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Clinical outcomes of people living with human immunodeficiency virus (HIV) with diffuse large B-cell lymphoma (DLBCL) in Shanghai, China

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Abstract

Background: Numerous studies have focused on lymphoma among patients infected with human immunodeficiency virus (HIV). However, little is known about the treatment options and survival rate of lymphoma in the Chinese people living with HIV (PLHIV). Our study aimed to investigate the prognosis and compare outcome of dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R) with standard cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab(R-CHOP) as front line therapy for PLHIV with diffuse large B-cell lymphoma (DLBCL) receiving modern combined antiretroviral therapy (cART).

Methods: A retrospective analysis evaluating PLHIV with DLBCL was performed in Shanghai Public Health Clinical Center from July 2012 to September 2019. The demographic and clinical data were collected, and overall survival (OS) and progression-free survival (PFS) analyses of patients receiving R-CHOP or DA-EPOCH-R therapy were performed by Kaplan-Meier analysis. Additionally, a Cox multiple regression model was constructed to identify related factors for OS.

Results: A total of 54 eligible patients were included in the final analysis with a median follow-up of 14 months (interquartile range [IQR]: 8–29 months). The proportion of high international prognostic index (IPI) patients was much larger in the DA-EPOCH-R group ($n = 29$) than that in the R-CHOP group ($n = 25$). The CD4 cell counts and HIV RNA levels were not significantly different between the two groups. The 2-year OS for all patients was 73%. However, OS was not significantly different between the two groups, with a 2-year OS rate of 78% for the DA-EPOCH-R group and 66% for the R-CHOP group. Only an IPI greater than 3 was associated with a decrease in OS, with a hazard ratio of 5.0. The occurrence of grade 3 and 4 adverse events of chemotherapy was not significantly different between the two groups.

Conclusions: Outcomes of R-CHOP therapy do not differ from those of DA-EPOCH-R therapy. No HIV-related factors were found to be associated with the OS of PLHIV in the modern cART era.

Keywords: Diffuse large B-cell lymphoma; HIV infection; Overall survival; Progression free survival

Introduction

Before the era of combined antiretroviral therapy (cART), immunosuppression caused by human immunodeficiency virus (HIV) infection inevitably progressed to acquired immunodeficiency syndrome (AIDS).[1,2] Indeed, the risk for HIV-associated opportunistic tumors was significantly higher than that in the non-AIDS population, particularly for both non-Hodgkin's lymphoma (NHL) and Hodgkin's lymphoma.[3] The risk of HIV-associated lymphoma was over 100 times greater than that in non-HIV-infected persons.[4] This situation has improved significantly with the wide availability of cART, but the incidence of these malignancies remains significantly higher than that in the general population.[5] The most common histological type of NHL associated with HIV infection is diffuse large B-cell lymphoma (DLBCL), accounting for 50% to 80% in the current era.[6,7] First-line chemotherapeutic regimens for DLBCL include cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab (R-CHOP) and dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R).[5] Currently, the results of comparisons of the clinical responses between these regimens in HIV-DLBCL are controversial.[8,9] In real clinical settings, R-CHOP is usually used in patients with low-risk factors, while DA-EPOCH-R is primarily used in patients with advanced-stage disease and much higher international prognostic index (IPI).[5] However, retrospective studies based on these settings are scarce.

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In addition to the above issues, Chinese HIV patients are somewhat unique in that the diagnosis of HIV infection is often late,[10,11] and many patients receive an HIV diagnosis after the diagnosis of lymphoma.[12] Considering previously published data, a low CD4 cell count and poorly controlled HIV replication lead to a poor prognosis of DLBCL in general for these patients.[13,14] Importantly, a paucity of information exists regarding the treatment of lymphoma in this population. The Shanghai Public Health Clinical Center (SPHCC) is a designated hospital for the care of AIDS patients in the Municipality of Shanghai, China. Many lymphoma patients are diagnosed and treated at SPHCC every year. Therefore, we retrospectively evaluated the chemotherapy regimens and prognosis of PLHIV with DLBCL over 7 years to provide more information about the prognosis and treatment of PLHIV with DLBCL.

Methods

Ethics approval

The research protocols received ethical approval from the SPHCC Ethics Committee (No. 2017-S022-04). The committee decided to waive the need for written informed consent from the participants in the study because the data were analyzed retrospectively and anonymously.

Study design

PLHIV who initiated chemotherapy for DLBCL from July 1, 2012 to September 1, 2019 were selected according to the following criteria: HIV-1 positive, age older than 18 years, and a diagnosis of DLBCL as determined by histological analysis using 2016 World Health Organization (WHO) classification of lymphoma. All the consecutive patients meeting the inclusion criteria were included in the study. Lymphoma staging was performed according to the Ann Arbor system and included physical examination, routine laboratory tests, computed tomography or positron emission tomography. Each patient was followed up every 6 months for a planned duration of 5 years. Tumor response was classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to the 2007 revised Cheson criteria.[15] Coinfections such as *Mycobacterium tuberculosis*, Hepatitis B virus and nontuberculosis mycobacteria were recorded, as well as the side effects of chemotherapy, such as anemia, leukopenia, and arrhythmia.

Overall survival (OS) was calculated from the date of diagnosis to February 1, 2020, 5 years after diagnosis, the date of death, or the date of last contact, whichever occurred first. Progression free survival (PFS) was measured from lymphoma diagnosis to progression, relapse or death. R-CHOP or DA-EPOCH-R administration was administered every 21 days for 6 to 8 cycles, as previously reported.[12] All the patients received central nervous system prophylaxis with intrathecal methotrexate (10 mg) and dexamethasone (5 mg) on day 1 or day 2 of every cycle.

Statistical analysis

Data analysis was performed using SPSS version 22.0 (IBM SPSS Inc., Armonk, NY, USA). Continuous variables were summarized as the medians and interquartile range (IQR), and categorical variables were expressed as frequencies and percentages. Chi-squared test was used for categorical variables, and the Mann-Whitney U test or t test for continuous variables. Follow up was measured from DLBCL diagnosis to the last follow-up. The probabilities of PFS and OS were estimated using the Kaplan-Meier method, and differences were compared using the log-rank test. Cox proportional hazards regression models were used to identify predictors of OS. Covariates considered in the first prognostic analysis were the CD4 cell count, gender, cART at DLBCL diagnosis, regimens for DLBCL, B symptoms, severity of leukopenia, infection after chemotherapy, IPI and its components (age, performance status, lymphoma stage, lactate dehydrogenase [LDH] level, and the number of extranodal sites). Covariates with $P < 0.20$ in univariate analysis and regimens for DLBCL were included in the multivariable model. All hypothesis testing was two-sided, with a level of $\alpha = 0.05$.

Results

Demographic and clinical data of PLHIV with DLBCL

Fifty-four PLHIVs met the inclusion criteria and were included in the study. The mean age was 48 years, and 48 were men (89%). Twenty-five (46%) PLHIVs had received R-CHOP, and 29 (54%) had received DA-EPOCH-R. The age ranged from 24 to 80 years, while the mean age of the R-CHOP group was older than that of the DA-EPOCH-R group ($t = 1.98$, $P = 0.05$). The median CD4 count was 130/μL, with no significant difference between the groups. Among the 54 PLHIVs, only 28 (52%) had received cART when DLBCL was confirmed. The HIV RNA load data were only available for 39 PLHIVs, with a median level of 30,300 (IQR: 0–99,500) copies/mL. No difference was found between the groups in the HIV RNA level, CD4 cell count, and cART regimen. However, the severity of DLBCL assessed according to both Ann Arbor stage and IPI was significantly worse in DA-EPOCH-R group than that in R-CHOP group ($\chi^2 = 9.718$, $P < 0.01$; $\chi^2 = 6.344$, $P = 0.04$). Thirty-eight PLHIVs had extranodal involvement, with the most frequent sites being the liver ($n = 9$), bone ($n = 8$), gut ($n = 6$), bone marrow ($n = 5$), spleen ($n = 4$), stomach ($n = 4$), lung ($n = 4$), kidney ($n = 4$), and testis ($n = 3$).

Regarding adverse effects of chemotherapy, one patient had severe anemia (hemoglobin <6 g/dL), two patients had renal function injury and one patient had premature ventricular extrasystole after treatment of R-CHOP, and two patients had severe anemia in DA-EPOCH-R group. Regarding leukopenia and infection after therapy, no significant difference was found between the groups. All the demographic and related clinical data are presented in Table 1.

The response to first-line therapy was CR in 35 PLHIVs (65%), PR in two (4%), and SD in nine (17%). Six (11%) of PLHIVs developed PD, and two (3%) relapsed after CR. Therapy of six PLHIVs switched from R-CHOP to DA-EPOCH-R because CR was not achieved, and two changed from DA-EPOCH-R to R-CHOP because of myelosuppression.

Table 1: Demographics and clinical characteristics of 54 people living with HIV (PLHIV) with diffuse large B-cell lymphoma (DLBCL).

Characteristics	Total (n = 54)	R-CHOP (n = 25)	DA-EPOCH-R (n = 29)	Statistics	P
Age (years)	48.0 ± 13.2	51.7 ± 15.1	44.8 ± 10.5	1.980	0.05[*]
Male	48 (89)	22 (88)	26 (90)	0.193	0.85
Age				1.665	0.10
18–60 years	44 (81)	18 (72)	26 (90)		
>60 years	10 (19)	7 (28)	3 (10)		
CD4 cell count	130.5 (54.0–270.8)	132 (54.0–228.5)	129 (54.0–294.5)	334.5	0.63[†]
>200/μL	20 (37)	8 (32)	12 (41)		
≤200/μL	34 (63)	17 (68)	17 (59)		
HIV RNA[‡]				1.035	0.30
>50 copies/mL	23 (59)	11 (69)	12 (52)		
<50 copies/mL	16 (41)	5 (31)	11 (48)		
cART before diagnosis of DLBCL	28 (52)	13 (52)	15 (52)	0.020	0.98
Regimen of initial cART[§]				0.449	0.65
2 NRTIs plus 1 NNRTI	30 (63)	13 (59)	17 (65)		
2 NRTIs plus 1 INSTI	18 (37)	9 (41)	9 (35)		
Length of cART (month)	1 (0–6)	1 (0–4)	1 (0.0–7.5)	333	0.59[†]
HBsAg+	4 (7)	2 (8)	2 (7)	0.154	0.88
Mycobacterium infection[‖]	13 (24)	8 (32)	5 (17)	1.265	0.21
Extranodal involvement (≥2 sites)	21 (39)	6 (24)	15 (52)	4.342	0.04
ECOG score				1.265	0.21
0–1	13 (24)	8 (32)	5 (17)		
2–4	41 (76)	17 (68)	24 (83)		
Abnormal LDH[¶] level	36 (67)	17 (68)	19 (66)	0.193	0.85
Ann Arbor stage				9.718	0.002
I–II	31 (57)	20 (80)	11 (38)		
III–IV	23 (43)	5 (20)	18 (62)		
IPI				6.344	0.04
0–1	16 (30)	9 (36)	7 (24)		
2–3	20 (37)	12 (48)	8 (28)		
4–5	18 (33)	4 (16)	14 (48)		
B symptoms	12 (22)	4 (16)	8 (28)	1.021	0.31
Severity of leukopenia (III–IV)	29 (54)	11 (44)	18 (62)	1.328	0.18
Infection after chemotherapy	30 (56)	13 (52)	17 (59)	0.488	0.63

The data are shown as n (%), mean ± standard deviation or median (interquartile range). B symptoms: consisting of fever >38°C, night sweats and/or unintentional weight loss of >10% the body weight over a period of up to 6 months. HIV: Human immunodeficiency virus; cART: Combined antiretroviral therapy; NRTI: Nucleoside reverse transcriptase inhibitor; NNRTI: Non-nucleoside reverse-transcriptase inhibitors; INSTI: Integrase strand transfer inhibitors; HBsAg: Hepatitis B surface antigen; ECOG: Eastern cooperative oncology group; LDH: Lactate dehydrogenase; IPI: International prognostic index; R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; DA-EPOCH-R: Dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab. [*]P values were calculated by t-test. [†]P value was analyzed by Mann-Whitney U test; the others were made by Chi-square test. [§]The regimen of cART including 3TC, TDF, FTC, EFV, RAL, DTG. AZT and booster was not administered during the chemotherapy. [‖]Including *Mycobacterium tuberculosis* and Nontuberculosis mycobacteria. [¶]LDH more than the upper normal range (245 U/L).

Comparison of OS and PFS in PLHIV with R-CHOP and DA-EPOCH-R chemotherapy

For both groups, the median follow-up period since diagnosis was 14 months (IQR: 8–29 months). The median follow-up of DLBCL patients treated with R-CHOP was 14 months (IQR: 7–30 months) and that of DLBCL patients treated with DA-EPOCH-R was 14 months (IQR: 8–30 months). Thirteen PLHIV died, and 37 had a PFS event, and 4 progressed without death. The two-year OS was 73% (95% Confidence interval [CI]: 59%–84%). The OS was not significantly different (HR: 0.79; 95% CI: 0.26–2.33; P = 0.67), with a 2-year OS rate of 78% (95% CI: 53%–90%) for DA-EPOCH-R and 66% (95% CI: 42%–83%) for R-CHOP. The 5-year OS rates were similar, 66% for the DA-EPOCH-R group and 65% for

the R-CHOP group. The 2-year PFS was 64% (95% CI: 48%–76%). The PFS was not significantly different between the groups (hazard ratio [HR]: 0.97; 95% CI: 0.37–2.51; P = 0.95], with a 2-year PFS rate of 64% (95% CI: 42%–80%) for the DA-EPOCH-R group and 64% (95% CI: 40%–81%) for the R-CHOP group. The 5-year PFS rate was 64% for both groups [Figures 1 and 2].

Factors associated with OS of PLHIV with DLBCL

Using a Cox proportional hazards regression model, we analyzed the factors associated with death of PLHIV with DLBCL. The covariates considered in the first prognostic analysis were the CD4 cell count, age, gender, number of extranodal sites, serum LDH level, and Ann Arbor stage. IPI analysis demonstrated that PLHIV had an IPI score
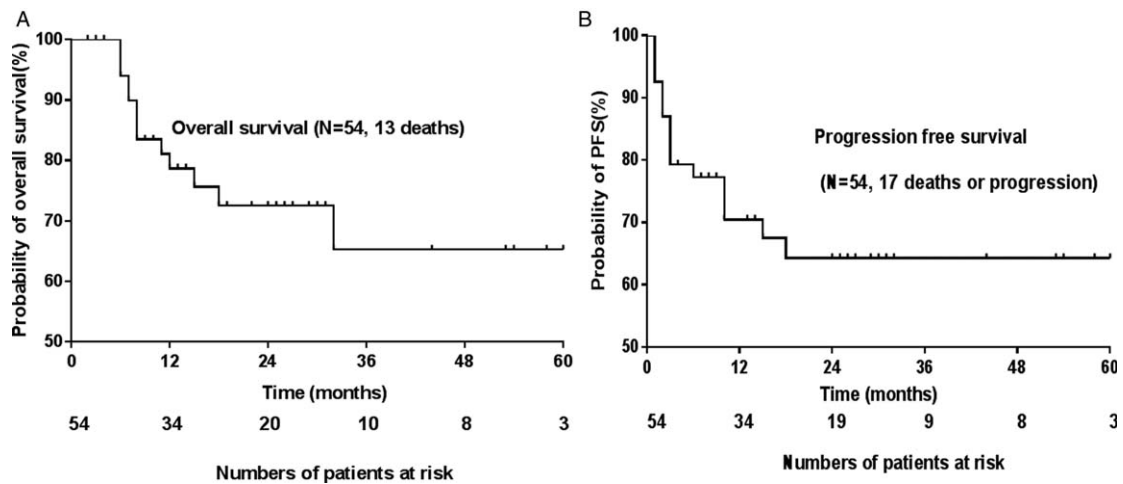
Figure 1: Overall (A) and progression free (B) survival rate of people living with HIV with diffuse large B-cell lymphoma. PFS: Progression-free survival.
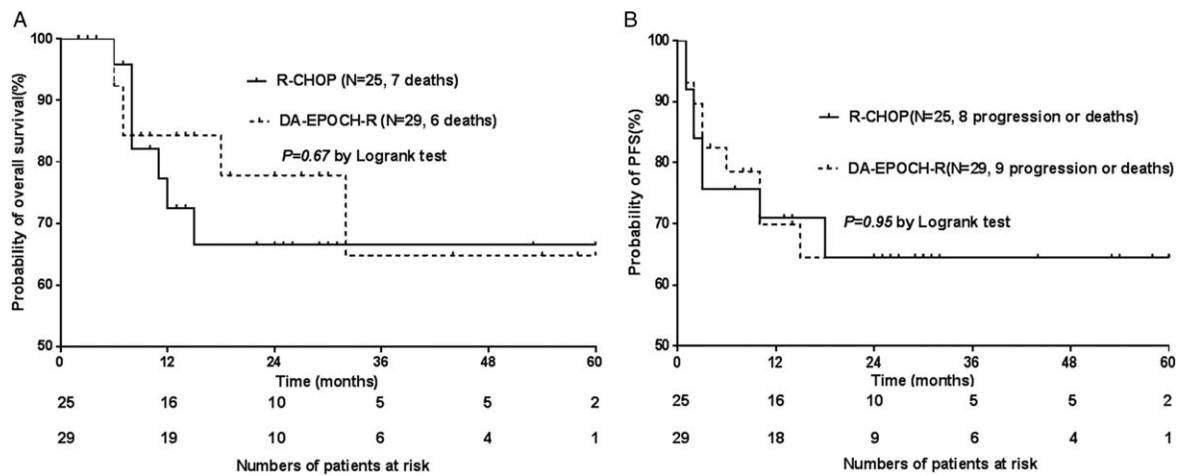
Figure 2: Overall (A) and progression free (B) survival among people living with HIV with diffuse large B-cell lymphoma treated with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone and dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab. PFS: progression free survival.

greater than 3 and a HR of 3.9 (1.1–14.3). No HIV-related factors were associated with OS. According to the clinical experience, we added the regimens of chemotherapy and cART to DLBCL diagnosis with IPI in the multivariable model, and only IPI ≥ 3 with a HR of 5.04 (1.28–19.79) was associated with a decrease in OS [Table 2].

Discussion

Our retrospective study evaluated the characteristics and outcomes of PLHIV with DLBCL over 7 years in China. We found that the 2-year OS and PFS rates were 73% and 64%, respectively. At diagnosis, the patients frequently had lymphoma with advanced clinical stage with more extranodal involvement, poorer performance status, and higher IPI.[5] A poor performance status, more than one extranodal site and high IPI were associated with poorer survival than in those without those characteristics.[16] HIV infection is a risk factor for the development of NHL, and PLHIV with DLBCL have a poorer prognosis than those with only DLBCL.[17,18] Before the wide availability

of modern cART, the 2-year OS rate of lymphoma among HIV-infected patients in China was approximately 37.5%[19] to 53.5%.[20] The two-year OS in our study was 73%, which is higher than that reported previously. The cause may be that our patients had higher CD4 cell counts and more robust cART regimens are available.[10,21,22] Furthermore, rituximab is associated with significant improvement in all outcomes for patients with HIV-associated, CD20-positive lymphomas.[23] However, it was not administered to every patient because of the paucity of prior treatment experience. Our results are consistent with those of Barta et al[13] who reported that the 2-year OS was 67% in the period of 2005 to 2010. This finding is also similar to that reported in the French R-CHOP trial.[24]

For the treatment of DLBCL in PLHIV, the choice is similar to that of the population without HIV infection.[25] R-CHOP is the first-line therapy. However, for those with high IPI, DA-EPOCH-R was used more frequently.[5,8] A prospective cohort study comparing HIV-infected DLBCL patients treated with R-CHOP with their HIV-negative counterparts demonstrated that the outcomes did not

Table 2: Cox regression analysis for the factors associated with overall survival of people living with HIV (PLHIV) with diffuse large B-cell lymphoma (DLBCL).

Factors	Hazard ratio	95% CI	P
Age			
≤60 years	1.00	—	—
>60 years	2.87	0.85–9.76	0.09
Gender			
Male	1.00	—	—
Female	0.99	0.13–7.68	0.99
CD4 cell count			
≤200/μL	1.00	—	—
>200/μL	0.80	0.26–2.44	0.70
cART at DLBCL diagnosis			
Yes	1.00	—	—
No	2.38, 2.38*	0.79–7.15, 0.78–7.29*	0.12, 0.13*
Extranodal involvement			
<2 sites	1.00	—	—
≥ 2 sites	2.81	0.91–8.67	0.07
ECOG score			
0–1	1.00	—	—
2–4	27.0	0.05–13687	0.30
LDH			
Normal	1.00	—	—
Abnormal	41.40	0.37–4700	0.12
Ann Arbor stage			
I–II	1.00	—	—
III–IV	1.87	0.63–5.57	0.26
IPI			
0–2	1.00	—	—
3–5	3.93, 5.04*	1.08–14.32, 1.28–19.79*	0.04, 0.02*
Chemotherapy			
R-CHOP	1.00	—	—
DA-EPOCH-R	0.79,0.41*	0.26–2.34, 0.13–1.32*	0.66, 0.14*
B symptoms			
No	1.00	—	—
Yes	1.27	0.39–4.16	0.69
Severity of leukopenia			
I-II	1.00	—	—
III-IV	1.98	0.61–6.49	0.25
Infection after chemotherapy			
No	1.00	—	—
Yes	1.61	0.49–5.23	0.43

*Adjusted hazard ratio. B symptoms: consisting of fever >38°C, night sweats and/or unintentional weight loss of >10% the body weight over a period of up to 6 months. CI: Confidnece interval; cART: Combined antiretroviral therapy; ECOG: Eastern cooperative oncology group; LDH: Lactate dehydrogenase; R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; DA-EPOCH-R: Dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab.

differ according to HIV status.[26] Additionally, a British retrospective study demonstrated that PLHIV with DLBCL treated with R-CHOP had a five-year OS rate of 78%, similar to that in the general DLBCL population.[27] Importantly, the HIV patients in both studies had a higher CD4 level (median: 233/μL) and earlier cART initiation. However, other studies showed that in patients included before 2010, the risk of death was three-fold higher among HIV-infected individuals with NHL than among NHL population.[28,29]

Regarding treatment of DLBCL with DA-EPOCH-R, a randomized clinical trial showed no improvement in PFS, OS, or the response rate but greater toxicity and complexity of the regimen.[8] In our study, we found that the OS and PFS rates were not significantly different for treatment with DA-EPOCH-R, although they were numerically better for DA-EPOCH-R than for R-CHOP. Given that patients with higher IPI were in the DA-EPOCH-R group, the DA-EPOCH-R regimen is likely more suitable in PLHIV with DLBCL in the severe stage. Additionally, no significant difference was found between the groups in adverse events of grade 3 and 4. All the patients had undergone risk-adapted treatment (R-CHOP for low-risk and DA-EPOCH-R for high-risk patients).

Regarding factors associated with OS, we found that only patients with an IPI > 3 and a HR of 3.93 had a worse prognosis than those who did not. No HIV-related factor was associated with OS. Other factors, such as more than

one extranodal site or a poor performance status were also not associated with the OS rate. Indeed, when we evaluated the type of chemotherapy and cART regimens with IPI in the multivariable Cox analysis model, only an IPI > 3 with a HR of 5.04 was significant. These results are similar to those of Schommers *et al*[14] in that the IPI and its components are predictive of the outcomes in HIV-related NHL. Finally, the CD4 cell count was shown to be a major determinant of survival in HIV-associated lymphoma.[13,17] However, this measurement is no longer associated with survival in the contemporary cART period,[6,30] which is consistent with our findings.

Our study possesses some limitations. First, the sample size ($n = 54$) was small and the follow-up interval (median, 14 months) was short. Second, the factors that might affect the prognosis of PLHIV with DLBCL, such as MYC, BCL-2, and BCL-6 rearrangements, were not available for our research.[31,32] These data may have affected our results and conclusions.

In this study, the outcome of R-CHOP therapy, however, does not differ from that of DA-EPOCH-R. Importantly, no HIV-related factors were found to be associated with the OS of PLHIV in the modern cART era.

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Conflicts of interest

None.

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