation of neutrophils, which function in the microenvironment required for tumor development, induce tumor angiogenesis, and thus promote the proliferation, invasion, and metastasis of tumor cells (21).

Previous research has reported that a Ki-67 cut-off value of 70% can be used to reliably discriminate between DLBCL patients with good and poor prognoses (22). Similarly, our results showed that a Ki-67 index >70% indicated worse OS

Table 4 Univariate and multivariate Cox analysis of PFS in DLBCL patients

Characteristics	3-year PFS (%), median (IQR)	5-year PFS (%), median (IQR)	Univariate		Multivariate	
			HR (95% CI)	P value	HR (95% CI)	P value
B symptoms						
Absent	72.26 (67.40–77.47)	70.18 (65.16–75.59)	Reference	1.00	Reference	1.00
Present	61.11 (52.02–71.79)	55.87 (46.50–67.13)	1.60 (1.16–2.17)	<0.001	1.13 (0.88–1.41)	0.48
Pathological subtype						
GCB	73.01 (65.64–81.21)	71.14 (63.58–79.59)	Reference	1.00	Reference	1.00
Non-GCB	68.06 (62.74–73.83)	64.82 (59.29–70.86)	1.51 (1.08–2.10)	0.006	1.37 (1.04–1.61)	0.07
IPI						
Low risk	77.62 (72.38–83.23)	75.52 (70.07–81.39)	Reference	1.00	Reference	1.00
Low-intermediate risk	65.41 (55.59–76.96)	65.41 (55.59–76.96)	1.88 (1.29–2.76)	0.014	1.29 (1.00–1.67)	<0.001
High-intermediate risk	57.63 (45.75–72.60)	43.58 (30.98–61.31)	3.0 (2.02–4.44)	<0.001	1.70 (1.27–2.28)	<0.001
High risk	48.95 (35.71–67.08)	45.68 (32.42–64.37)	3.66 (2.42–5.53)	<0.001	1.83 (1.30–2.60)	<0.001
First-line treatment						
CHOP-like	63.52 (57.46–70.21)	59.44 (53.16–66.47)	Reference	1.00	Reference	1.00
R-CHOP-like	77.20 (71.29–83.60)	75.90 (69.85–82.47)	0.62 (0.46–0.84)	0.002	0.58 (0.52–1)	<0.001
LMR						
≤3	61.52 (54.37–69.37)	57.29 (49.99–65.65)	Reference	1.00	Reference	1.00
>3	75.34 (70.01–81.06)	73.44 (67.97–79.35)	0.53 (0.40–0.71)	<0.001	0.76 (0.52–1.11)	0.004
NLR						
≤2.5	71.68 (65.85–78.03)	69.94 (63.96–76.48)	Reference	1.00	Reference	1.00
>2.5	67.30 (60.91–74.36)	63.22 (56.54–70.69)	1.45 (1.09–1.94)	0.002	0.92 (0.64–1.33)	0.66
Ki-67						
≤70%	71.97 (66.56–77.82)	69.13 (63.53–75.23)	Reference	1.00	Reference	1.00
>70%	65.86 (58.76–73.82)	63.08 (55.71–71.43)	1.49 (1.12–2.00)	0.002	1.36 (0.99–1.95)	0.001

B symptoms: unexplained fever above 38 ℃, night sweats, or weight loss of >10% within 6 months. PFS, progression-free survival; DLBCL, diffuse large B-cell lymphoma; IQR, interquartile range; GCB, germinal center B-cell-like; IPI, International Prognostic Index; R-CHOP, rituximab plus cyclophosphamide, adriamycin, vincristine, and prednisone; LMR, lymphocyte-to-monocyte ratio; NLR, neutrophil-to-lymphocyte ratio.

and PFS. Other researches have also shown that a high Ki-67 index is associated with survival in patients with NHL, such as DLBCL, mantle cell lymphoma (23), and natural killer/T cell lymphoma (24). However, since the introduction of rituximab, a high Ki-67 index in DLBCL patients has been considered an indicator of a favorable prognosis (25). High Ki-67 expression might be indicative of a tumor with an elevated risk for regeneration and mutations, leading to treatment failure, or active proliferation, meaning that the tumor is more susceptible to treatment (26). In our view, it is important to consider differences in how Ki-67 is measured at different medical institutions (e.g., the staining method used to determine the proportion of positive Ki-67 cells). In this study, all the pathology reports were re-evaluated by a pathologist at our institution, and Ki-67 was included as a factor in our nomograms.

The present study differs from previous studies because we established and validated nomograms for use in a

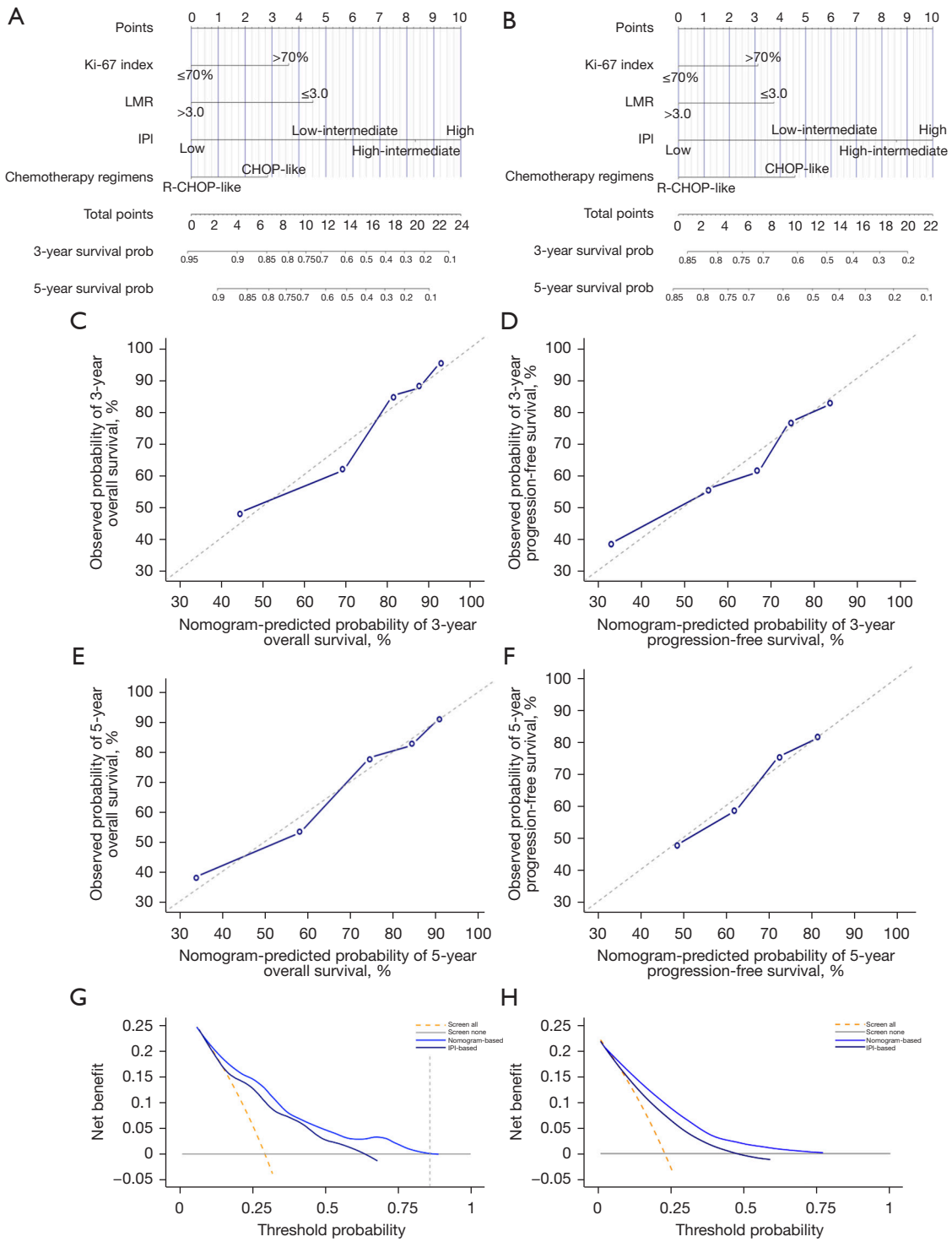

Figure 3 Nomograms for predicting 3-year and 5-years OS (A) and PFS (B). Calibration curves for 3-year and 5-year OS (C,E) and PFS (D,F). DCA for 5-year OS (G) and PFS (H). OS, overall survival; PFS, progression-free survival; DCA, decision curve analysis.

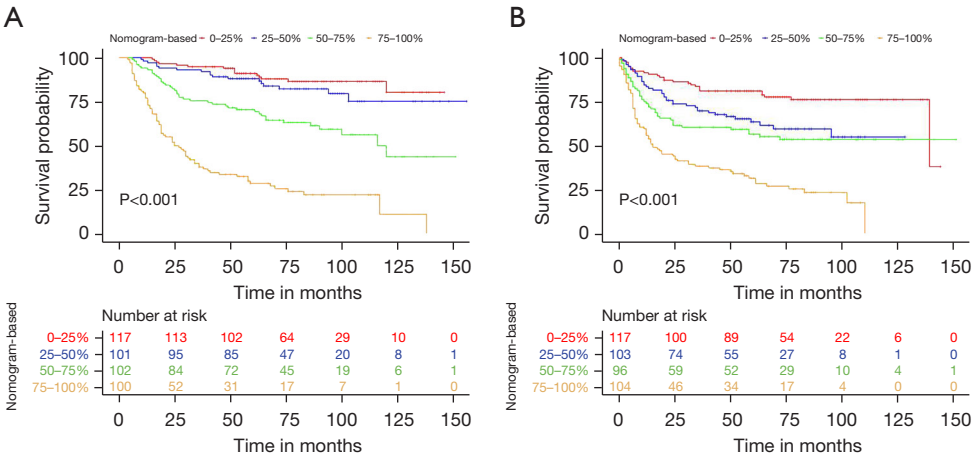

Figure 4 Kaplan-Meier curves of OS and PFS with risk stratification based on the modified IPI. See *Figures 1E*,*2E* for comparison. OS, overall survival; PFS, progression-free survival; IPI, International Prognostic Index.

population of DLBCL patients who received standard first-line treatment regimens either with or without rituximab. We also considered the IPI, along with features of the tumor micro-environment and patient pathological characteristics, in developing our nomograms. Our approach provided improved predictions of patient survival and identified high-risk patients who may need novel or aggressive therapies or who may be suitable for enrolment in clinical trials that aim to prolong survival time.

Our study also had some limitations. First, it was conducted at a single-center with a relatively small number of patients, so validation is needed by a large multi-center study. Second, due to the retrospective nature of this study, we will continue to collect clinically relevant data for analysis at a later time. Third, there may be additional opportunities to improve the nomogram so that it better satisfies clinical requirements.

Conclusions

In conclusion, our study identified prognostic factors in patients who were newly diagnosed with DLBCL and constructed an individualized risk prediction model. We found that LMR, Ki-67, the use of rituximab in the first-line treatment, and IPI score were significantly associated with OS and PFS. Our modified IPI scoring system, might be a valuable tool that can be used to reliably predict. It enables clinicians to identify patients with possible poor prognosis and choose more active treatment for patients, so as to prolong the PFS and OS of patients.

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Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-6023/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-6023/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-6023/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The individuals in our study signed informed consent forms. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of the HMU Cancer Hospital (approval No. GZR2014-069).

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