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Research article

Clinical characteristics and treatment outcomes of Chinese diffuse large B-cell lymphoma patients in the era of rituximab (2005–2018)☆

Yuankai Shi [a,*], Haizhu Chen [a], Yan Qin [a], Jianliang Yang [a], Peng Liu [a], Xiaohui He [a], Shengyu Zhou [a], Liqiang Zhou [a], Changgong Zhang [a], Yongwen Song [a], Yueping Liu [b], Lin Gui [a], Shulian Wang [b], Jing Jin [b], Hui Fang [b], Shunan Qi [b], Ning Li [b], Yu Tang [b], Xin Wang [b], Sheng Yang [a]

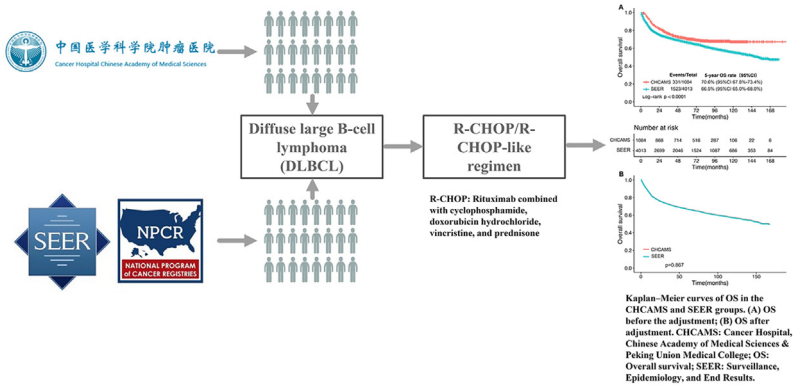
[a] *Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, Beijing 100021, China*

[b] *Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100021, China*

HIGHLIGHTS

- The clinical characteristics and treatment outcomes of Chinese diffuse large B-cell lymphoma (DLBCL) patients and those from the United States Surveillance, Epidemiology, and End Results (SEER) database are summarized and compared in detail.
- The prognostic factors for Chinese DLBCL patients are investigated.
- The adjusting overall survival of Chinese DLBCL patients and those from the SEER database show no significant difference in the rituximab era.

GRAPHICAL ABSTRACT



Kaplan–Meier curves of OS in the CHCAMS and SEER groups. (A) OS before the adjustment; (B) OS after adjustment. CHCAMS: Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College; OS: Overall survival; SEER: Surveillance, Epidemiology, and End Results.

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ABSTRACT

Background: Rituximab combined with cyclophosphamide, doxorubicin hydrochloride, vincristine, and prednisone (R–CHOP) regimen has improved the survival of diffuse large B-cell lymphoma (DLBCL) patients worldwide, compared with CHOP alone. Several limitations were seen in previous studies of Chinese DLBCL patients treated with R–CHOP or R-CHOP-like regimens. This study aimed to investigate the clinical characteristics and treatment outcomes of Chinese DLBCL patients treated with the standard first-line treatment.

Methods: Clinical data were collected from DLBCL patients who received frontline R–CHOP or R-CHOP–like regimens at the Cancer Hospital Chinese Academy of Medical Sciences & Peking Union Medical College (CHCAMS) between January 1, 2005, and December 31, 2018. The treatment outcomes were compared with

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* Corresponding author. Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, Panjiayuan Nanli, Beijing, 100021, China.

E-mail address: syuankai@cicams.ac.cn (Y. Shi).

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those of patients diagnosed with DLBCL between 2004 and 2017 and who received immunochemotherapy from the United States Surveillance, Epidemiology, and End Results (SEER) database. Survival rates were estimated using the Kaplan–Meier method and compared using the log-rank test. Multivariate analysis of progression-free survival (PFS) and overall survival (OS) was performed using Cox proportional hazard regression.

Results: Overall, 1084 patients from the CHCAMS and 4013 patients from the SEER database were included in the study. As of April 30, 2022, the median follow-up period for the CHCAMS group was 87.3 (range: 0.5–195.4) months. For the CHCAMS group, the 5-year PFS and OS rates were 61.7% (95% confidence interval [CI]: 58.8–64.7%) and 70.6% (95% CI: 67.8–73.4%), respectively. For the SEER group, the 5-year OS rate was 66.5% (95% CI: 65.0–68.0%), which was inferior to that of the CHCAMS group ($P < 0.001$). After adjusting for clinical factors and treatment, no significant difference was observed in the OS between the CHCAMS and SEER groups ($P = 0.867$). In the CHCAMS group, multivariate analysis showed that an Eastern Cooperative Oncology Group performance status score ≥2, presence of B symptoms, Ann Arbor stage III–IV, elevated serum β2-microglobulin levels, and bulky mass were independent adverse prognostic factors affecting PFS and OS ($P < 0.05$). Additionally, patients aged over 60 years, elevated lactate dehydrogenase levels, and more than two extranodal sites were independent adverse prognostic factors for OS ($P < 0.05$). Local radiotherapy was significantly associated with better PFS ($P < 0.001$) and OS ($P = 0.001$).

Conclusion: After adjusting for clinical and treatment-related factors, no significant difference was observed in the 5-year OS rate between Chinese DLBCL patients treated with standard first-line treatment and those from the SEER database.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin's lymphoma (NHL), accounting for 30–34% and 40% of adult cases of the disease in Western countries and China, respectively.[1–4] In the 1970s, combination chemotherapy with anthracycline-based regimens became the mainstay of therapy for DLBCL.[5] A randomized controlled phase III trial showed comparable efficacies of the cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regime and traditional anthracycline-based regimens but lower toxicity of the former.[6] Since the late 1990s, considerable improvements have been achieved in clinical outcomes with the rituximab combined with CHOP (R–CHOP) regimen compared with CHOP alone. Accordingly, R–CHOP has become the standard first-line regimen for DLBCL.[7–12] Despite these improvements, 10–15% of patients with DLBCL refractory to frontline therapies, and 20–25% of those with relapsed disease experience dismal outcomes.[13–15]

Several studies have explored the clinical characteristics and treatment outcomes of Chinese DLBCL patients. However, these studies had small sample sizes and involved the use of nonuniform first-line regimens. Therefore, this study aimed to analyze the clinical characteristics and treatment outcomes of DLBCL patients who uniformly received standard first-line R–CHOP or R-CHOP–like regimens at the Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College (CHCAMS). Furthermore, the clinical characteristics and survival of these patients were compared with those of patients whose information was recorded in the United States Surveillance, Epidemiology, and End Results (SEER) database.

Methods

Population

We retrospectively identified DLBCL patients treated at the CHCAMS between January 1, 2005, and December 31, 2018. The inclusion criteria were as follows: (1) patients with histologically confirmed, previously untreated DLBCL; (2) patients aged ≥12 years; (3) patients treated with curative intent; (4) patients treated with R–CHOP or R-CHOP–like regimens as first-line treatment; and (5) patients whose follow-up data were available. The exclusion criteria were: (1) patients who received regimens without rituximab and (2) patients with human immunodeficiency virus infection or other primary malignancies before DLBCL was diagnosed.

The eligibility criteria for patients from the SEER database were as follows: (1) patients with histologically diagnosed, previously untreated DLBCL (including primary mediastinal large B-cell lymphoma) between 2004 and 2017; (2) patients aged ≥12 years; and (3) patients for whom information on the International Prognostic Index (IPI) was available. The exclusion criteria were as follows: (1) patients whose diagnosis was not histologically confirmed; (2) patients whose survival data were unavailable (survival time was unknown or recorded as 0); (3) patients who did not receive chemotherapy; and (4) patients with other primary malignancies before DLBCL was diagnosed.

Data collection and definition

The following baseline clinical information was collected for the CHCAMS group: time of diagnosis, age, sex, the Ann Arbor stage, cell-of-origin subtype, the Eastern Cooperative Oncology Group (ECOG) performance status (PS) score, B symptoms, primary site, number of extranodal sites involved, bulky disease, serum lactate dehydrogenase (LDH) levels, β2-microglobulin (β2M) levels, and the IPI score. In addition, information about the treatment (i.e., starting time, chemotherapy regimens, number of cycles, radiotherapy, and surgery), efficacy, and survival outcomes was collected.

Baseline clinical characteristics and treatment outcomes of DLBCL patients in the SEER database were also extracted. These included the time of diagnosis, age, sex, Ann Arbor stage, primary site, B symptoms,

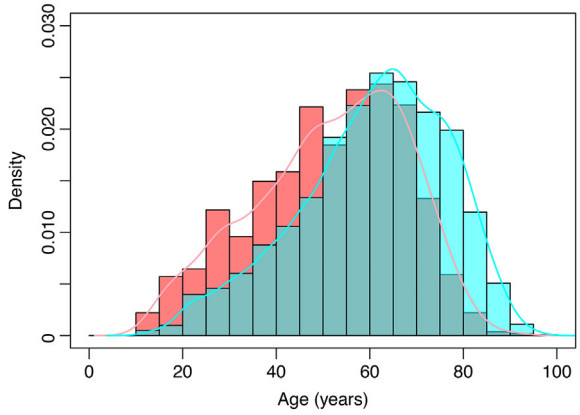

Figure 1. Histogram of age distribution in DLBCL patients. Note: Pink represents patients from CHCAMS, and blue represents patients from the SEER database. CHCAMS: Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College; DLBCL: Diffuse large B-cell lymphoma; SEER: Surveillance, Epidemiology, and End Results.

Table 1
Baseline characteristics of DLBCL patients from the CHCAMS and the SEER database.

Characteristics	CHCAMS	SEER database	*P*
	Value,*n* (%)	Value,*n* (%)	
Age (years)			
Median (years)	54 (12–91)	63 (12–96)	<0.001
≤60	712 (65.68)	1811 (45.13)	<0.001
>60	372 (34.32)	2202 (54.87)	
Sex			
Male	593 (54.70)	2270 (56.57)	0.289
Female	491 (45.30)	1743 (43.43)	
ECOG PS score			
0–1	967 (89.21)	NA	
≥2	117 (10.79)	NA	
Cell of origin type			
GCB	336 (31.00)	NA	
Non-GCB	653 (60.24)	NA	
Unknown	95 (8.76)	NA	
B symptoms[a]			
Yes	215 (19.83)	829 (20.66)	<0.001
No	869 (80.17)	1291 (32.17)	
Unknown	0 (0.00)	1893 (47.17)	
Primary site			
Nodal	641 (59.13)	2887 (71.94)	<0.001
Extranodal	443 (40.87)	1126 (28.06)	
Ann Arbor Stage[a]			
I	254 (23.43)	634 (15.80)	<0.001
II	405 (37.36)	723 (18.02)	
III	171 (15.77)	703 (17.52)	
IV	254 (23.43)	1305 (32.52)	
Unknown	0	648 (16.15)	
IPI risk group (score)			
Low (0–1)	599 (55.26)	1341 (33.42)	<0.001
Low-intermediate (2)	222 (20.48)	917 (22.85)	
High-intermediate (3)	167 (15.41)	890 (22.18)	
High (4–5)	96 (8.86)	865 (21.55)	
Lactate dehydrogenase levels			
Normal	598 (55.17)	NA	
Elevated	486 (44.83)	NA	
β2M levels			
Normal	664 (61.25)	NA	
Elevated	379 (34.96)	NA	
Bulky disease			
Yes	160 (14.76)	NA	
No	924 (85.24)	NA	
Extranodal involvement sites			
<2	823 (75.92)	NA	
≥2	261 (24.08)	NA	
Bone marrow involvement			
Yes	1002 (92.44)	NA	
No	60 (5.54)	NA	
Unknown	0	NA	
Period of diagnosis[b]			
2004–2011	474 (43.73)	2281 (56.84)	
2012–2018	610 (56.27)	1732 (43.16)	
Radiotherapy[c]			
Yes	460 (42.44)	945 (23.55)	<0.001
No	624 (57.56)	3068 (76.45)	
Surgery[c]			
Yes	85 (7.84)	970 (24.17)	<0.001
No	999 (92.16)	3043 (75.83)	

[a] *P*-values for differences in B symptoms and Ann Arbor staging between the two groups were calculated after excluding unknown cases.

[b] The period of diagnosis was 2005–2018 for the CHCAMS group and 2004–2017 for the SEER group. Therefore, the *P*-value for the difference in the period of diagnosis between the two groups was not calculated.

[c] In the SEER group, patients who did not receive radiotherapy (or surgery) and a small number of patients for whom whether radiotherapy (or surgery) was performed was unknown were categorized together and could not be shown separately.CHCAMS: Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College; ECOG: Eastern Cooperative Oncology Group; GCB: Germinal center B-cell; IPI: International Prognostic Index; Non-GCB: Non-germinal center B-cell; PS: Performance status; SEER: Surveillance, Epidemiology, and End Results; β2M: β2-microglobulin.

IPI score, whether radiotherapy or surgery was performed, survival status and time, and cause of death. The clinical stages for these patients were determined based on the Ann Arbor staging system.[16] The cell-of-origin subtype was determined according to the Hans classification system and classified as germinal center B-cell and non-germinal center B-cell subtypes.[17] The bulky disease was defined as any mass with the largest diameter of ≥7.5 cm.

Treatment and response assessments

All patients from the CHCAMS received R–CHOP or R-CHOP–like regimens as first-line treatment. Efficacy was evaluated using computed tomography and/or magnetic resonance imaging or positron emission tomography/computed tomography, according to the International Working Group criteria[18] or the 2014 Lugano criteria.[19] It was classified as complete response (CR), unconfirmed CR (CRu), partial response (PR), stable disease (SD), and progressive disease (PD). Efficacy assessment was performed every two treatment cycles.

Statistical analysis

The study endpoints included overall survival (OS) and progression-free survival (PFS). OS was defined as the time from the initial diagnosis to

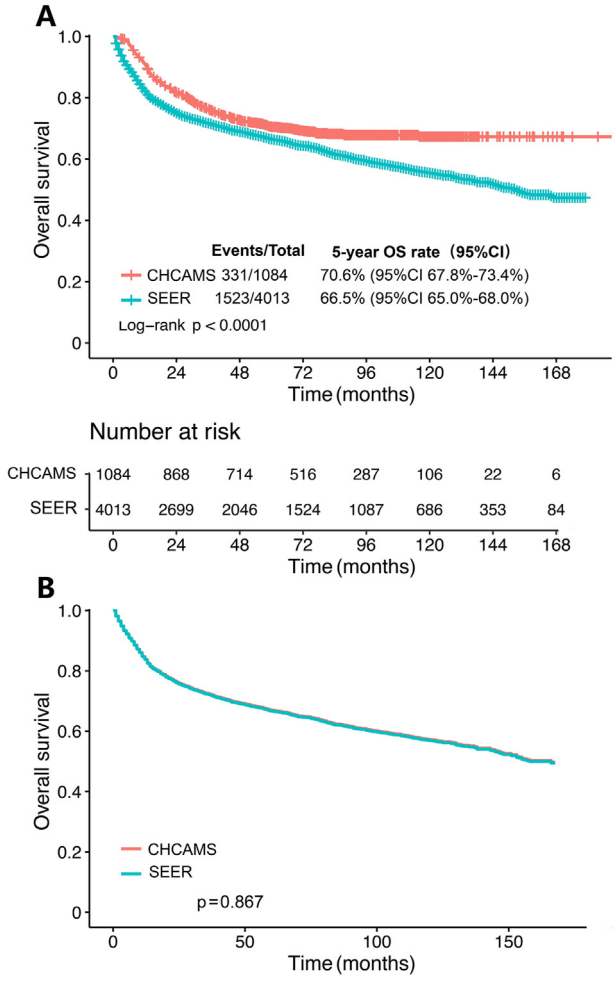

Figure 2. Kaplan–Meier curves of OS in the CHCAMS and SEER groups. (A) OS before the adjustment; (B) OS after adjustment. CHCAMS: Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College; OS: Overall survival; SEER: Surveillance, Epidemiology, and End Results.

death from any cause or the last follow-up date. PFS was defined as the time between the initial diagnosis and first disease progression, relapse, death from any cause, or the last follow-up date. Continuous variables were compared between the groups using the Mann–Whitney *U* test. Categorical variables are presented as numbers and percentages and were compared using the chi-squared test and Fisher's exact test. The Kaplan–Meier method was used to plot survival curves, and the log-rank test was used to compare survival rates between groups. All statistical analyses were performed using the R software version 3.6.2 (The R Foundation for Statistical Computing, Vienna, Austria). $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

Overall, 1084 and 4013 patients from the CHCAMS and the SEER database, respectively, who met the inclusion criteria, were included in this study. The corresponding median ages were 54 (range: 12–91) and 63 (range: 12–96) years. Age distribution was left-skewed in the CHCAMS and SEER groups [Figure 1]. The proportion of patients aged ≤60 years was significantly higher in the CHCAMS group than that in the SEER group (65.68% *vs.* 45.13%, $P < 0.001$). In addition, the CHCAMS group was significantly more likely to have primary extranodal DLBCL than the SEER group (40.87% *vs.* 28.06%, $P < 0.001$). However, stage III–IV disease (59.7% *vs.* 39.2%, $P < 0.001$) and B symptoms (39.1% *vs.* 19.83%, $P < 0.001$) occurred more frequently in the SEER group than those in the CHCAMS group. Furthermore, based on the IPI scores, 55.26%, 20.48%, 15.41%, and 8.86% of patients from the CHCAMS were in the low-risk, low-intermediate–risk, high-intermediate–risk, and high-risk groups, respectively. The corresponding proportions in the SEER group were 33.42%, 22.85%, 22.18%, and 21.55%. There was a significant difference in the distribution of the IPI risk groups between the CHCAMS and SEER groups ($P < 0.001$). In addition to immunochemotherapy, some patients also received local radiotherapy or surgical resection. Compared with the SEER group, the CHCAMS group included a significantly high number of patients who received local radiotherapy (42.44% *vs.* 23.55%, $P < 0.001$) but a significantly low number of patients who underwent surgery (7.84% *vs.* 24.17%, $P < 0.001$). Furthermore, in the CHCAMS group, 58.7% (387/659) had stage I–II disease, and 17.1% (73/428) of patients with stage III–IV disease received radiotherapy. The corresponding percentages for the SEER group were 39.1% (531/1357) and 14.0% (282/2008). The baseline characteristics of patients are listed in Table 1.

Treatment and its efficacy among patients from the CHCAMS

All 1084 patients treated at the CHCAMS received R–CHOP or R-CHOP–like regimens as first-line treatment. Among them, 542, 457, and 85 received first-line immunochemotherapy alone, local radiotherapy after or during first-line immunochemotherapy, and palliative or radical surgical resection combined with immunochemotherapy and/or radiotherapy, respectively. Furthermore, 17 (1.6%), 6 (0.6%), 602 (55.5%), 341 (31.5%), 13 (1.2%), and 105 (9.7%) patients had no measurable lesions because of surgical resection, had unknown treatment efficacy, achieved CR or CRu, achieved PR, had SD, and had PD, respectively.

Survival outcomes

The median follow-up time for the CHCAMS group was 87.3 months (range: 0.5–195.4) as of April 18, 2022. Among the 1084 patients, 430 experienced disease progression or relapse, and 331 died. The median follow-up time for the SEER group was 86.0 months (range: 1.0–179.0), and 1523 patients died. For the CHCAMS group, the median PFS was not reached (95% confidence interval [CI]: 138 months to not reached), and the 5-year PFS rate was 61.7% (95% CI: 58.8–64.7%). The median OS was not reached in these patients (95% CI: 143 months to not), and the 5-year OS rate was 70.6% (95% CI: 67.8–73.4%). For the SEER group, the median OS was 153 months (95% CI: 143 months to not reached), and the 5-year OS

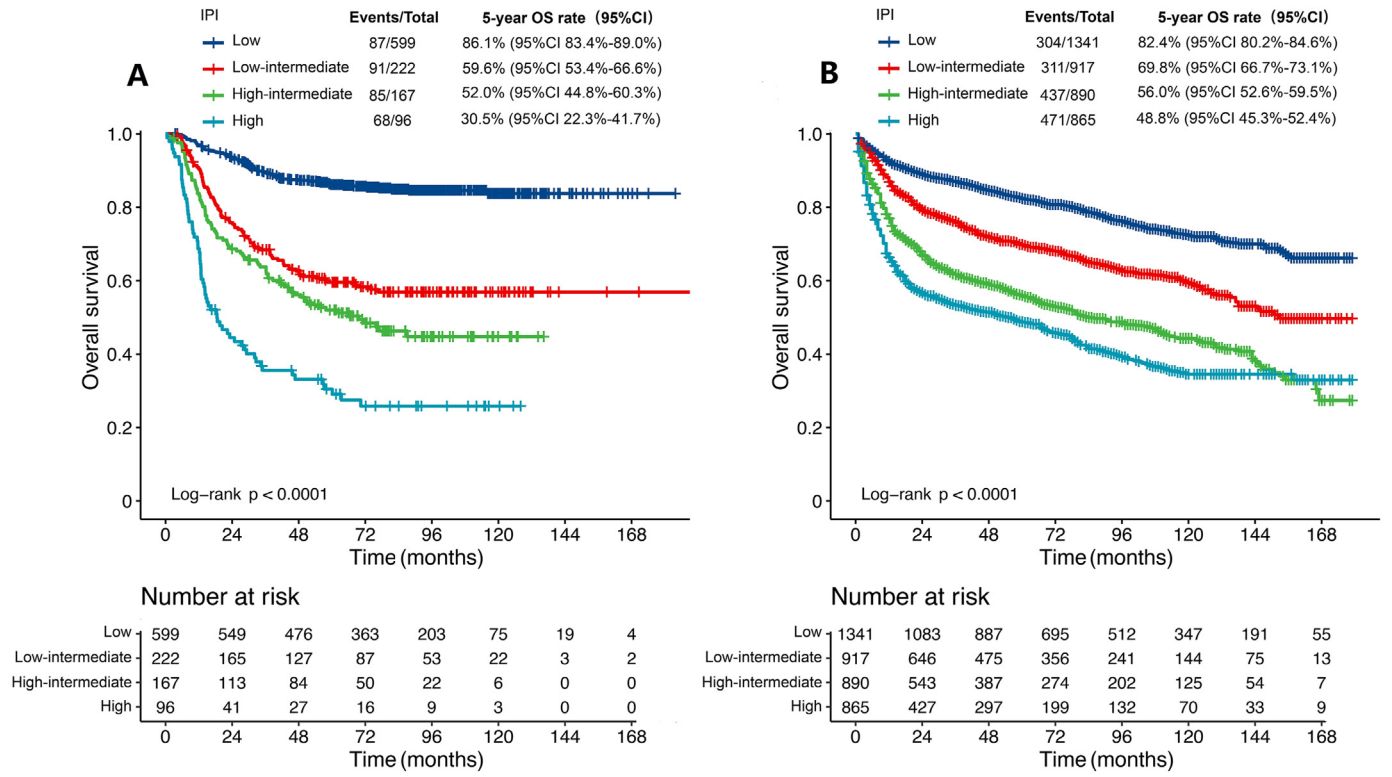

Figure 3. Kaplan–Meier curves of OS stratified by the IPI risk group. (A) OS of patients in the CHCAMS group; (B) OS of patients in the SEER group. CHCAMS: Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College; IPI: International Prognostic Index; OS: Overall survival; SEER: Surveillance, Epidemiology, and End Results.

rate was 66.5% (95% CI: 65.0–68.0%). The CHCAMS group had significantly better 5-year OS rate than the SEER group ($P < 0.001$) [Figure 2A]. Because the distribution of age, disease stage, IPI risk group, primary site, surgery, and radiotherapy significantly differed between the CHCAMS and SEER groups, adjusted survival between the two groups was compared using the IPI score, primary site, surgery, and radiotherapy as covariates. After adjusting for these covariates, no significant difference in 5-year OS rate was observed between the two groups ($P = 0.867$) [Figure 2B].

According to the IPI risk categorization, the 5-year PFS rates for the low-, low-intermediate–, high-intermediate–, and high-risk groups among the patients from the CHCAMS were 78.3% (95% CI: 75.1–81.7%), 51.8% (95% CI: 45.5–58.8%), 36.3% (95% CI: 29.6–44.5%), and 23.9% (16.5–34.7%), respectively ($P < 0.001$). The corresponding 5-year OS rates were 86.1% (95% CI: 83.4–89.0%), 59.6% (95% CI: 53.4–66.6%), 52.0% (95% CI: 44.8–60.3%), and 30.5% (95% CI: 22.3–41.7%)($P < 0.001$) [Figure 3A]. The 5-year OS rates for the low-, low-intermediate–, high-intermediate–, and high-risk groups among the patients from the SEER database were 82.4% (95%CI: 80.2–84.6%), 69.8% (95%CI: 66.7–73.1%), 56.0% (95%CI: 52.6–59.5%), and 48.8% (95%CI: 45.3–52.4%), respectively ($P < 0.001$) [Figure 3B]. We compared the 5-year OS rate of the CHCAMS and SEER groups in each IPI risk group. In the IPI low-risk group, 5-year OS rate was significantly superior for patients from the CHCAMS than for those from the SEER database ($P < 0.001$) [Figure 4A]. However, in the IPI high-risk group, the CHCAMS group had significantly inferior OS than the SEER group ($P = 0.015$) [Figure 4D]. There was no significant difference in OS between the two groups of patients in the IPI low-intermediate– and high-intermediate–risk groups ($P = 0.11$ and $P = 0.83$, respectively) [Figure 4B and 4C]. In the CHCAMS group, there was no significant difference in PFS ($P = 0.520$) and OS ($P = 0.830$) between patients diagnosed during 2005–2011 and those diagnosed during 2012–2018. In the SEER group, OS significantly improved for patients diagnosed during 2012–2017 compared with those diagnosed during 2004–2011 (5-year OS rate: 72.7% *vs.* 62.2%, $P < 0.001$).

Prognostic factors for the CHCAMS group

Univariate analysis of the CHCAMS group demonstrated that age (<60 years *vs.* ≥60 years), the ECOG PS score (0-1 *vs.* ≥2) cell-of-origin

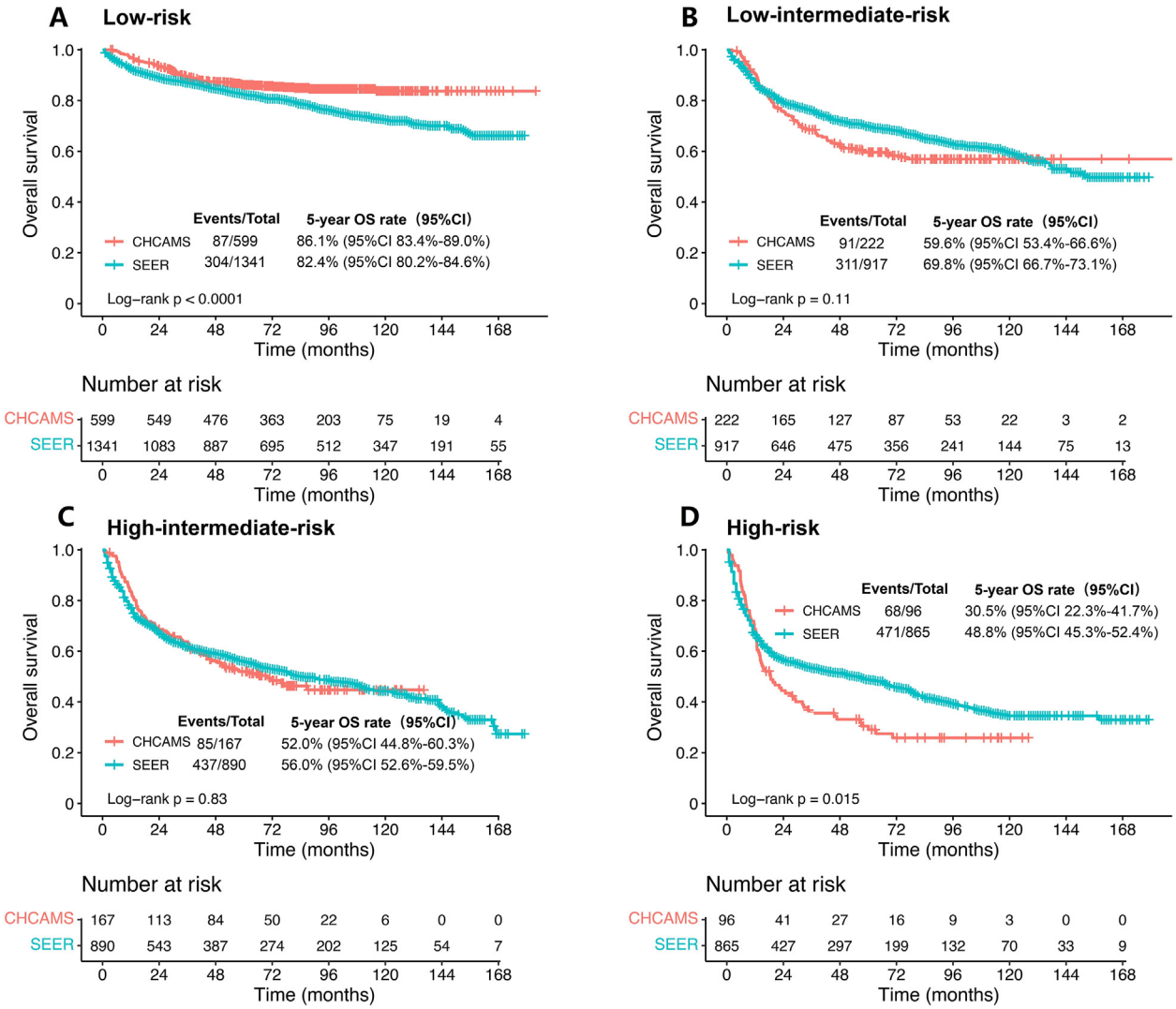

Figure 4. Comparison of overall survival in each IPI risk group between patients from the CHCAMS and the SEER database. (A) IPI low-risk group; (B) IPI low-intermediate-risk group; (C) IPI high-intermediate–risk group; (D) IPI high-risk group. CHCAMS: Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College; IPI: International Prognostic Index; SEER: Surveillance, Epidemiology, and End Results.

subtype, B symptoms, The Ann Arbor stage (I-II *vs.* III-IV), the IPI score, LDH, and β2M levels, bulky disease, number of extranodal sites (<2 *vs.* ≥2), and bone marrow involvement were prognostic factors for PFS and OS (all $P < 0.05$). Meanwhile, the primary site difference (nodal *vs.* extranodal) was associated with OS ($P = 0.033$) but not PFS ($P = 0.150$). Regarding treatment-related variables, patients who received local radiotherapy had superior 5-year PFS rate (76.2% [95% CI: 72.4–80.2%] vs. 50.8% [95% CI: 46.9–54.9%], $P < 0.001$) and 5-year OS rate (82.9% [95% CI: 79.5–86.5%] vs. 61.2% [95% CI: 57.3–65.2%], $P < 0.001$) than those who did not [Figure 5]. However, surgical resection was not associated with PFS ($P = 0.200$) or OS ($P = 0.390$) [Table 2].

The prognostic factors ($P < 0.05$) in the univariate analysis were included in the multivariate analysis. The IPI as a whole was not included in the multivariate analysis because it comprised five clinical variables (age, ECOG PS, Ann Arbor stage, LDH levels, and the number of extranodal sites involved), although it was significantly prognostic in the univariate analysis. Results of the multivariate analysis confirmed that an ECOG PS score of ≥2, presence of B symptoms, Ann Arbor stage III–IV, elevated β2M levels, and presence of bulky disease were independent adverse prognostic factors for PFS (for all, $P < 0.05$). Age >60 years, an ECOG PS score ≥2, presence of B symptoms, Ann Arbor stage III-IV, elevated LDH and β2M levels, presence of bulky disease, and extranodal involvement of two or more sites were independent advrse prognostic factors for OS (for all, $P < 0.05$). Furthermore, local radiotherapy was significantly associated with better PFS ($P < 0.001$) and OS ($P = 0.001$) [Table 3].

Discussion

The addition of rituximab to the CHOP regimen has been proven to significantly improve the survival outcomes of DLBCL patients in multiple prospective randomized controlled clinical trials[7–12] and population-based studies.[20,21] A previous study indicated that DLBCL patients receiving standard immunochemotherapy and having an event-free survival status at 24 months from diagnosis exhibited subsequent OS equivalent to that in the age- and sex-matched general population.[14] In this study, we retrospectively included 1084 patients who received R–CHOP and R-CHOP–like regimens between January 1, 2005, and December 31, 2018, at the CHCAMS and compared their clinical characteristics and survival with those in the SEER database during the same period for the first time, thereby providing useful information about Chinese DLBCL patients.

The median age at diagnosis of DLBCL patients in Western countries has been reported to be 60 years, with 30% of patients being older than 75 years.[22] The median age of Chinese patients at diagnosis was lower than that reported in Western countries. A study from Southwest China showed that the median age of DLBCL patients was 55 years.[4] In this study, the median ages at diagnosis were 54 and 63 years for the CHCAMS and SEER groups, respectively, which further confirmed that Chinese DLBCL patients were younger than their American counterparts. The proportions of patients with Ann Arbor stage III-IV disease and classified as being at IPI high-intermediate or high risk were significantly lower in the CHCAMS group than those in the SEER group. The distribution of Ann Arbor stage and IPI risk groups in our study is consistent with the results of another study from Guangdong, China.[23] Regarding treatment, a significantly higher proportion of patients received local radiotherapy in the CHCAMS group than that in the SEER group. This might be attributed to the higher proportion of patients with Ann Arbor stage I–II disease in the CHCAMS group who were more likely to receive local radiotherapy after first-line immunochemotherapy. In contrast, the proportion of patients receiving surgical treatment in the CHCAMS group was significantly lower than that in the SEER group, which might partly reflect the difference in treatment choice between Chinese and American patients. However, the reason for this difference remains unclear and needs to be investigated further.

The LNH98-5 trial conducted by the Groupe d' Etude des Lymphomes de l' Adulte showed that the CR or CRu rate was 75%, and the PD rate was 9% in elderly DLBCL patients (60–80 years old) treated with R–CHOP.[7] The results of the MabThera International Trial (MInT) showed that young patients (aged 18–60 years) receiving a first-line R-CHOP–like regimen achieved a CR or CRu rate of 86% and a PD rate of 4%.[11] In this study, patients from the CHCAMS receiving first-line standard R–CHOP or R-CHOP–like regimens showed a lower CR or CRu rate (55.5%) but a similar PD rate (9.7%). The difference in the CR or CRu rate may be partly explained by the heterogeneity of the included patients. For example, all patients enrolled in the MInT had no risk factors or only one risk factor, according to the age-adjusted IPI.[11] Nevertheless, the 5-year OS and PFS rates for the CHCAMS group were 70.6% and 61.7%, respectively, which were comparable to the survival data reported in previous clinical trials.[8,9,12,24]

There were significant differences in the distribution of age, B symptoms, primary site, the Ann Arbor stage, the IPI score, radiotherapy, and surgery between the CHCAMS and SEER groups, which indicated high heterogeneity in the clinical characteristics between the groups. As these

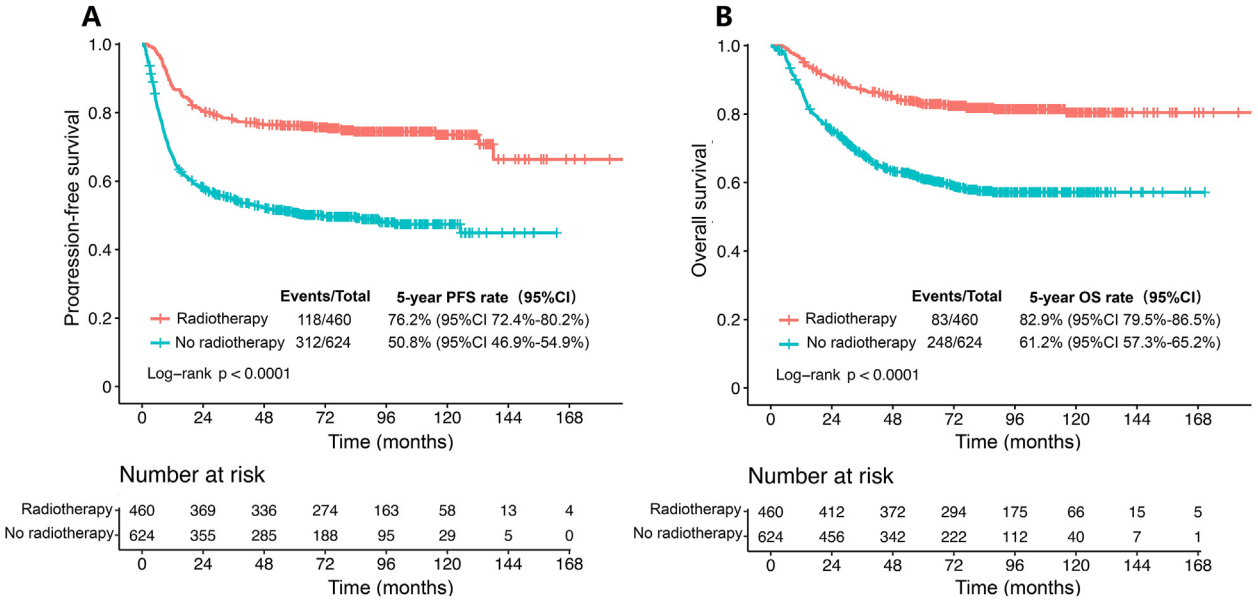

Figure 5. Kaplan–Meier curves of survival stratified by radiotherapy for the CHCAMS group. (A) Progression-free survival; (B) Overall survival.CHCAMS: Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College

variables are well-known prognostic factors for DLBCL, survival adjustments were made to mitigate the effects of these confounding factors. Interestingly, the OS of the CHCAMS group was better than that of the SEER group before adjustment. However, no significant difference was observed between the two groups after adjusting for the IPI score, primary site, radiotherapy, and surgery. It is worth noting that detailed information on chemotherapy (including chemotherapy regimens and the number of cycles) in the SEER database was not available. Therefore, it remains unclear whether all the patients from the SEER database included in this study received standard immunochemotherapy containing rituximab. A previous study based on the SEER database showed that 79% of DLBCL patients in the United States had received rituximab combined with anthracycline-based chemotherapy as the first-line therapy since 2002.[25] Considering that patients from the SEER database included in this study were diagnosed from 2005 to 2017, most of these patients may have received rituximab combined with chemotherapy regimens. Therefore, the overall results of this study were not significantly affected.

This study found that in the CHCAMS group, there was no significant difference in survival between patients diagnosed during 2005–2011 and those diagnosed during 2012–2018. However, in the SEER group, the OS of the patients diagnosed during 2012–2017 was better than those diagnosed during 2004–2011, albeit modestly. This finding was consistent with the results of a previous study.[26] Recently, a study from The Netherlands showed that the survival of patients diagnosed from 2003 to 2010 was better than patients diagnosed from 1989 to 2002 but worse than that of patients diagnosed from 2011 to 2018.[20] The authors believe that the improvement in survival over time might be attributable to the following reasons. First, progress has been made in reducing the radiation field in recent years, reducing the dose intensity of the R–CHOP regimen, and optimizing supportive care (including growth factor support and infection prevention and treatment), which makes the treatment safer. Second, significant advances have been made in the treatment of patients with relapsed or refractory disease.[20] However, in this study, treatment data for patients with relapsed or refractory disease were unavailable, which impedes the assessment of salvage treatment patterns over time. In addition, some clinical information, such as age and clinical stage, was not adjusted for when comparing the survival of patients in different years. Therefore, caution must be exercised when interpreting the results.

In the era of rituximab, the role of radiotherapy in DLBCL has been explored in several single-center series, large database analyses, and subgroups of prospective clinical trials. Most studies have demonstrated that the addition of radiotherapy could benefit select patients.[27] Based on these findings, therapeutic strategies, including a three-cycle R–CHOP regimen followed by involved site radiotherapy and 4–6 cycles of R-CHOP-14 regimen with or without involved site radiotherapy, are recommended by the National Comprehensive Cancer Network guidelines[28] and the Chinese lymphoma guidelines[29,30] as the standard frontline therapy for Ann Arbor stage I-II patients without the bulky disease

Table 2
Univariate analysis of PFS and OS in the CHCAMS group.

Variables	5-year PFS rate % (95% CI)	*P*	5-year OS rate % (95% CI)	*P*
Age (years)				
<60	65.4 (61.9–69.0)	<0.001	74.8 (71.7–78.1)	<0.001
≥60	54.5 (49.6–59.8)		62.4 (57.5–67.6)	
Sex				
Male	63.0 (58.8–67.4)	0.450	71.9 (67.9–76.1)	0.240
Female	60.6 (56.8–64.7)		69.4 (65.8–73.3)	
ECOG PS score				
0–1	64.9 (62.0–68.0)	<0.001	74.3 (71.5–77.1)	<0.001
≥2	34.4 (26.7–44.4)		39.7 (31.7–49.9)	
Cell of origin type				
GCB	66.4 (61.4–71.7)	0.009	75.2 (70.7–80.1)	0.025
Non-GCB	57.7 (54.0–61.7)		67.1 (63.5–70.9)	
Unknown	72.5 (64.1–82.1)		77.7 (69.8–86.6)	
B symptoms				
Yes	41.7 (35.5–48.9)	<0.001	52.8 (46.5–60.1)	<0.001
No	66.6 (63.5–69.9)		74.9 (72.0–77.9)	
Primary site				
Nodal	63.3 (59.7–67.2)	0.150	73.2 (69.8–76.8)	0.033
Extranodal	59.3 (54.8–64.1)		66.7 (62.3–71.3)	
Ann Arbor stage				
I–II	77.4 (74.2–80.7)	<0.001	83.0 (80.2–86.0)	<0.001
III–IV	37.3 (32.9–42.2)		51.0 (46.3–56.1)	
IPI risk group				
Low	78.3 (75.1–81.7)	<0.001	86.1 (83.4–89.0)	<0.001
Low-intermediate	51.8 (45.5–58.8)		59.6 (53.4–66.6)	
High-intermediate	36.3 (29.6–44.5)		52.0 (44.8–60.3)	
High	23.9 (16.5–34.7)		30.5 (22.3–41.7)	
Lactate dehydrogenase levels				
Normal	72.0 (68.4–75.7)	<0.001	80.4 (77.2–83.8)	<0.001
Elevated	49.0 (44.8–53.7)		58.4 (54.1–63.0)	
β2M levels				
Normal	72.8 (69.5–76.3)	<0.001	80.3 (77.3–83.4)	<0.001
Elevated	43.7 (38.9–49.1)		53.8 (48.8–59.2)	
Unknown	43.9 (30.6–62.9)		63.6 (50.0–80.9)	
Bulky disease				
Yes	41.9 (34.9–50.4)	<0.001	52.3 (45.0–60.8)	<0.001
No	65.1 (62.1–68.3)		73.7 (70.9–76.7)	
Extranodal involvement sites				
<2	68.9 (65.7–72.1)	<0.001	77.2 (74.3–80.2)	<0.001
≥2	38.9 (33.3–45.4)		49.5 (43.7–56.1)	
Bone marrow involvement				
Yes	39.0 (28.3–53.7)	<0.001	47.2 (35.7–62.3)	<0.001
No	62.5 (59.6–65.6)		71.6 (68.8–74.5)	
Radiotherapy				
Yes	76.2 (72.4–80.2)	<0.001	82.9 (79.5–86.5)	<0.001
No	50.8 (46.9–54.9)		61.2 (57.3–65.2)	
Surgery				
Yes	66.7 (57.0–78.0)	0.200	74.1 (64.8–84.7)	0.390
No	61.2 (58.3–64.3)		70.2 (67.4–73.2)	

CHCAMS: Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College; ECOG: Eastern Cooperative Oncology Group; GCB: Germinal center B-cell; IPI: International Prognostic Index; Non-GCB: Non-germinal center B-cell; PFS: Progression-free survival; OS: Overall survival; PS: Performance status; β2M: β2-microglobulin.

Table 3
Multivariate analysis of PFS and OS in the CHCAMS group.

Variables	PFS		OS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Age >60 years	1.07 (0.87–1.31)	0.512	1.3 (1.03–1.64)	0.026
ECOG PS score of ≥2	1.72 (1.33–2.22)	<0.001	1.96 (1.49–2.59)	<0.001
Non-GCB cell-of-origin type	1.18 (0.95–1.47)	0.1416	1.16 (0.9–1.5)	0.238
Presence of B symptoms	1.56 (1.26–1.94)	<0.001	1.56 (1.22–2)	<0.001
Primary site	NA		0.86 (0.68–1.08)	0.191
Ann Arbor stage III–IV	2.11 (1.65–2.70)	<0.001	1.85 (1.39–2.46)	<0.001
Elevated LDH levels	1.22 (0.99–1.52)	0.065	1.45 (1.36–1.85)	0.003
Elevated β2M levels	1.52 (1.22–1.89)	<0.001	1.49 (1.15–1.92)	0.002
Bulky disease	1.59 (1.24–2.03)	<0.001	1.60 (1.22–2.10)	<0.001
Extranodal involvement ≥2 sites	1.23 (0.98–1.55)	0.074	1.39 (1.08–1.80)	0.012
Bone marrow involvement	1.41 (0.99–2.02)	0.056	1.02 (0.69–1.51)	0.928
No local radiotherapy	1.60 (1.27–2.03)	<0.001	1.59 (1.20–2.10)	0.001

CHCAMS: Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College; CI: Confidence interval; ECOG: Eastern Cooperative Oncology Group; PS: Performance status; GCB: Germinal center B-cell; HR: Hazard ratio; LDH: Lactate dehydrogenase; Non-GCB: Non-germinal center B-cell; OS: Overall survival; PFS: Progression-free survival; β2M: β2-microglobulin.

(<7.5 cm). Ann Arbor stage I-II patients with bulky disease (≥7.5 cm) can receive six cycles of the R–CHOP regimen with or without involved site radiotherapy. For some patients with Ann Arbor stage III-IV disease, local consolidative radiotherapy can also reduce the local recurrence rate, improve PFS, and prolong OS.[31,32] The results of this study also showed a significant improvement in survival with the addition of local radiotherapy during or after first-line R-CHOP or R-CHOP-like immunochemotherapy. In addition, radiotherapy remained an independent favorable factor for PFS and OS after controlling for confounders in the multivariable analysis. The use of radiotherapy in clinical practice may be determined based on various factors, such as the physical condition of the patients (e.g., age, ECOG PS score, and underlying co-morbidities), disease status (e.g., presence or absence of bulky disease and local or extensive involvement), and patient preferences. In addition, multidisciplinary team involvement facilitates the selection of candidates for radiotherapy.[33]

Regarding prognostic markers of DLBCL, a variety of indicators can provide prognostic information.[34] The results of this study further confirm the prognostic value of several clinical indicators. Despite its retrospective and single-center nature, this study provides useful information on Chinese DLBCL patients in the rituximab era, owing to the large sample size, use of a uniform first-line regimen, and long follow-up time. With the rapid development of clinical trials of new drugs for lymphoma in recent years,[35–39] more Chinese DLBCL patients will benefit from significantly improved agent accessibility. More research is needed in the future to improve the survival of DLBCL patients in the era of new drugs.

This study had several limitations. The SEER database only provides data on whether chemotherapy or radiotherapy was performed. Detailed information on chemotherapy or radiotherapy, including specific chemotherapy regimens, number of cycles used, and radiotherapy dosage, is unavailable. As stated previously, we only included patients registered after 2004; hence, most patients might have received rituximab therapy. The lack of detailed information on radiotherapy limited our ability to evaluate the effect of radiotherapy dosage on survival. However, the adjusted survival of patients between the CHCAMS and SEER groups was compared using radiotherapy as a covariate. Despite these limitations, this study represents a rare attempt to compare the clinical characteristics and survival of Chinese DLBCL patients with those in the SEER database.

In conclusion, after adjusting for clinical and treatment-related factors, there was no significant difference in 5-year OS rate between Chinese DLBCL patients and those from the SEER database in the rituximab era. In the CHCAMS group, the ECOG PS score, B symptoms, Ann Arbor stage, serum β2M levels, bulky disease and local radiotherapy were independent prognostic factors for both PFS and OS. Age, serum LDH levels, and extranodal involvement were also independent prognostic factors for OS.

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Authors contribution

Yuankai Shi: Conceptualization, Methodology, Manuscript Writing-Revising and Editing; Haizhu Chen: Data analysis and visualization, Manuscript writing, revising, and editing; Yuankai Shi, Yan Qin, Jianliang Yang, Peng Liu, Xiaohui He, Shengyu Zhou, Liqiang Zhou, Changgong Zhang, Yongwen Song, Yueping Liu, Lin Gui, Shulian Wang, Jing Jin, Hui Fang, Shunan Qi, Ning Li, Yu Tang, Xin Wang and Sheng Yang: Data curation.

Ethics statement

This study was conducted per the *Declaration of Helsinki* and approved by the Institutional Review Board of the National Cancer Center/National Clinical Research Center for Cancer/CHCAMS & Peking Union Medical College (approval number: NCC2018JJJ-004).

Data availability statement

The datasets used in the current study are available from the corresponding author on reasonable request.

Conflict of interest

None.

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