A retrospective analysis of real-world outcomes of elderly Chinese patients with diffuse large B-cell lymphoma

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Abstract

Background: Elderly patients with diffuse large B-cell lymphoma (DLBCL) have a worse prognosis than younger patients, and the optimal treatment strategy for this group remains controversial. We conducted a retrospective analysis to investigate the clinical features and outcomes of elderly patients (>60 years) and to assess the impact of clinical and molecular factors on outcome in this age group.

Methods: From April 2006 to December 2012, a total of 349 elderly patients with DLBCL from the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, and Peking Union Medical College were included in this analysis. Patients were further divided into two age groups (61–69 years and ≥70 years). We compared clinical characteristics and outcomes between groups.

Results: Of 349 total patients, 204 (58.5%) were aged 61 to 69 years, and 145 (41.5%) patients were aged 70 years or older. Except for the Eastern Cooperative Oncology Group performance status, clinical characteristics were comparable between the two groups. With a median follow-up of 82 (range, 1–129) months, the 5-year overall survival (OS) and progression-free survival (PFS) rates were 51.9% and 45.8%, respectively. The 5-year OS rates for patients aged 61 to 69 years and those over 70 years were 58.3% and 42.8% ($P = 0.007$), respectively, and the 5-year PFS rates were 51.0% and 38.6% ($P = 0.034$). Treatment regimens including rituximab provided a higher 5-year OS rate (63.1% *vs.* 37.1%, $P < 0.001$) and PFS rate (56.6% *vs.* 31.8%, $P < 0.001$) than chemotherapy alone. For patients aged 61 to 69 years, chemotherapy plus rituximab resulted in a higher 5-year OS rate (66.7% *vs.* 46.4%, $P = 0.002$) and PFS rate (60.0% *vs.* 38.1%, $P = 0.002$) than chemotherapy alone. For patients aged ≥70 years, there was a marked survival advantage in patients who received chemotherapy plus rituximab (5-year OS rate: 57.7% *vs.* 25.4%, $P < 0.001$; 5-year PFS rate: 51.3% *vs.* 23.9%, $P < 0.001$) compared with that seen in those who received chemotherapy alone. Multivariate analysis established that stage III/IV disease, elevated lactate dehydrogenase (LDH), initial treatment, and chemotherapy with rituximab were independent risk factors for 5-year OS, and stage III/IV disease, elevated LDH, and chemotherapy with rituximab were independent risk factors for 5-year PFS for elderly patients with DLBCL.

Conclusions: In comparison to patients aged 61 to 69 years, those aged ≥70 years have poorer survival. Prolonged survival is obtainable with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP)-like in elderly Chinese patients in all age groups, indicating that the R-CHOP-like regimen should be considered for this population, even for those aged 70 years or older.

Keywords: Elderly; Diffuse large B-cell lymphoma; Rituximab; Prognosis

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive lymphoma, and the incidence increases with age.[1-3] Approximately two-thirds of DLBCL cases occur in patients older than 65 years, with a median age of diagnosis between 70 and 75 years.[4] Elderly patients with DLBCL have a worse prognosis, which may be explained by poorer tolerance to full-dose therapies and the presence of comorbidities.[5,6] Therefore, older age (age >60 years) has been recognized as an adverse prognostic factor in the international prognostic index (IPI) for predicting survival in patients with DLBCL, leaving a therapeutic challenge for the elderly population.[7] The event-free survival (EFS) was reported to be only 12 to 18 months in previous randomized studies evaluating chemotherapy among elderly patients with DLBCL.[8-10]

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The introduction of rituximab-based immunochemotherapy into the treatment of DLBCL has significantly improved survival, with the 5-year DLBCL-specific survival rate rising from 37% in 1975 to 66% in 2005.[11] Elderly patients have always been underrepresented in prospective clinical studies; however, several studies have investigated the application of rituximab-based immunochemotherapy in elderly DLBCL, showing favorable survival benefits with reported 5-year overall survival (OS) rates of 50% to 80%.[12,13] Moreover, patients older than 80 years can also benefit from rituximab plus reduced-dose cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), except for those who have severe organ failure secondary to other diseases.[14] So far, a limited number of studies have described clinical patterns and outcomes in Chinese patients with DLBCL. Here, we reported the clinical features and outcomes of patients with DLBCL from a retrospective analysis that was restricted to patients >60 years and investigated the impact of clinical and molecular factors on outcome in this age group.

Methods

Ethical approval

This study was approved by the Ethics Committee of Cancer Hospital, Chinese Academy of Medical Sciences, and Peking Union Medical College (No. 19-018/1803). Written consent was not needed because only non-identifiable information was used.

Patients and data collection

A retrospective review of the clinical characteristics and outcomes of patients who were aged over 60 years and diagnosed with DLBCL (according to the World Health Organization classification of tumors of hematopoietic and lymphoid tissue[15]) between June 2006 and December 2012 at the National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences, and Peking Union Medical College was conducted. During the study period, 1742 patients were screened. Of these, 736 patients were younger than 60 years old, 562 did not have available data on treatment or outcome, and 95 were lost to follow-up, leaving 349 eligible patients.

Evaluation and treatment

All patients underwent diagnostic procedures, molecular evaluations, and treatment according to the local practice and national guidelines. Pre-treatment evaluations included patient demographics, physical examination, Eastern Cooperative Oncology Group (ECOG) performance status (PS), complete blood count, blood chemistry, computed tomography scans of the neck, chest, abdomen, and pelvis or positron emission tomography scans of the whole body, and bone marrow biopsy. The staging was determined according to the Ann Arbor staging system. Patients were classified into germinal center B-cell-like (GCB) and non-GCB types based on the Hans algorithm.[16] IPI scores were also calculated.[7]

The standard regimens included 3 to 4 cycles (for early-stage disease) or six cycles (for advanced disease) of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone-like treatment courses (R-CHOP) followed by two cycles of rituximab for suitable patients, R-miniCHOP for unsuitable patients, and R-CE (etoposide) OP for frail elderly patients.

Definition of endpoint

The co-primary endpoints of this study were OS and progression-free survival (PFS). OS was defined as the interval between the date of initial treatment and the date of death of any cause or the date of the last follow-up. PFS was defined as the interval from the date of first treatment to the date of disease progression, recurrence, or death due to any cause.

Statistical analysis

Differences in clinicopathological characteristics between groups were assessed by Student's t test and Chi-square test. Survival curves were estimated using the Kaplan-Meier method and compared with the log-rank test between the two age groups. Unless otherwise stated, $P < 0.05$ was considered statistically significant. IBM SPSS Statistics (Version 21.0; IBM Corp., Armonk, NY, USA) was used for data analysis.

Results

Patient characteristics

Table 1 lists the baseline demographics and clinical characteristics of elderly patients with DLBCL. The median age of patients was 68 (range, 61–92) years. Elderly DLBCL was most frequently diagnosed among patients 61 to 64 years of age [Figure 1]. There were more men than women in this cohort, with a male/female ratio of 1.14. Patients were grouped by age, with a cut-off of 70 years in this study: 204 (58.5%) patients were aged 61 to 69 years, and 145 (41.5%) patients were aged 70 years or older. More patients aged over 70 years had an ECOG PS ≥2 ($P < 0.001$), while other clinical features were comparable between the groups.

Treatment

Overall, most patients ($n = 209$, 59.9%) received initial treatment with chemotherapy alone, followed by chemoradiotherapy ($n = 114$, 32.7%), surgery plus chemoradiotherapy ($n = 15$, 4.3%), and other treatments or no treatment for DLBCL ($n = 11$, 3.2%). More patients aged 61 to 69 years ($n = 74$, 36.3%) received initial chemotherapy with radiotherapy than those aged over 70 years ($n = 40$, 27.6%); however, the difference was not statistically significant ($P = 0.278$). The addition of rituximab occurred in 199 patients (57.0%). In total, 121 (59.3%) patients aged 61 to 69 years and 78 (53.8%) patients aged older than 70 years received chemotherapy plus rituximab; this difference was not significant ($P = 0.349$).

Table 1: Baseline characteristics for 349 elderly patients with DLBCL.

Parameters	All patients ($n = 349$)	61–69 years ($n = 204$)	≥70 years ($n = 145$)	χ^2	*P*
Age (years)	–	64.5 ± 2.9	74.5 ± 4.3	–	–
Gender				0.025	0.875
Male	186 (53.3)	108 (52.9)	78 (53.8)		
Female	163 (46.7)	96 (47.1)	67 (46.2)		
Number of extra-nodal sites				0.065	0.799
0 or 1	260 (74.5)	153 (75.0)	107 (73.8)		
≥2	89 (25.5)	51 (25.0)	38 (26.2)		
Ann Arbor stage				0.012	0.912
I or II	213 (61.0)	125 (61.3)	88 (60.7)		
III or IV	136 (39.0)	79 (38.7)	57 (39.3)		
B symptoms				0.002	0.961
Presence	63 (18.1)	37 (18.1)	26 (17.9)		
Absence	286 (81.9)	167 (81.9)	119 (82.1)		
Bone marrow involvement				2.194	0.139
Presence	31 (8.9)	22 (10.8)	9 (6.2)		
Absence	318 (91.1)	182 (89.2)	136 (93.8)		
Bulky disease				2.895	0.089
Presence	21 (6.0)	16 (7.8)	5 (3.4)		
Absence	328 (94.0)	188 (92.2)	140 (96.6)		
ECOG performance status				12.339	<0.001
0 or 1	245 (70.2)	158 (77.5)	87 (60.0)		
≥2	104 (29.8)	46 (22.5)	58 (40.0)		
Pathological classification				0.170	0.918
GCB	97 (27.8)	58 (28.4)	39 (26.9)		
Non-GCB	244 (69.9)	141 (69.1)	103 (71.0)		
Other	8 (2.3)	5 (2.5)	3 (2.1)		
Ki-67 index (%)				2.644	0.267
≤90	279 (79.9)	162 (79.4)	117 (80.7)		
>90	59 (16.9)	33 (16.1)	26 (17.9)		
Unknown	11 (3.2)	9 (4.5)	2 (1.4)		
LDH level				0.024	0.878
Normal	174 (49.9)	101 (49.5)	73 (50.3)		
Elevated	175 (50.1)	103 (50.5)	72 (49.7)		
IPI score				5.477	0.140
0–1	109 (31.2)	72 (35.3)	37 (25.5)		
2	105 (30.1)	61 (29.9)	44 (30.3)		
3	65 (18.6)	37 (18.1)	28 (19.3)		
4–5	70 (20.1)	34 (16.7)	36 (24.9)		
Initial treatment				5.088	0.278
CT alone	209 (59.9)	115 (56.4)	94 (64.8)		
CT and RT	114 (32.7)	74 (36.3)	40 (27.6)		
S ± CT ± RT	15 (4.3)	10 (4.9)	5 (3.4)		
RT alone	1 (0.2)	0	1 (0.7)		
No therapy	10 (2.9)	5 (2.4)	5 (3.5)		
First-line therapy				0.878	0.349
CT alone	140 (40.1)	78 (38.2)	61 (42.1)		
R + CT	199 (57.0)	121 (59.3)	78 (53.8)		

Data are presented as *n* (%) or mean ± standard deviation. DLBCL: Diffuse large B-cell lymphoma; ECOG: Eastern Cooperative Oncology Group; GCB: Germinal center B-cell-like; LDH: Lactate dehydrogenase; IPI: International prognostic index; CT: Chemotherapy; RT: Radiotherapy; S: Surgery; R: Rituximab.

Clinical outcomes

With a median follow-up of 82 (range, 1–129) months, the 5-year OS and PFS values were 51.9% and 45.8%, respectively [Figure 1]. The 5-year OS rates for patients aged 61 to 69 years and aged 70 years or older were 58.3% and 42.8%, respectively ($P = 0.007$) [Figure 2A], and the 5-year PFS values were 51.0% and 38.6%, respectively ($P = 0.034$) [Figure 2B].

An exploratory analysis was conducted to evaluate the impact of rituximab on OS and PFS in elderly patients. Regimens including rituximab resulted in a higher 5-year OS rate (63.1% *vs.* 37.1%, $P < 0.001$) [Figure 3A] and

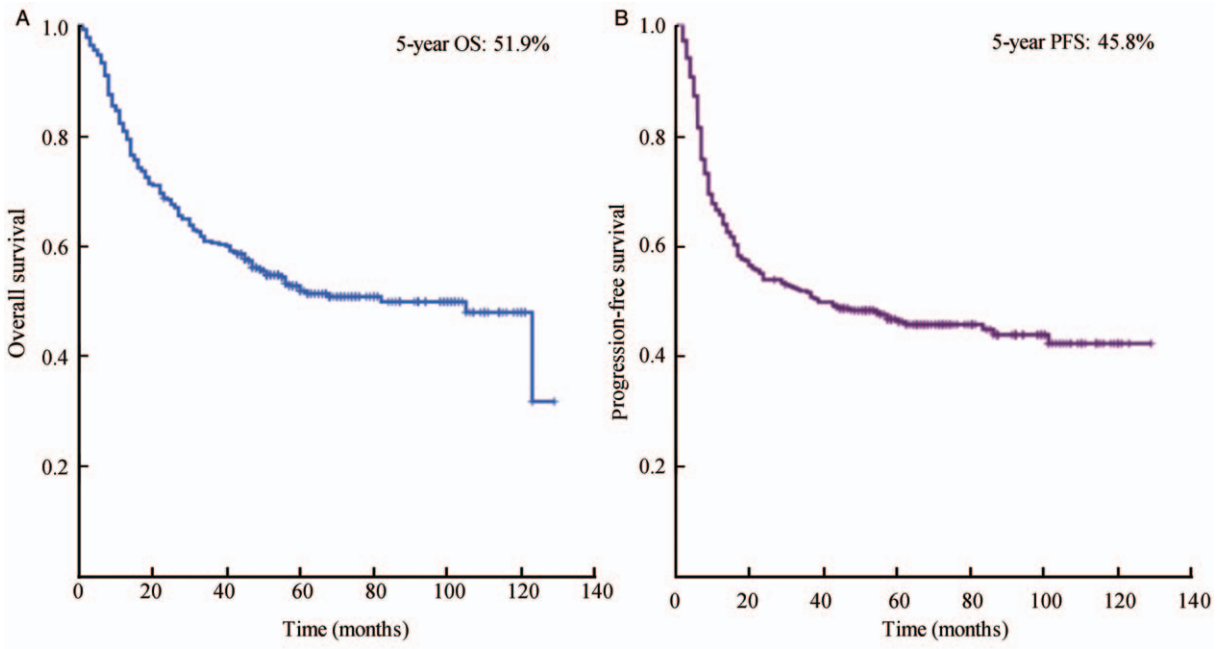

Figure 1: OS (A) and PFS (B) for elderly patients with diffuse large B-cell lymphoma. OS: Overall survival; PFS: Progression-free survival.

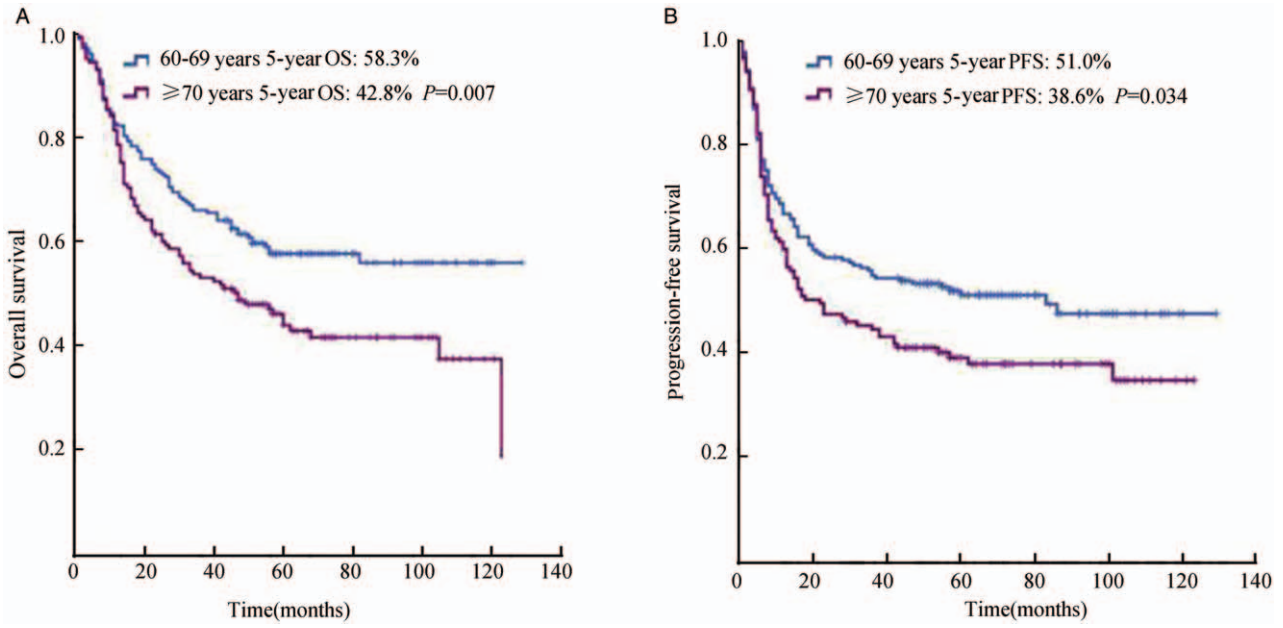

Figure 2: OS (A) and PFS (B) for elderly patients with diffuse large B-cell lymphoma according to age. OS: Overall survival; PFS: Progression-free survival.

PFS rate (56.6% *vs.* 31.8%, $P < 0.001$) [Figure 3B] than chemotherapy alone in the overall population. For patients aged 61 to 69 years, treatment with chemotherapy plus rituximab was associated with a higher 5-year OS rate (66.7% *vs.* 46.4%, $P = 0.002$) [Figure 4A] and PFS rate (60.0% *vs.* 38.1%, $P = 0.002$) [Figure 4B] than that achieved with chemotherapy alone. Similar results were also seen in patients aged ≥70 years. A marked survival advantage was found in patients who received chemotherapy plus rituximab, with a 5-year OS rate of 57.7% [Figure 5A] and a PFS rate of 51.3% [Figure 5B], compared to that seen in patients who received chemotherapy alone (25.4% [$P < 0.001$] and 23.9% [$P < 0.001$], respectively).

Univariate analysis showed that age, ECOG PS score, disease stage, the presence of B symptom, the number of extra-nodal involvement sites, Ki-67 expression, classification according to the Han algorithm, the lactate dehydrogenase (LDH) level, the initial treatment, and chemotherapy with rituximab were prognostic factors for 5-year OS and 5-year PFS. In the multivariate analysis,

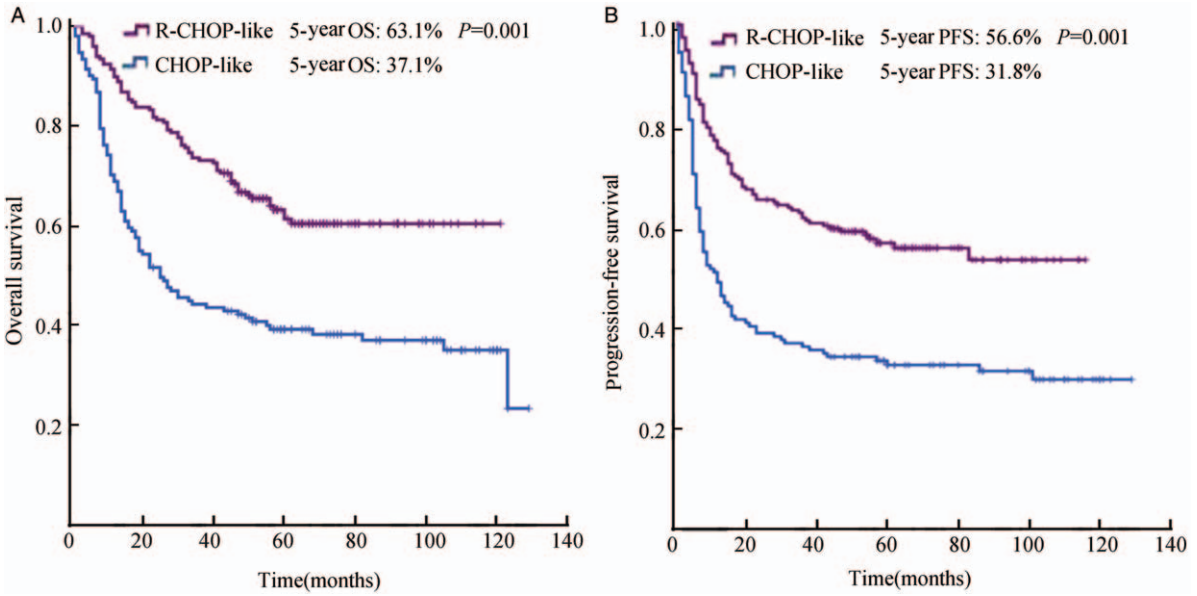

Figure 3: OS (A) and PFS (B) for elderly patients according to the treatment regimen. OS: Overall survival; PFS: Progression-free survival; R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

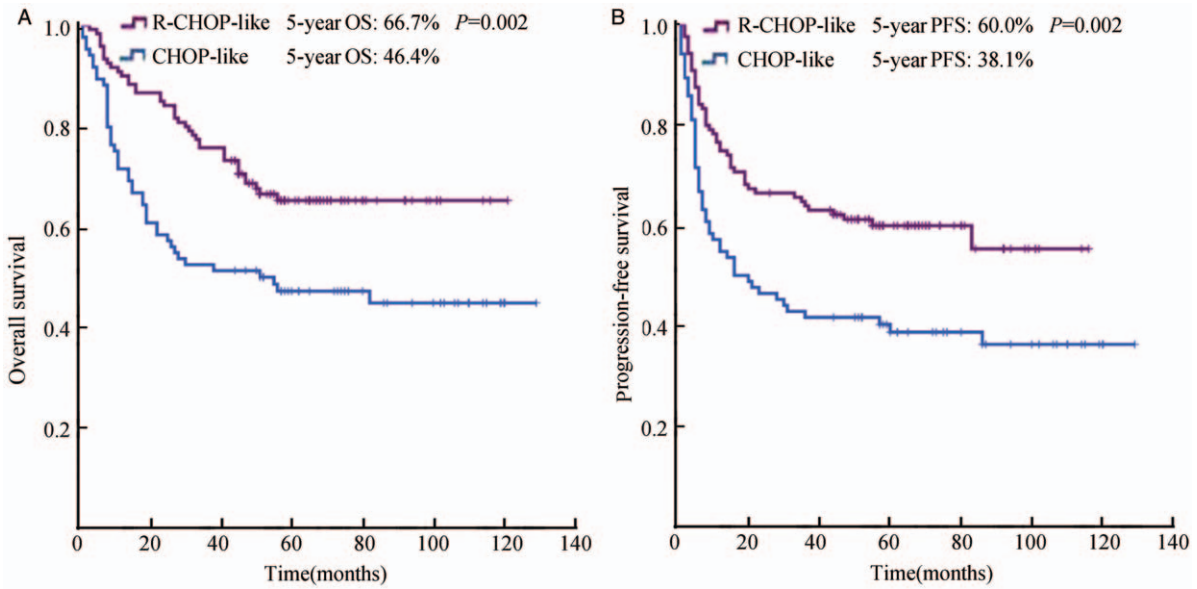

Figure 4: OS (A) and PFS (B) for 204 patients aged 61 to 69 years according to the treatment regimen. OS: Overall survival; PFS: Progression-free survival; R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

disease stage ≥III, elevated LDH, the initial treatment, and chemotherapy with rituximab were independent risk factors for 5-year OS [Table 2], while disease stage ≥III, elevated LDH, and chemotherapy with rituximab were independent risk factors for 5-year PFS [Table 3] for elderly patients with DLBCL.

Discussion

The current study investigated the patterns of patient characteristics and outcomes in Chinese patients older than 60 years with newly diagnosed DLBCL in a real-life setting. A total of 349 patients were further sub-divided into two age sub-groups. We found no difference in characteristics between patients aged 61 to 69 years and those aged ≥70 years, with the exception of the ECOG PS score. Similar treatment strategies were used in different age sub-groups. The addition of rituximab significantly improved survival compared to chemotherapy alone in elderly patients with DLBCL regardless of age. Multivariate analysis established that advanced disease stage (Ann Arbor stage III/IV), elevated LDH, the initial treatment, and chemotherapy alone were independent

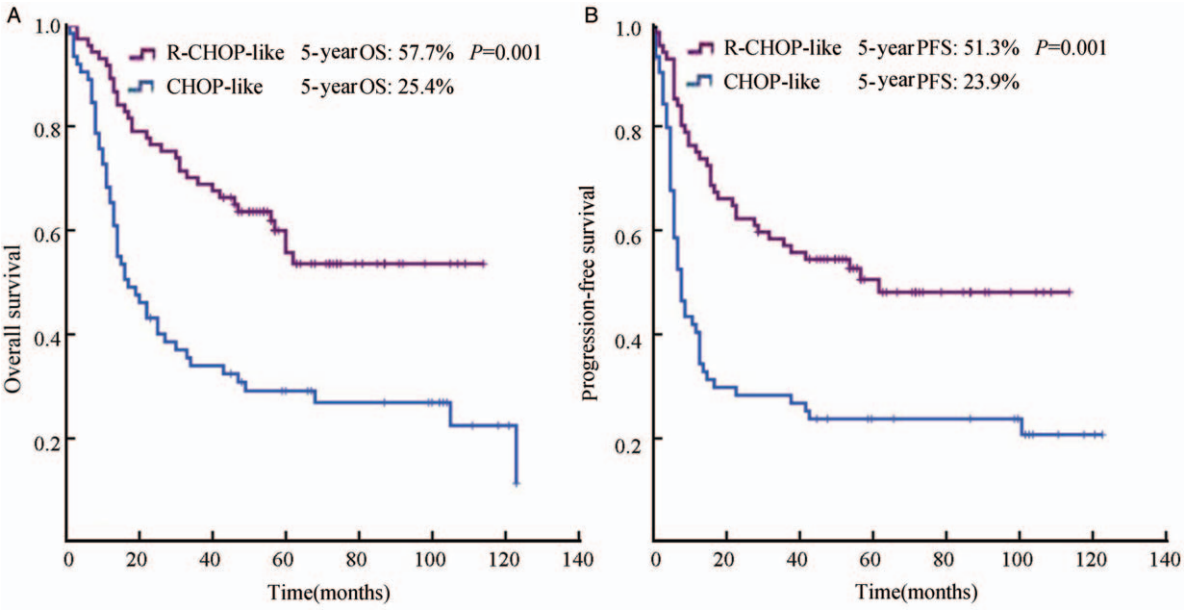

Figure 5: OS (A) and PFS (B) for 145 patients aged ≥70 years according to the treatment regimen. OS: Overall survival; PFS: Progression-free survival; R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.

Table 2: Multivariate analysis of overall survival in 349 elderly patients with DLBCL.

Parameter	β	Wald	HR	95% CI	P
Age ≥70 years	0.282	2.961	1.326	0.962–1.830	0.085
Pathological classification	0.258	2.411	1.295	0.935–1.794	0.120
Ki-67 index >90%	0.278	3.820	1.321	0.999–1.745	0.051
Number of extra-nodal sites	0.299	2.494	1.349	0.930–1.956	0.114
Ann Arbor stage III or IV	0.719	13.536	2.053	1.399–3.011	<0.001
Absence of B symptom	−0.336	2.890	0.715	0.485–1.053	0.089
Elevated LDH	0.592	12.422	1.808	1.301–2.512	<0.001
Initial treatment	0.224	7.684	1.251	1.068–1.466	0.006
Treatment with rituximab	−0.738	20.042	0.478	0.346–0.660	<0.001

DLBCL: Diffuse large B-cell lymphoma; HR: Hazard ratio; CI: Confidence interval; LDH: Lactate dehydrogenase.

Table 3: Multivariate analysis of progression-free survival in 349 elderly patients with DLBCL.

Parameter	β	Wald	HR	95% CI	P
Age ≥70 years	0.135	0.763	1.144	0.846–1.548	0.382
Pathological classification	0.141	0.787	1.151	0.843–1.573	0.375
Ki-67 index >90%	0.254	3.512	1.289	0.988–1.681	0.061
Number of extra-nodal sites	0.290	2.650	1.336	0.943–1.895	0.104
Ann Arbor stage III or IV	0.789	18.288	2.202	1.533–3.161	<0.001
Absence of B symptom	−0.289	2.415	0.749	0.520–1.078	0.120
Elevated LDH	0.340	4.760	1.405	1.035–1.908	0.029
Initial treatment	0.100	1.483	1.105	0.941–1.296	0.223
Treatment with rituximab	−0.688	20.060	0.503	0.372–0.679	<0.001

DLBCL: Diffuse large B-cell lymphoma; HR: Hazard ratio; CI: Confidence interval; LDH: Lactate dehydrogenase.

risk factors associated with poorer OS, and advanced disease stage, elevated LDH, and chemotherapy alone were independent risk factors for poorer PFS in elderly Chinese patients with DLBCL.

In this analysis of 349 patients with DLBCL who were >60 years old, patient characteristics were similar between patients aged 61 to 69 years and those aged ≥70 years; however, patients older than 70 years had a poorer ECOG PS and a trend of a higher IPI score. Only 23 (6%) patients did not receive any treatment for DLBCL, and more than half of the patients received a regimen including rituximab. Treatment strategies did not differ between the two age groups.

Anthracycline-based treatment in combination with rituximab offers a potential cure for elderly patients. This evidence was first provided by the French GELA (Groupe d'Etudes des Lymphomes de l'Adulte) study, showing an increased complete response rate, prolonged EFS and OS, and tolerable toxicity in elderly patients treated with eight cycles of the R-CHOP regimen; the 5-year EFS, PFS, and OS values were 47%, 54%, and 58%, respectively.[12,17] Subsequent studies further confirmed these findings. An Italian study found that the 5-year EFS and OS values were 46% and 62%, respectively, for patients with DLBCL over 65 years who received the R-CHOP regimen,[18] and a US study confirmed the superiority of R-CHOP in untreated patients with DLBCL who were 60 years or older, with a 3-year failure-free survival of 53% compared with 46% for CHOP ($P = 0.04$).[19] Clinical benefits from rituximab were even seen in very elderly patients. In an analysis of 1156 patients aged >80 years from the surveillance, epidemiology, and end results medicare database, R-CHOP was the only regimen associated with improved OS (hazard ratio [HR] = 0.45) and lymphoma-related survival (HR = 0.58).[20] Efforts were also made to optimize the treatment regimen to reduce toxicity and improve efficacy in elderly patients with DLBCL. R-CHOP-21 has been established as the standard regimen for elderly patients with DLBCL, and a superior outcome was reported in a German study for a regimen that shortened the intervals between six cycles of treatment with CHOP from 3 weeks to 2 weeks (CHOP-14).[21] The RICOVER-60 study compared six cycles with eight cycles of R-CHOP-14/CHOP-14, showing that only six-cycle R-CHOP-14 was associated with improved EFS, PFS, and OS.[22] Combinations of rituximab and other regimens have been used in elderly patients.[18,23]

In the present study, we evaluated the patient characteristics and outcomes of elderly patients with DLBCL in a real-life setting with a median follow-up of 6.8 years. Median survival by age group declined dramatically with increasing age (OS: 58.3% [60–69 years] *vs.* 42.8% [≥70 years], $P = 0.007$; PFS: 51.0% [60–69 years] *vs.* 38.6% [≥70 years], $P = 0.030$). We also found that advanced disease stage (Ann Arbor stage III/IV), elevated LDH, and a rituximab-free regimen were associated with poorer OS and PFS. Consistent with previous studies, the R-CHOP regimen significantly improved the survival of elderly patients with DLBCL in both age groups.

The current study had several limitations arising from its retrospective nature. We failed to collect data to assess the short-term efficacy as well as the impact of radiotherapy on the outcome. The lack of information on comorbidities at diagnosis, safety, and tolerability was another limitation that might contribute to dose reduction/interruption/discontinuation, poor quality of life, and adverse outcomes.[24-26] We also failed to analyze the molecular characteristics of elderly patients and their influence on survival. Finally, the findings of the study would have been stronger if a comprehensive geriatric assessment (CGA) was implemented; CGA is a multidisciplinary evaluation tool that can be used to independently predict survival, tolerance to chemotherapy, and mortality.[27]

In conclusion, we find that in comparison to patients aged 61 to 69 years, those patients aged ≥70 years have poorer survival. Prolonged survival is obtainable with R-CHOP-like in elderly Chinese patients in all age groups, indicating that the R-CHOP-like regimen should be considered for this population, even for those aged 70 years or older. Treating this subset of patients requires more careful evaluation for toxicities throughout the treatment, and CGA or a similar assessment is needed for decision making to further optimize treatment recommendations for elderly patients with DLBCL.

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Conflicts of interest

None.

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