Original Article

Clinical characteristics and outcomes of patients with diffuse large B cell lymphoma treated with R-CHOP-like or CHOP-like regimens: an 8-year experience from a single center

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Background: The CHOP regimen comprising cyclophosphamide, doxorubicin, vincristine, and prednisone is a basic chemotherapeutic regimen for diffuse large B cell lymphoma (DLBCL). Addition of rituximab (R) to chemotherapy has led to better efficacy than other regimens in clinical trials. However, data of clinical characteristics and outcomes of patients with DLBCL are scarce. Therefore, this study reports the clinical characteristics, treatment, and outcomes of patients with DLBCL in our hospital.

Methods: We conducted a retrospective analysis of newly diagnosed DLBCL patients treated with CHOP-like or R-CHOP-like regimens at our hospital between 2011 and 2018. We analyzed the data on demography, clinical characteristics, treatment, treatment response, and survival time. Both univariate and multivariate analyses were applied.

Results: In total, 570 newly diagnosed DLBCL patients were included, of which 133 were treated with CHOP-like regimens and 437 with R-CHOP-like regimens. The overall response rate was 83.3%. Germinal center B-cell-like (GCB) subtype, R-CHOP-like treatment, Ann Arbor stage I–II, not more than 1 extranodal disease site, Eastern Cooperative Oncology Group (ECOG) score ≤1, normal serum lactate dehydrogenase (LDH) level, normal serum β2 microglobulin (β2-MG) level, absence of B symptoms, and lower International Prognostic Index (IPI) or National Comprehensive Cancer Network-International Prognostic Index (NCCN-IPI) scores were associated with longer overall survival (OS) and progression-free survival (PFS), and were favorable prognostic factors for OS and PFS. Only GCB subtype, R-CHOP-like treatment, absence of B symptoms, and lower IPI or NCCN-IPI scores were independent favorable prognostic factors for OS and/or PFS. Neither IPI nor NCCN-IPI could accurately and precisely predict the prognosis of high-risk DLBCL patients.

Conclusions: This analysis of newly diagnosed DLBCL patients indicates that patients treated with R-CHOP-like regimens or with GCB subtype exhibited better outcomes. Further, IPI and NCCN-IPI have limited prognostic values in high-risk DLBCL patients.

Keywords: Clinical characteristic; diffuse large B cell lymphoma (DLBCL); outcome; prognostic factor; treatment

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Introduction

Diffuse large B cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma, characterized by aggressive and heterogeneous features. Although DLBCL can be classified into two categories, namely, germinal center B-cell-like (GCB) and non-germinal center B-cell-like (non-GCB), the standard therapy for these two subtypes is the chemotherapeutic regimen called CHOP, which comprises cyclophosphamide, doxorubicin, vincristine, and prednisone. In the last decade, the addition of rituximab (R), an anti-CD20 monoclonal antibody, to the standard chemotherapy regimen has dramatically improved the outcomes of patients with DLBCL (1). Since then, several studies have demonstrated the inability of the International Prognostic Index (IPI) to effectively predict the prognosis of patients with DLBCL. Hence, revised IPI (R-IPI) and National Comprehensive Cancer Network IPI (NCCN-IPI) were generated (2,3). However, the efficacy of these two indicators in prognosis prediction of patients with DLBCL was still insufficient. Although new indicators based on IPI have been proposed, their efficiency in prognosis prediction remains to be tested (4).

About 30–50% patients with DLBCL show resistance to, or relapse after, R-CHOP treatment (5,6). Chimeric antigen receptor (CAR) T cell therapy has been reported as a novel promising therapy for refractory or relapse (R/R) DLBCL patients. In clinical trials, the overall response rate of CAR-T cell therapy in R/R DLBCL patients was more than 80%, and a few patients achieved long-term remission (7,8). In general, the lack of standard techniques for T cell or peripheral blood mononuclear cell harvesting and CAR-T cell manufacturing and quality control may limit the clinical applications of this therapeutic regimen (9). The efficacy of novel target drugs in R/R DLBCL patients was not better than that of CAR-T cell therapy in clinical trials (10-17).

Here, we report the real-world data of the clinical characteristics and outcomes of patients with DLBCL that were treated with or without rituximab.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/apm-19-589).

Methods

Ethics approval

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the ethics committee of Fujian Medical University Union Hospital (No. 2019KJCX047). As this study performed retrospective data analysis and had no effect on patients' treatments, patients' consents were not obtained. Use of patients' data and/or test results for this study was approved by the ethics committee of our institute.

Patients

Diagnosis was confirmed through tissue biopsy or surgical excision according to the World Health Organization (WHO) classification (18). Newly diagnosed patients with DLBCL who were 14 years or older and received no less than four cycles of immunochemotherapy or chemotherapy were included in the study. Patients with primary mediastinal lymphoma, primary central nervous system (CNS) lymphoma, or positive serology for human immunodeficiency virus were excluded. Data were collected from the medical records of patients included from 1 January 2011 to 31 December 2018 at Fujian Medical University Union Hospital, Fujian province, China.

Treatment and evaluation

Treatment response was evaluated according to the International Working Group Response Criteria for Malignant Lymphoma (19). Newly diagnosed patients with DLBCL were treated with CHOP-like or R-CHOP-like regimens. In case of disease progression or relapse, patients were treated with second-line regimens as recommended by NCCN guidelines, such as R-DHAP or R-DA-EPOCH (20).

Routine laboratory tests and clinical assessment were performed at the beginning of each treatment cycle. Interim assessment, including laboratory tests and imaging examinations, was performed no later than the sixth cycle. Treatment response was determined by interim assessment. Bone marrow biopsy was repeated at the interim assessment and at the end of treatment if initially involved.

Overall survival (OS) was defined as the time from the date of treatment inception to the date of death or last follow-up. Progression-free survival (PFS) was defined as the time from the date of treatment inception to the date of disease progression, relapse, or death, whichever was reported first. Death from all causes was included. Survival time was measured until 10 June 2019.

Table 1 Demographic and clinical characteristics of enrolled patients

Characteristics	Classification	N (%)
Age (years)	>60	202 (35.4)
	≤60	368 (64.6)
Gender	Male	351 (61.6)
	Female	219 (38.4)
B symptoms	Absent	425 (74.6)
	Present	145 (25.4)
LDH	High	261 (45.8)
	Normal	309 (54.2)
ECOG score	0–1	445 (78.1)
	2–4	125 (21.9)
Ann Arbor stage*	I–II	209 (36.7)
	III–IV	359 (63.0)
	Undetermined	2 (0.4)
Extranodal disease	>1	182 (31.9)
	≤1	388 (68.1)
IPI	Low risk [0–1]	231 (40.7)
	Low-intermediate risk [2]	122 (21.5)
	High-intermediate risk [3]	132 (23.2)
	High risk [4–5]	83 (14.6)
NCCN-IPI*	Low risk [0–1]	107 (18.8)
	Low-intermediate risk [2–3]	257 (45.2)
	High-intermediate risk [4–5]	158 (27.8)
	High risk (≥6)	46 (8.1)
Serum β2-MG	High	88 (24.9)
	Normal	265 (75.1)
Ki-67	Median (range)	80 [35–100]
Subtype*	GCB	194 (34.0)
	Non-GCB	336 (58.9)
	Undetermined	40 (7.0)

*, the mantissa of one digit is now the result. The mantissa of two digits adds up to 100%. LDH, lactate dehydrogenase; ECOG, eastern cooperative oncology group; IPI, international prognostic index; NCCN, national comprehensive cancer network; β2-MG, β2 microglobulin.

Statistical analysis

All statistical analyses were performed using SPSS 19.0 for Windows. Dichotomous and continuous variables were compared using the Chi-square test and *t*-test, respectively. Time-to-event data were analyzed using the Kaplan-Meier method, and differences between them were analyzed using the log-rank test. Variables known to be significant prognostic factors in the univariate analysis were further used for multivariate analysis. Two-sided P values <0.05 were considered statistically significant.

Results

Demographic and clinical characteristics of patients

Between January 2011 and December 2018, 570 patients with newly diagnosed DLBCL who met the inclusion criteria were included in this study. The demographic and clinical characteristics of these patients are listed in *Table 1*. Their median age at diagnosis was 55 [14–86] years. Of them, 351 (61.6%) were male, 145 (25.4%) had B symptoms, 261 (45.8%) had serum lactate dehydrogenase (LDH) levels higher than normal, 125 (21.9%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 2–4, and 182 (31.9%) had more than one extranodal disease site. As the imaging data for two patients before treatment were insufficient for precise staging, only 568 patients could be staged. Among them, 359 (63.0%) were in advanced stages (III–IV). IPI scores for 568 patients were as follows: 231 (40.7%) low-risk, 122 (21.5%) low-intermediate-risk, 132 (23.2%) high-intermediate-risk, and 83 (14.6%) high-risk. As classified by NCCN-IPI, 107 (18.8%) patients were low-risk, 257 (45.2%) were low-intermediate-risk, 158 (27.8%) were high-intermediate-risk, and 46 (8.1%) were high-risk. Detection of serum macroglobulin (β2-MG) level was performed in 353 patients, of which 88 (24.9%) had serum β2-MG levels higher than normal.

The expression of the proliferative marker, Ki-67, was detected in the tissues of 481 patients. The median positive rate of Ki-67 in tumor cells was 80%, and the positive rate of Ki-67 in tumor cells was higher than 50% in 461 of 481 samples. According to the Hans Criteria, 194 (34.0%) patients were classified into GCB subtype and 336 (58.9%) into non-GCB subtype; 40 (7.0%) patients could not be classified, as their biopsy tissues were insufficient to perform immunohistochemical detection (*Table 1*).

Treatment and response of patients

All 570 patients enrolled received no less than four cycles of CHOP-like or R-CHOP-like regimens. Of them,

Table 2 Treatment and response of patients enrolled

Characteristics	Classification	N (%)
Chemotherapy	R-CHOP-like	437 (76.7)
	CHOP-like	133 (23.3)
Combined with radiation		45 (7.9)
Response to treatment	CR+PR	475 (83.3)
	SD+PD	67 (11.8)
	Undetermined	28 (4.9)
Relapse/refractory		156 (27.4)
Stem cell transplantation	Autologous	24 (4.2)
	Allogeneic	2 (0.4)
CAR-T cell therapy		8 (1.4)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; CAR-T, chimeric antigen receptor T.

133 patients who received less than three cycles of rituximab were assigned to the CHOP-like regimen. The remaining 437 patients were assigned to the R-CHOP-like regimen. Patients were assessed for response after 2–5 cycles of initial therapy using the Revised Response Criteria for Malignant Lymphoma (8).

The overall response rate was 83.3%, and 67 (11.8%) patients achieved stable disease (SD) or suffered from progressive disease (PD) after receiving CHOP-like or R-CHOP-like regimen. Response to chemotherapy or immunochemotherapy could not be assessed in 28 patients, as their imaging assessments were incomplete. A total of 156 (27.3%) patients became primarily refractory to the therapeutic regimen, suffered from PD, or relapsed after achieving complete response (CR) during treatment or follow-up. Further, 34 patients received different types of cell therapy as follows: 24 received autologous stem cell transplantation (SCT), 2 received allogeneic SCT, and 8 received CAR-T cell therapy. Radiation was administered to 45 patients because they had residual disease after chemotherapy or immunochemotherapy or suffered from PD or relapse with CNS involvement (*Table 2*).

Survival and prognostic factors

The median follow-up period for the entire group was 25.77 months (range, 2.73–102.33 months), and 100 patients died. The median OS and PFS were not reached in the entire group (*Figure 1*).

Kaplan-Meier curve and univariate analysis showed that GCB subtype, R-CHOP-like treatment, Ann Arbor stage I-II, not more than 1 extranodal disease site, ECOG score ≤1, normal serum LDH level, normal serum β2-MG level, absence of B symptoms, and lower IPI or NCCN-IPI score were associated with longer OS and PFS, and were favorable prognostic factors for OS and PFS. Age ≤60 years was associated with longer OS and served as a favorable prognostic factor for OS but not PFS (*Tables 3*,*4*, *Figure 1*). Kaplan-Meier curves for OS and PFS showed convergence of high-intermediate-risk and high-risk subgroups classified by both IPI and NCCN-IPI (*Figure 1*).

In the multivariate analysis, absence of B symptoms and R-CHOP-like treatment were independent favorable prognostic factors for OS. GCB subtype and R-CHOP-like treatment similarly served as independent favorable factors associated with PFS (*Table 5*). IPI and NCCN-IPI scores had no prognostic values for OS between high-intermediate- and high-risk subgroups. Moreover, IPI and NCCN-IPI scores had no prognostic values for PFS among low-intermediate-, high-intermediate-, and high-risk subgroups.

Discussion

DLBCL accounts for 31% and 40–50% of newly diagnosed NHL in developed countries and China, respectively. According to its origin, DLBCL may be classified into two subtypes GCB and non-GCB by immunochemistry or three subtypes by gene expression profiling, including GCB, activated B-cell (ABC), and unclassified (UNC) (21). Several studies have shown that the survival of patients with non-GCB subtype was worse than that of patients with GCB subtype (22,23). A similar phenomenon has been reported in patients with ABC subtype (24). Other characteristics that were either included or excluded in IPI were associated with the prognosis of patients with DLBCL (4,25-27). In the last decade, the use of rituximab was shown to improve the treatment response and survival of patients with DLBCL (1,28,29). However, long-term follow-up data for newly diagnosed patients with DLBCL in the real-world setting are scarce. Therefore, in the present study, we investigated the clinical characteristics and outcomes of newly diagnosed patients with DLBCL treated at our single center.

We found that most patients were not more than 60 years, male, and had non-GCB subtype. Most patients had IPI scores 2 and NCCN-IPI scores ≤3. ECOG score for most

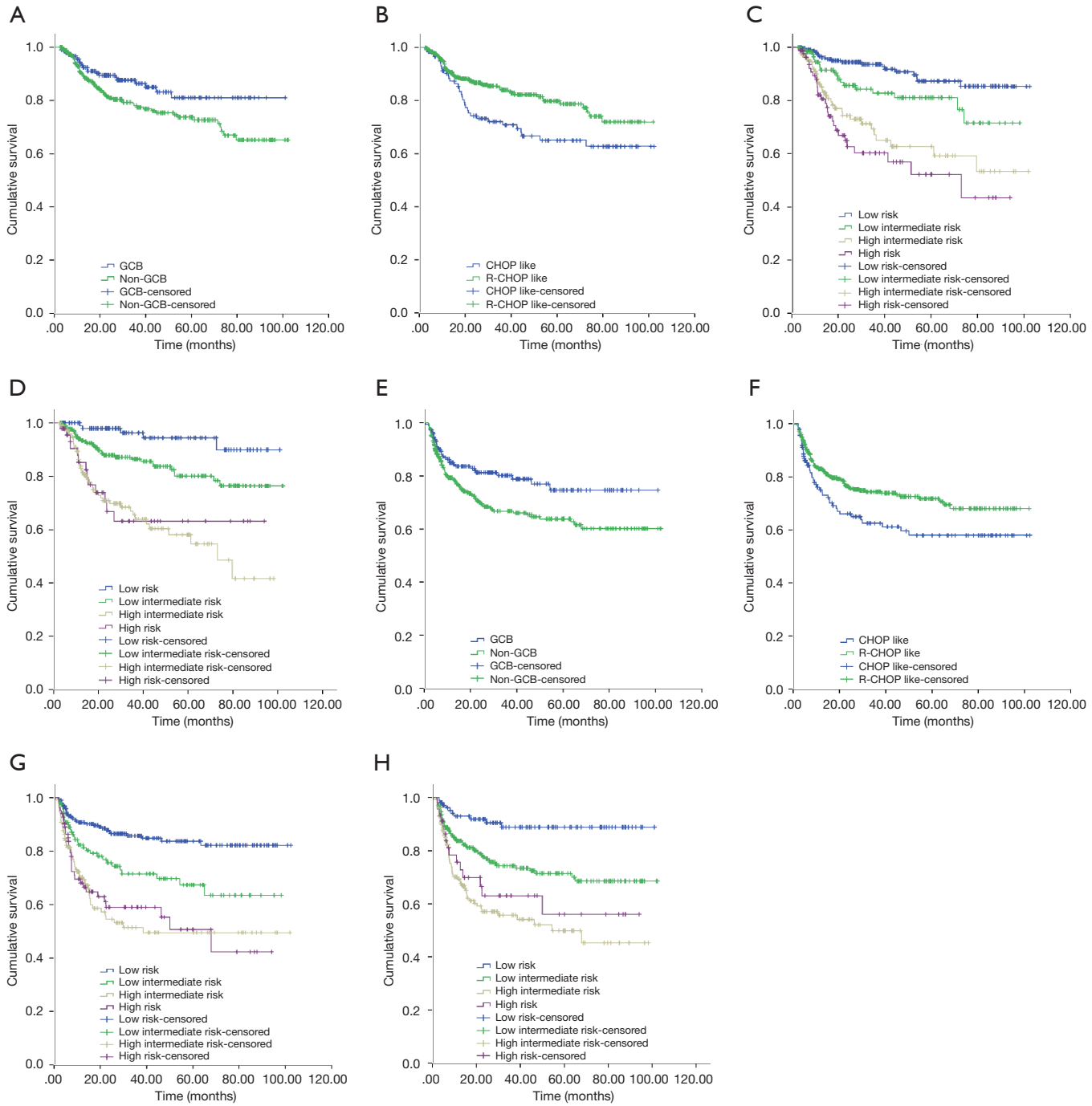

Figure 1 Kaplan-Meier curves of OS (A,B,C,D) and PFS (E,F,G,H) based on cell of origin, chemotherapy regimen, and different IPI. (A,E) Patients with GCB subtype had longer OS and PFS than patients with non-GCB subtype. (B,F) Patients treated with R-CHOP-like regimens had longer OS and PFS than patients treated with CHOP-like regimens. (C,G) Patients with low and low-intermediate risk classified by IPI had longer OS than patients with high-intermediate and high risk. Patients with low risk classified by IPI had longer PFS than patients with and low-intermediate, high-intermediate, and high risk. (D,H) Patients with low and low-intermediate risk classified by NCCN-IPI had longer OS than patients with high-intermediate and high risk. Patients with low risk classified by NCCN-IPI had longer PFS than patients with and low-intermediate, high-intermediate, and high risk. OS, overall survival; PFS, progression-free survival; IPI, International Prognostic Index; GCB, germinal center B-cell-like.

Table 3 Survival analysis for OS and PFS in newly diagnosed DLBCL patients

Characteristics	Classification	n	OS			PFS		
			Mean	Log-rank test	P value	Mean	Log-rank test	P value
Gender	Male	351	79.57	0.988	0.320	72.57	0.652	0.419
	Female	219	83.33			74.79		
Age (years)	>60	202	72.51	5.427	0.020	65.76	3.801	0.051
	≤60	368	84.30			76.00		
Ann Arbor staging	I–II	209	89.90	17.068	0.000	85.72	22.694	0.000
	III–IV	359	75.25			65.25		
Extranodular disease	>1	182	72.27	9.812	0.002	61.57	19.424	0.000
	≤1	388	84.86			78.86		
ECOG score	0–1	446	86.05	28.322	0.000	77.46	15.307	0.000
	2–4	124	61.80			56.56		
LDH (IU/L)	High	261	70.60	30.459	0.000	62.80	24.559	0.000
	Normal	309	89.41			81.82		
B symptoms	Absent	425	85.22	20.156	0.000	75.10	3.597	0.058
	Present	145	66.05			64.78		
Serum β2-MG	High	88	58.81	18.392	0.000	53.69	7.894	0.005
	Normal	265	86.30			77.45		
IPI	Low risk [0–1]	231	92.66	49.921	0.000	87.59	44.489	0.000
	LI risk [2]	122	80.73			70.25		
	HI risk [3]	132	68.30			56.26		
	High risk [4–5]	84	56.68			52.97		
NCCN-IPI	Low risk [0–1]	107	95.52	40.089	0.000	91.25	31.588	0.000
	LI risk [2–3]	257	85.94			76.18		
	HI risk [4–5]	158	61.36			54.57		
	High risk [≥6]	46	64.86			59.82		
Cell of origin	GCB	193	86.33	4.301	0.038	79.86	6.868	0.009
	Non-GCB	337	78.27			68.91		
Regimen	CHOP-like	133	73.22	6.628	0.010	65.18	5.643	0.018
	R-CHOP-like	437	83.49			75.62		

DLBCL, diffuse large B cell lymphoma; ECOG, eastern cooperative oncology group; LDH, lactate dehydrogenase; β2-MG, β2 microglobulin; IPI, international prognostic index; NCCN, national comprehensive cancer network; LI, low-intermediate; HI, high-intermediate.

patients was less than 2. Serum β2-MG levels were higher than normal in some patients, while the positive rate of Ki-67 expression in most patients was higher than 80%. These results are similar to those reported by other studies from China (30,31). Survival analysis showed that some clinical characteristics such as age >60 years, Ann Arbor stage III–IV, extranodular disease >1 site, ECOG score 2–4, serum LDH >245 IU/L, serum β2-MG >3 g/L, presence of B symptoms, and non-GCB subtype were associated with shorter PFS and/or OS, and were unfavorable

Table 4 Univariate analysis for survival time in newly diagnosed DLBCL patients

Characteristics	Classification	OS			PFS		
		HR	95% CI	P value	HR	95% CI	P value
Gender	Male *vs.* female	1.230	0.817–1.851	0.321	1.148	0.821–1.603	0.420
Age (years)	>60 *vs.* ≤60	1.595	1.073–2.371	0.021	1.387	0.997–1.929	0.052
Ann Arbor staging	III–IV *vs.* I–II	2.700	1.653–4.411	0.000	2.563	1.715–3.831	0.000
Extranodular disease	>1 *vs.* ≤1	1.870	1.256–2.784	0.002	2.050	1.479–2.840	0.000
ECOG score	2–4 *vs.* 0–1	2.836	1.899–4.237	0.000	1.973	1.394–2.792	0.000
LDH	High *vs.* normal	3.059	2.014–4.645	0.000	2.265	1.624–3.158	0.000
B symptoms	Absent *vs.* present	2.423	1.626–3.611	0.000	1.405	0.987–2.000	0.059
Serum β2-MG	High *vs.* normal	3.187	1.824–5.568	0.000	1.889	1.203–2.965	0.006
IPI	Low risk [0–1]	0.169	0.094–0.304	0.000	0.264	0.161–0.434	0.000
	LI risk [2]	0.350	0.195–0.627	0.000	0.566	0.346–0.924	0.023
	HI risk [3]	0.754	0.457–1.243	0.268	1.063	0.684–1.651	0.787
	High risk [4–5]	Reference			Reference		
NCCN-IPI	Low risk [0–1]	0.118	0.042–0.331	0.000	0.218	0.098–0.485	0.000
	LI risk [2–3]	0.405	0.214–0.765	0.005	0.635	0.360–1.117	0.115
	HI risk [4–5]	1.128	0.610–2.086	0.701	1.128	0.728–2.251	0.391
	High risk [≥6]	Reference			Reference		
Cell of origin	Non-GCB *vs.* GCB	1.643	1.023–2.638	0.040	1.656	1.131–2.425	0.010
Regimen	R-CHOP-like *vs.* CHOP-like	0.585	0.387–0.884	0.011	0.655	0.461–0.931	0.018

DLBCL, diffuse large B cell lymphoma; OS, overall survival; PFS, progression-free survival; ECOG, eastern cooperative oncology group; LDH, lactate dehydrogenase; β2-MG, β2 microglobulin; IPI, international prognostic index; NCCN, national comprehensive cancer network; LI, low-intermediate; HI, high-intermediate.

prognostic factors for patients with DLBCL in our study. Similar results have been observed by other researchers worldwide (28,30-32).

IPI score served as the most important prognostic indicator for non-Hodgkin lymphoma, including DLBCL. It comprises age, Ann Arbor staging, extranodular disease, ECOG score, and serum LDH level. Several reports have demonstrated that risk stratification based on IPI in DLBCL is of limited value, owing to the inclusion of rituximab to standard chemotherapy (2). Therefore, NCCN-IPI was proposed and applied to many studies in recent years (3). We analyzed the role of these two indices in determining the prognosis of patients with DLBCL who received regimens containing rituximab. According to both IPI and NCCN-IPI, patients could be divided into four groups as follows: low-risk, low-intermediate-risk, high-intermediate-risk, and high-risk. Although IPI and NCCN-IPI were independent prognostic factors for all patients with DLBCL in our study, univariate and multivariate analyses showed us that IPI and NCCN-IPI had limited prognostic values for the OS and/or PFS of patients that are at higher risk, especially high-intermediate- and high-risk patients. These results declined the prognostic values of IPI and NCCN-IPI for patients with DLBCL who received no less than three cycles of rituximab. A new index GELTAMO-IPI combining serum β2-MG levels with NCCN-IPI has been recently proposed (4). As we lacked data on serum β2-MG in approximately 40% patients, we could not objectively evaluate this index or compare it with other indices.

The R-CHOP-like regimen is the first-line regimen for DLBCL. However, some patients still could not receive sufficient doses of rituximab. In the early period of our study, most patients received CHOP-like regimens and could not use rituximab owing to financial constraints.

Table 5 Multivariate analysis for survival time in patients with primary DLBCL

Characteristics	Classification	OS			PFS		
		HR	95% CI	P value	HR	95% CI	P value
B symptoms	Absent *vs.* present	1.679	1.080–2.609	0.021	1.034	0.705–1.516	0.866
Cell of origin	Non-GCB *vs.* GCB	1.528	0.949–2.461	0.081	1.539	1.050–2.258	0.027
Regimen	R-CHOP-like *vs.* CHOP-like	0.478	0.308–0.744	0.001	0.597	0.412–0.864	0.006
IPI	Low risk [0–1]	0.201	0.103–0.392	0.000	0.279	0.161–0.484	0.000
	LI risk [2]	0.430	0.230–0.804	0.008	0.650	0.386–1.095	0.105
	HI risk [3]	0.762	0.440–1.319	0.331	1.093	0.680–1.759	0.713
	High risk [4–5]	Reference			Reference		
NCCN-IPI	Low risk [0–1]	0.134	0.042–0.430	0.001	0.225	0.096–0.527	0.001
	LI risk [2–3]	0.449	0.220–0.917	0.028	0.613	0.336–1.119	0.111
	HI risk [4–5]	1.149	0.585–2.256	0.687	1.221	0.676–2.207	0.508
	High risk [≥6]	Reference			Reference		

DLBCL, diffuse large B cell lymphoma; OS, overall survival; PFS, progression-free survival; IPI, international prognostic index; LI, low-intermediate; HI, high-intermediate; NCCN, national comprehensive cancer network.

However, in the later stage, most patients received CHOP-like regimens due to hepatitis B virus (HBV) infection. Patients treated with R-CHOP-like regimens had longer PFS and OS than others. Furthermore, multivariate analysis showed that the use of regimens comprising rituximab was an independent favorable prognostic factor for patients with DLBCL, consistent with the previously reported result (1,29-31). This observation provides further evidence of the use of rituximab for patients with DLBCL. Antibody-dependent cell-mediated cytotoxicity (ADCC) targeting CD20 induced by rituximab may enhance the antitumor effect of CHOP-like regimens owing to the expression of CD20 antigen on the membrane of B lymphocytes. Thus, prophylactic antiviral therapy was deemed effective along with rituximab in DLBCL patients with HBV infection (33,34). Recent studies have shown that different expression levels of antiapoptotic BCL-2 family proteins in DLBCL cells, existence of cancer stem-like cells, and high expression of CD47 antigen contribute to the chemosensitivity of CHOP-like or R-CHOP-like regimens. Therefore, detection of the expression of certain genes in DLBCL tissues may be useful for the selection of R-CHOP-like or CHOP-like regimen and addition of small-molecule inhibitors in patients with DLBCL (35-37). In our study, radiation was an essential supplement for patients who had CNS or testis involvement in the course of treatment or residual disease after completion of treatment.

Several reports have demonstrated primary refractory, secondary refractory, and relapse in 30–50% of DLBCL patients after comprehensive treatment. Survival of these patients was worse than that of other patients without these complications (5,6,38). The ratio of R/R in patients with DLBCL was not more than 30% in our study. Most patients were at low- and low-intermediate-risk, thereby contributing to this phenomenon. Hematopoietic SCT was considered as an effective approach for DLBCL patients with high-risk, poor prognosis, and relapse/refractory disease (39). However, some patients could not benefit from this method in our study. Therefore, the mechanisms underlying R/R DLBCL and development of therapeutic methods remain to be elucidated.

Several studies have shown that small-molecule inhibitors such as selective inhibitors of nuclear export, dual mTORC1/2 inhibitors, and aurora A kinase inhibitors alone or in combination with chemotherapy exhibited antitumor effects in patients with R/R DLBCL. However, these inhibitors were not more effective than CAR-T cell therapy, a novel cellular immunotherapy (10-17,40-42). No patient in our study participated in clinical trials of small-molecule inhibitors. As far as CAR-T cells are concerned, T cells are genetically modified to express an artificial receptor comprising an antigen recognition domain, a co-stimulatory domain, and an intracellular signaling domain to facilitate recognition of a specific antigen expressed on tumor

cells (43). Two products of CAR-T cells, axicabtagene ciloleucel (axi-cel) and tisagenlecleucel, targeting CD19 specifically expressed on B lymphocytes have been shown to be effective for R/R B cell malignancies with high response rates and potential cure (44,45). However, limitations related to T cell harvesting and CAR-T cell manufacturing, disease progression during manufacturing, and resistance to CAR-T cell therapy have impeded their clinical applications (9,46). Only eight patients received CAR-T cell therapy and all of them achieved PR and survived; however, the long-term effects remain to be studied, as some patients with R/R DLBCL relapsed after receiving CAR-T cell therapy (44,45).

In conclusion, rituximab has been proven to be an important drug to improve the survival of patients with DLBCL. The prognostic values of IPI and NCCN-IPI have declined for patients with DLBCL in the rituximab era. New prognostic indices, thus, need to be proposed and validated to accurately and precisely predict the prognosis of patients. Novel prognostic markers based on molecular or cytogenetic aberrance may be more effective than others in prognostic prediction. New therapeutic approaches such as CAR-T cell therapy and novel drugs have demonstrated significant efficacy in anti-lymphoma treatment of relapse/refractory DLBCL patients and could serve as powerful strategies for treating DLBCL patients in future.

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Footnote

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