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Original Article

Complete response to front-line therapies is associated with long-term survival in HIV-related lymphomas in Taiwan

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Abstract *Background:* The prognosis for people living with HIV (PLWH) who develop lymphomas has been greatly improved by combination antiretroviral therapy (cART) and anti-CD20 monoclonal antibodies. However, real-world clinical data on this patient group in Asia are limited.
Methods: Treatment outcomes were retrospectively examined for 104 PLWH with lymphomas between 2000 and 2019. The cohort comprised five PLWH with Hodgkin lymphoma (HL) and 99 with non-Hodgkin lymphomas, including 61 with diffuse large B-cell lymphoma (DLBCL), 19 with Burkitt lymphoma (BL), nine with primary central nervous system lymphoma (PCNSL) and ten with other subtypes.
Results: The 5-year overall survival (OS) rates were as follows: HL (100%), PCNSL (76.2%), other subtypes (60.0%), BL (57.4%), and DLBCL (55.6%). Individuals who achieved complete response (CR) to front-line therapies had a significantly better 5-year OS rate than those without (96.2% vs. 17.8%, $p < 0.001$). PLWH who received cART for ≤6 months had significantly lower CD4+ T-cell counts at lymphoma diagnosis than those who received cART for longer periods ($p = 0.048$).

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Additionally, the 5-year OS rate was better for PLWH who received cART for ≤6 months before lymphomas diagnosis than those who received cART for longer periods (64.5% vs. 51.9%, $p = 0.114$).

Conclusions: PLWH with DLBCL or BL had OS rates compatible to patients without HIV infection. Better outcomes for patients achieving CR to front-line therapy and those with shorter cART duration before lymphoma diagnosis suggest an underlying biological distinction in the lymphomas and the involvement of immunity, which warrants further studies.

Background

People living with HIV (PLWH) are at higher risk for developing many malignancies. They are considered to have acquired immunodeficiency syndrome (AIDS) when diagnosed with Kaposi's sarcoma, cervical cancer, and/or aggressive non-Hodgkin lymphomas (NHLs).[1] With the successful implementation of combination antiretroviral therapy (cART), the incidence of NHLs has significantly decreased in PLWH.[2] However, aggressive NHLs remain one of the most common AIDS-defining illnesses, and NHLs still occur in some PLWH with cART-based viral suppression.[3] In the cART era, the most common subtypes of HIV-related lymphomas are diffuse large B-cell lymphoma (DLBCL, 42%), followed by Hodgkin lymphoma (HL, 17%), Burkitt lymphoma (BL, 12%), and primary central nervous system lymphoma (PCNSL, 11%).[4]

The overall survival (OS) of PLWH with and without NHLs has significantly improved with the introduction of cART. Although standard front-line chemotherapy regimens have not been established for rare subtypes of HIV-associated NHLs (e.g., primary-effusion lymphoma or plasmablastic lymphoma),[5–7] PLWH with NHLs who receive cART generally have better OS than those who do not.[8] Whether the improved OS of PLWH with NHLs has become similar to that of people without HIV infection remains debated. In one study conducted by Gopal et al., the 5-year OS rates of PLWH with DLBCL and BL were worse than those in people without HIV infection.[4] On the other hand, studies by Besson et al. and Alderuccio et al. showed that PLWH with DLBCL and BL had OS rates similar to those without HIV infection.[9,10] In addition, the immune status of PLWH is thought to impact the risk of developing lymphoma and also influence the treatment outcome. At the time of lymphoma diagnosis, PLWH with HL had higher CD4+ T-cell counts and lower plasma HIV RNA load (PVL) than those with NHLs. Among PLWH with AIDS-defining NHL subtypes, those with BL had higher CD4+ T-cell counts, while those with PCNSL had relatively lower counts.[4,11] Very low CD4+ T-cell counts (<50–100 cells/mm^3) may impact survival, especially when PLWH receive a rituximab-based treatment.[12,13] Despite these intriguing findings, further exploration is needed to precisely define how immune status may impact the risk of developing lymphoma and treatment outcomes.

In addition to the inconsistency of findings in studies on HIV-related NHLs, most available data are from studies on Western populations. Real-world information on Asian populations of PLWH are highly limited.[14] This is an important consideration, as the incidences and distributions of lymphoid cancers may be markedly different in Asian and Western regions.[15,16] For example, the overall incidence of HL in Asia is much lower than that in the West, as are the incidence rates of most subtypes of B-cell lymphomas. In addition, the distributions of lymphoma subtypes differ between Asian and Western populations. The proportion of T/NK lymphoma and the relative ratio of DLBCL among common B-cell subtypes are higher in Asia than in the West.[15,16] Whether such population differences are also found in PLWH remains to be investigated. In this study, we sought to examine the rates of HIV-related lymphoma subtypes in the cART era and to assess the treatment outcomes for PLWH with lymphomas in Taiwan.

Methods

Study population

This retrospective study included PLWH diagnosed with lymphomas at National Taiwan University Hospital between 2000 and 2019. Lymphomas were diagnosed according to the revised criteria of the 2016 World Health Organization classification.[17] Information on age, sex, Eastern Cooperative Oncology Group (ECOG) performance status, complete blood count, blood chemistry analysis, serological status of hepatitis B and C virus, and histopathologic findings of bone marrow studies of the affected PLWH at the time of lymphoma diagnosis were retrieved. HIV-related information was also recorded, including the dates of HIV diagnosis and cART initiation, PVL, CD4+ T-cell counts, and types of cART administered upon lymphoma diagnosis.

Staging and treatment of HIV-related lymphomas

Positron emission tomography-computed tomography (PET-CT) or whole-body CT was performed for staging of lymphoma at the initial diagnosis. We used Lugano classification to determine the clinical stages of lymphomas.[18] Since most PLWH with lymphomas were aged less than 60 years, the age-adjusted international prognostic index (aaIPI) scoring system was used for prognosis stratification; scores were calculated according to the serum LDH level (above the upper limit of the normal reference), Ann Arbor stage III or IV disease, and ECOG performance status (≥2).[6,9] The front-line chemotherapy regimens by PLWH with different subtypes of lymphomas were listed on Table 1 and Supplementary Table 1.[6,19–24] Generally, most of the included patients received 4–6 cycles of the front-line

Table 1 Characteristics of people living with HIV who had lymphomas (N = 104).

	Non-Hodgkin lymphomas (N = 99)				
	DLBCL (N = 61)	BL (N = 19)	PCNSL (N = 9)	Others (N = 10)	HL (N = 5)
Sex, n (%)					
Male	60 (98)	17 (89)	7 (78)	10 (100)	5 (100)
Female	1 (2)	2 (11)	2 (22)	0 (0)	0 (0)
Median age (years) at HIV diagnosis (IQR)	36 (31–45)	34 (27–42)	32 (26–39)	42 (25–52)	32 (25–41)
At lymphoma diagnosis					
Median age (years) (IQR)	37 (34–47)	37 (29–43)	34 (28–39)	44 (27–54)	33 (28–52)
CD4+ T cells (cells/mm^3)					
Median (IQR)	142 (39–351)	200 (61–303)	47 (19–106)	36 (11–263)	424 (320–821)
< 200 cells/mm^3, n (%)	31 (51)	9 (47)	9 (100)	7 (70)	0 (0)
PVL (log_{10}/mL)					
Median (IQR)	3.89 (1.69–5.03)	4.56 (0–5.24)	5.16 (1.54–5.79)	4.97 (3.48–5.68)	0 (0–1.25)
>10^5 copies/mm^3, n (%)	15 (25)	7 (37)	6 (67)	4 (40)	0 (0)
cART use					
>6 months before lymphoma diagnosis, n (%)	19 (31)	8 (42)	2 (22)	2 (20)	3 (60)
NRTIs	61 (100)	19 (100)	9 (100)	10 (100)	5 (100)
NNRTIs	29 (48)	10 (53)	2 (22)	7 (70)	2 (40)
PIs	13 (21)	4 (21)	3 (33)	3 (30)	2 (40)
InSTIs	18 (30)	5 (26)	6 (67)	0 (0)	1 (20)
Viral hepatitis					
HBsAg, n (%)	26 (43)	6 (32)	6 (67)	5 (50)	3 (60)
Anti-HCV, n (%)	6 (10)	3 (16)	1 (11)	1 (10)	1 (20)
Front-line systemic treatments for lymphomas, n (%)[a]					
R-EPOCH, R–CHOP or other rituximab-based regimens	42 (69)				
DA-EPOCH-R, R-HyperCVAD or other rituximab-based regimens		13 (68)			
HDMTX-based regimens with or without rituximab			8 (89)		
CHOP-based or more intensive regimens				8 (80)	
ABVD					5 (100)
Stages, n (%)					
I and II	16 (26)	4 (21)	9 (100)	2 (20)	1 (20)
III and IV	45 (74)	15 (79)	0 (0)	8 (80)	4 (80)
aaIPI scores, n (%)					
0–1	26 (43)	3 (16)	8 (89)	6 (60)	0 (0)
2–3	35 (57)	16 (84)	1 (11)	4 (40)	5 (100)
Pathology subtypes				PBL: 2 PTCL-NOS: 2 NK cell: 2 MZL: 1 FL: 1 PEL: 1 CTCL: 1	

[a] The full names about regimens to treat lymphomas were listed on Supplementary Table 1.

Abbreviations. DLBCL: diffuse large B-cell lymphoma; BL: Burkitt lymphoma; PCNSL: primary CNS lymphoma; HL: Hodgkin lymphoma; IQR: interquartile range; PVL: plasma viral load; cART: combination antiretroviral therapy; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; InSTI: integrase strand transfer inhibitor; HBsAg: hepatitis B virus surface antigen; Anti-HCV: anti-hepatitis C virus antibody; aaIPI: age-adjusted international prognostic index; PBL: plasmablastic lymphoma; PTCL-NOS: peripheral T-cell lymphoma, not otherwise specified; NK cell: natural killer cell; MZL: marginal zone lymphoma; FL: follicular lymphoma; PEL: primary effusion lymphoma; CTCL: cutaneous T-cell lymphoma.

regimens, with the final dosage and cycle adjusted to the clinical condition of the individual.

Outcome assessment

The included individuals were followed for all-cause mortality from the diagnosis of lymphoma. After the initial anticancer treatments, all PLWH underwent whole-body CT or PET-CT at least every 3–6 months to evaluate disease status, according to the Taiwan National Health Insurance regulations or clinical judgments. Achievement of complete response (CR) to front-line therapy was determined based on whole-body CT or PET-CT, according to the Lugano classification.[18]

Statistical analysis

The U.S. Department of Health and Human Services (HHS) Panel on Antiretroviral Guidelines for Adults and Adolescents recommends that PVL and CD4+ T-cell counts from PLWH should be monitored every 3–6 months from the initiation of cART.[25] In this study, PLWH with lymphomas were stratified as having received cART for longer than 6 months versus cART for 6 months or less before lymphoma diagnosis, with the assumption that the HIV treatment with cART was stable. We used Fisher's exact test to compare distributions of categorical variables, and Mann–Whitney U test to compare continuous variables and median values. The OS rates were estimated using the Kaplan–Meier method. Cox proportional hazards models were used to estimate the unadjusted and adjusted hazard ratios (HRs) for all-cause mortality within five years after the lymphoma diagnosis. Models were adjusted for CD4 count, PVL and duration of cART use at lymphoma diagnosis, aaIPI scores, presence of CNS involvement, front-line therapy of rituximab, and CR to front-line therapies. A two-tailed p-value less than 0.05 was considered statistically significant. All analyses were performed using Stata/SE software, Version 17.0 (https://www.stata.com).

Results

Characteristics of the included PLWH

Table 1 shows the clinical characteristics of PLWH with lymphomas included in this cohort. DLBCL was the most common type of lymphoma (n = 61, 59%), followed by BL (n = 19, 18%), PCNSL (n = 9, 8%), and HL (n = 5, 4%). The "others" subgroup comprised PLWH with rare lymphoma subtypes, including 2 plasmablastic lymphomas, 3 T-cell lymphomas, 2 NK cell lymphomas, and 3 other subtypes (total n = 10, 10%). In every subgroup, 80–100% of the PLWH were males between 30 and 40 years of age at the diagnosis of HIV-related lymphoma. Among the different PLWH subgroups, patients who had stage III/IV disease accounted for the following: DLBCL, 45 (74%); BL, 15 (79%); HL, 4 (80%); and other, 8 (80%). The numbers of individuals with aaIPI scores of 2–3 were: DLBCL, 35 (57%); BL, 16 (84%); HL, 5 (100%); and other, 4 (40%).

The median CD4+ T-cell count at lymphoma diagnosis was 142 cells/mm^3 (interquartile range [IQR], 39–351) in the DLBCL subgroup, 200 cells/mm^3 (IQR, 61–303) in the BL subgroup, 47 cells/mm^3 (IQR, 19–106) in the PCNSL subgroup, 424 cells/mm^3 (IQR, 320–821) in the HL subgroup, and 36 cells/mm^3 (IQR, 11–263) in the others subgroup. Nine (100%) PLWH with PCNSL, 9 (47%) with BL, and none (0%) with HL had baseline CD4+ T-cell counts less than 200 cells/mm^3. The baseline PVL was highest in PLWH with PCNSL and lowest in those with HL. The cART regimens included two nucleoside reverse-transcriptase inhibitors in combination with one non-nucleoside reverse-transcriptase inhibitor, protease inhibitor or integrase strand-transfer inhibitor.

Outcomes and clinical courses of PLWH with lymphomas

The front-line systemic treatments in each subgroup of lymphomas were listed on Table 1. CR to front-line therapies was achieved in 34 (56%) PLWH with DLBCL, 10 (53%) with BL, 4 (44%) with PCNSL, 3 (60%) with HL, and 4 (40%) with other lymphomas (Fig. 1A). The 5-year OS rates of PLWH were as follows: HL, 100%; PCNSL, 76.2%; others, 60.0%; BL, 57.4%; and DLBCL, 55.6% ($p = 0.402$; Fig. 1B). PLWH with DLBCL having aaIPI scores of 0–1 had a significantly better 5-year OS rate than those with scores of 2–3 (73.1% vs. 40.7%, $p = 0.009$; Fig. 1C). PLWH with BL having aaIPI scores of 0–1 showed a trend toward better 5-year OS rate as compared to those with scores of 2–3 (71.4% vs. 48.6%, $p = 0.508$; Fig. 1D).

PLWH with total lymphomas or DLBCL receiving cART for more than 6 months before lymphomas diagnosis had significantly higher median CD4+ T-cell counts and lower baseline PVL than those receiving cART for 6 months or less (Table 2 and Table 3). In contrast, although PLWH with BL receiving cART longer than 6 months before lymphoma diagnosis had significantly lower baseline PVL than those receiving cART for 6 months or less, the median CD4+ T cells were not significantly different by cART duration (Supplementary Table 2).

Among all included PLWH with lymphoma, a significantly better 5-year OS rate was observed for PLWH achieving CR after front-line therapies than those who without CR (96.2% vs. 17.8%, $p < 0.001$; Fig. 2A). Moreover, PLWH with DLBCL or BL achieving CR after front-line therapies had significantly better 5-year OS rate compared to those without CR (DLBCL: 97.0% vs. 0%, $p < 0.001$; Fig. 2B; BL: 90.0% vs. 0%, $p < 0.001$; Fig. 2C). PLWH receiving cART for 6 months or less before lymphoma diagnosis showed a trend toward more favorable 5-year OS rate than those receiving cART for longer than 6 months (64.5% vs. 51.9%, $p = 0.114$; Fig. 2D). PLWH receiving cART for 6 months or less before DLBCL diagnosis had a more favorable 5-year OS rate than those receiving cART for longer than 6 months (62.7% vs. 40.6%; $p = 0.030$, Fig. 2E). However, there was no significant difference in the 5-year OS rates between PLWH with BL receiving cART for 6 months or less or greater than 6 months (53.0% vs. 62.5%, $p = 0.791$; Supplementary Fig. 1).

The associations between duration of cART before lymphoma diagnosis, rituximab in front-line regimens, and

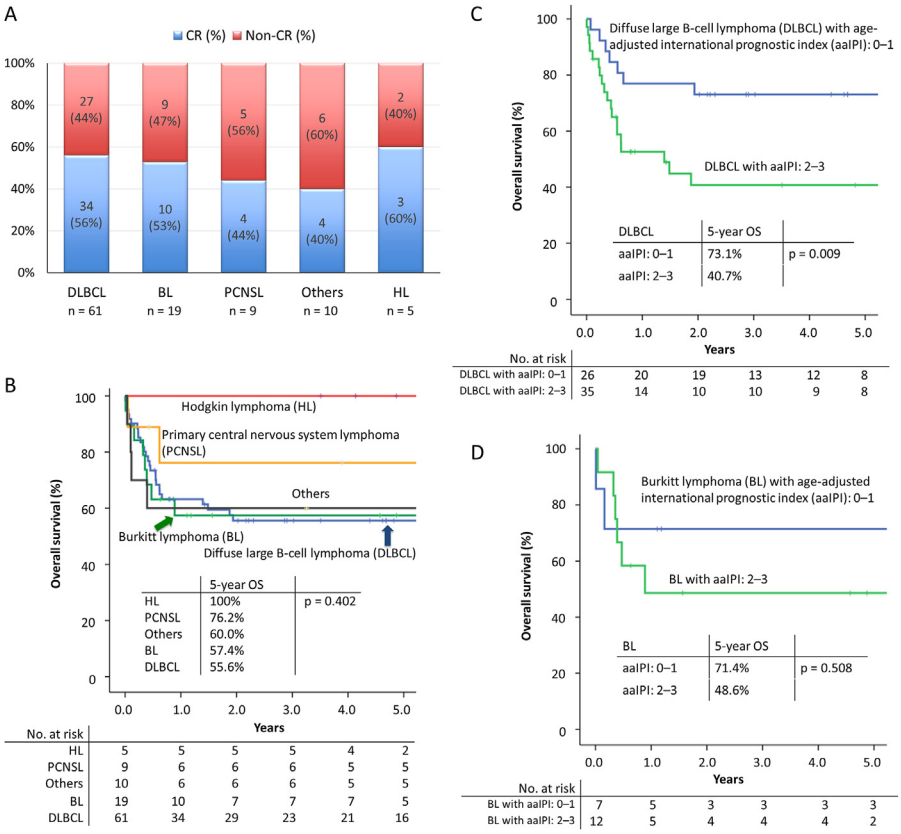


Figure 1. Complete response (CR) rates after front-line therapies in people living with HIV (PLWH) who were diagnosed with diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL), primary central nervous system lymphoma (PCNSL), others or Hodgkin lymphoma (HL). Overall survival (OS) in PLVH with HL, PCNSL, others, BL, and DLBCL. OS in PLWH with DLBCL or BL who had age-adjusted international prognostic index (aaIPI) of 0—1 versus 2—3. (A) Case numbers and percentages achieving or not achieving CR after front-line therapies. (B) The 5-year OS rates in PLWH with HL, PCNSL, others, BL, and DLBCL were 100%, 76.2%, 60.0%, 57.4%, and 55.2%, respectively ($p = 0.402$). (C) The 5-year OS rates of PLWH with DLBCL who had aaIPI scores of 0—1 and 2—3 were 73.1% and 40.7%, respectively ($p = 0.009$). (D) The 5-year OS rates of PLWH with BL with aaIPI scores of 0—1 and 2—3 were 71.4% and 48.6%, respectively ($p = 0.508$).

achievement of CR were analyzed in Supplementary Table 3 and summarized in Fig. 3A. Despite a trend showing that PLWH with DLBCL who had received cART for 6 months or less had higher odds of CR after chemotherapy, the difference did not reach statistical significance ($p = 0.174$). PLWH with DLBCL receiving cART for more than 6 months had a significantly higher median CD4+ T-cell count at lymphoma diagnosis than those receiving cART for 6 months or less (Fig. 3B; $p = 0.026$).

Supplementary Table 4 shows the numbers of PLWH with lymphomas with or without CR to front-line therapies, second-line therapies, and survival outcomes. Few patients achieving CR had disease relapse necessitating salvage therapy. On the contrary, only a few patients not achieving CR to front-line therapies responded well to later therapies.

Factors associated with OS in the DLBCL subgroup

We analyzed whether different clinical characteristics were correlated with OS in PLWH with DLBCL, the largest subgroup in this cohort. Univariate analyses of OS in PLWH with DLBCL were performed to assess the potential prognostic effects of CD4+ T-cell count <200 cells/mm^3 and PVL $>10^5$ copies/mm^3 at lymphoma diagnosis, duration of cART before lymphoma diagnosis, aaIPI, CNS involvement, front-line rituximab use, and CR to front-line therapies. Parameters that showed significant associations with poor survival included cART for longer than 6 months before lymphoma diagnosis (HR, 2.320; 95% confidence interval [CI], 1.060—5.077; $p = 0.035$), aaIPI scores of 2—3 (HR, 2.985; CI, 1.255—7.104; $p = 0.013$), and CNS involvement (HR, 3.022; CI, 1.400—6.523; $p = 0.005$). The favorable survival was significantly associated with CR to front-line therapies (HR, 0.010; CI, 0.001—0.079; $p < 0.001$). In the multivariate analysis of cART for longer than 6 months before lymphoma diagnosis, aaIRI scores 2—3 and CNS involvement, cART for longer than 6 months before lymphoma diagnosis (HR, 3.257; CI, 1.448—7.324; $p = 0.004$) and CNS involvement (HR, 2.461; CI, 1.035—5.850; $p = 0.042$) were associated with poor survival. In another multivariate analysis of aaIRI scores 2—3, CNS involvement and CR to front-line therapies, CR to front-line therapies (HR, 0.009; CI, 0.001—0.070; $p < 0.001$) was associated with favorable survival (Table 4).

Table 2 Characteristics of people living with HIV who had lymphomas, according to duration of combination antiretroviral therapy before lymphoma diagnosis (N = 104).

	cART use ≦ 6 months before lymphoma diagnosis (N = 70)	cART use >6 months before lymphoma diagnosis (N = 34)	P value
Sex, n (%)			0.327
Male	68 (97)	31 (91)	
Female	2 (3)	3 (9)	
Median age (years) at HIV diagnosis (IQR)	37 (31–43)	33 (25–43)	0.091
At lymphoma diagnosis			
Median age (years) (IQR)	37 (32–43)	38 (31–48)	0.493
CD4+ T cells (cells/mm^3)			
Median (IQR)	83 (33–321)	240 (73–381)	**0.048**[a]
< 200 cells/mm^3, n (%)	42 (60)	14 (41)	0.092
PVL (log$_{10}$/mL)			
Median (IQR)	4.81 (3.64–5.35)	0 (0–2.18)	**<0.001**[a]
>10^5 copies/mm^3, n (%)	30 (43)	2 (6)	**<0.001**[a]
Stages, n (%)			0.120
I and II	19 (27)	13 (38)	
III and IV	51 (73)	21 (62)	
aaIPI scores, n (%)			0.535
0–1	34 (49)	19 (56)	
2–3	36 (51)	15 (44)	
Pathology subtypes	DLBCL: 42 BL: 11 PCNSL: 7 HL: 2 PBL: 2 PTCL-NOS: 1 NK cell: 1 MZL: 1 FL: 1 PEL: 1 CTCL: 1	DLBCL: 19 BL: 8 PCNSL: 2 HL: 3 PTCL-NOS: 1 NK cell: 1	

[a] Bold represents p <0.05 (statistically significant).
Abbreviations. cART: combination antiretroviral therapy; IQR: interquartile range; PVL: plasma viral load; aaIPI: age-adjusted international prognostic index; DLBCL: diffuse large B-cell lymphoma; BL: Burkitt lymphoma; PCNSL: primary CNS lymphoma; HL: Hodgkin lymphoma; PBL: plasmablastic lymphoma; PTCL-NOS: peripheral T-cell lymphoma, not otherwise specified; NK cell: natural killer cell; MZL: marginal zone lymphoma; FL: follicular lymphoma; PEL: primary effusion lymphoma; CTCL: cutaneous T-cell lymphoma.

Table 3 Characteristics of people living with HIV who had diffuse large B-cell lymphoma, according to duration of combination antiretroviral therapy before lymphoma diagnosis (N = 61).

	cART use ≦ 6 months before DLBCL diagnosis (N = 42)	cART use >6 months before DLBCL diagnosis (N = 19)	P value
Sex, n (%)			1.000
Male	41 (98)	19 (100)	
Female	1 (2)	0 (0)	
Median age (years) at HIV diagnosis (IQR)	37 (31–43)	35 (25–45)	0.327
At lymphoma diagnosis			
Median age (years) (IQR)	37 (32–43)	43 (35–48)	0.290
CD4+ T cells (cells/mm^3)			
Median (IQR)	72 (33–336)	280 (142–375)	**0.026**[a]
< 200 cells/mm^3, n (%)	26 (62)	5 (26)	**0.022**[a]
PVL (log$_{10}$/mL)			
Median (IQR)	4.50 (3.16–5.33)	0 (0–2.26)	**<0.001**[a]
>10^5 copies/mm^3, n (%)	13 (31)	2 (11)	0.116
Stages, n (%)			
I and II	8 (19)	8 (42)	0.190
III and IV	34 (81)	11 (58)	
aaIPI scores, n (%)			0.781
0–1	17 (40)	9 (47)	
2–3	25 (60)	10 (53)	

[a] Bold represents p <0.05 (statistically significant).
Abbreviations. DLBCL: diffuse large B-cell lymphoma; cART: combination antiretroviral therapy; IQR: interquartile range; PVL: plasma viral load; aaIPI: age-adjusted international prognostic index.

Discussion

In this single-center retrospective analysis, we analyzed the outcomes of 104 PLWH with HIV-related lymphomas in the era of cART. The three most common lymphoma subtypes in our cohort were DLBCL, BL and PCNSL. HL was a relatively rare subtype. The distribution of subtypes in this study was in line with the findings of Hagiwara et al., who reported that DLBCL, BL and PCNSL were the most common subtypes of HIV-related lymphomas in Japan.[26] The rarity of HL is also in line with epidemiological studies of non-HIV-positive populations in Asia, where HL is much less prevalent than in Western populations.[16] The high prevalence of DLBCL and

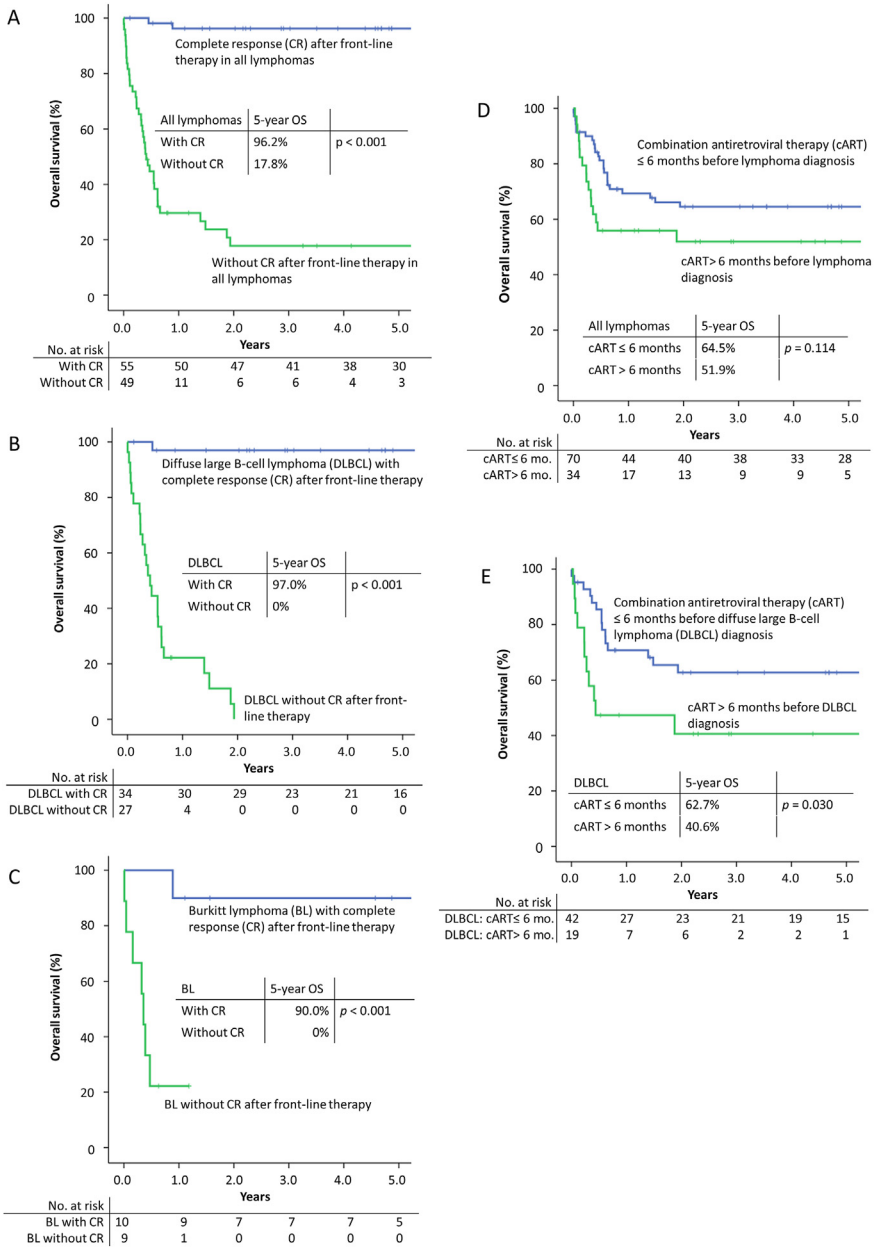


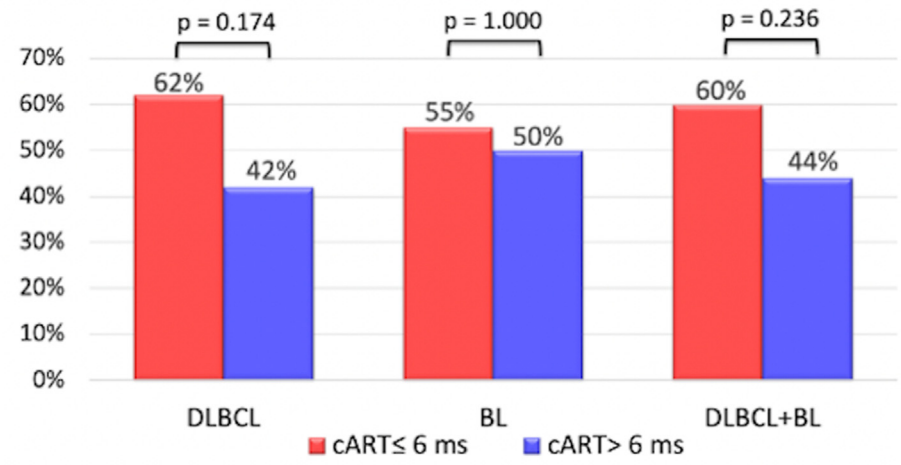
Figure 2. OS in PLWH with lymphomas, DLBCL or BL, with or without CR to front-line therapies. OS in PLWH with lymphomas or DLBCL who received combination antiretroviral therapy (cART) for $\leq$ six months versus $>$ six months before diagnosis. (A) The 5-year OS rates of PLWH with lymphomas with or without CR to front-line therapies were 96.2% and 17.8%, respectively ($p < 0.001$). (B) The 5-year OS rates of PLWH with DLBCL with or without CR to front-line therapies were 97.0% and 0%, respectively ($p < 0.001$). (C) The 5-year OS rates of PLWH with BL with or without CR to front-line therapies were 90.0% and 0%, respectively ($p < 0.001$). (D) The 5-year OS rates of PLWH with lymphomas receiving cART for $\leq$6 months and $>$6 months before lymphomas diagnosis were 64.5% and 51.9%, respectively ($p = 0.134$). (E) The 5-year OS rates of PLWH with DLBCL receiving cART for $\leq$6 months and $>$6 months before DLBCL diagnosis were 62.7% and 40.6%, respectively ($p = 0.030$).

BL in HIV-related lymphomas is compatible with reports on Western populations.[4] PLWH with BL and HL in this cohort typically had higher CD4+ T-cell counts than those with other subtypes, and those with PCNSL had generally lower CD4+ T-cell counts at lymphoma diagnosis. This finding is also similar to observations in Western populations.[4]

In this study, the 5-year OS rates of PLWH with HL, PCNSL, BL, and DLBCL were 100%, 76.2%, 57.4%, and 55.6%, respectively. These rates are generally higher than those reported in a study by Gopal et al., who found OS rates of 61.6%, 50.0%, 44.1%, and 22.8% for PLWH with HL, BL, DLBCL, and PCNSL, respectively.[4] In fact, two recent studies showed that the 2-year OS rate of PLWH with DLBCL and the 3-year OS rate for HIV-BL have improved to 75% and 66%, respectively.[9,10] Furthermore, a study conducted by Pei et al. in Taiwan showed that HIV-negative people with

A

	DLBCL (n=61) CR patients (%)	BL (n=19) CR patients (%)	DLBCL+BL (n=80) CR patients (%)
cART≤ 6 mo. before lymphoma diagnosis	26 (62%)	6 (55%)	32 (60%)
cART> 6 mo. before lymphoma diagnosis	8 (42%)	4 (50%)	12 (44%)



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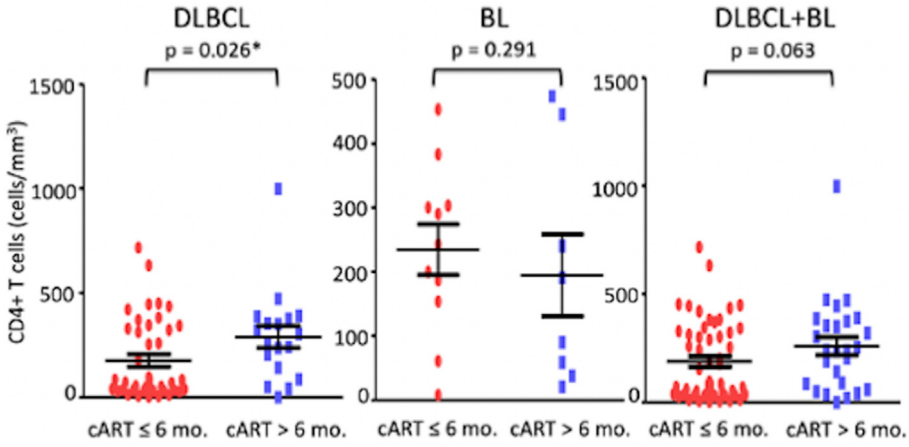

Figure 3. (A) Numbers and ratios of PLWH achieving CR after front-line therapies for DLBCL, BL, and DLBCL + BL groups. (B) Distributions of CD4+ T-cell counts at lymphoma diagnosis in DLBCL, BL and DLBCL + BL groups.

DLBCL had a 5-year OS rate of 52.7%.[27] Overall, around 60% of PLWH with DLBCL and BL appear to have been cured in this cohort, an outcome that is comparable to populations without HIV infection.

In the general population, outcomes for PCNSL are considered to be poor.[28] In this cohort, the small group of PLWH with PCNSL had a 5-year OS rate of 76.2%, which was not inferior to the OS rates of other PLWH with NHL or to people without HIV infection.[28] Epstein—Barr virus is commonly pathogenic in PLWH with PCNSL, and PCNSL tends to occur when PLWH have low CD4+ T-cell counts.[29—31] Historically, PLWH with PCNSL are expected to have a median survival of less than three months.[32] In the studies by Gupta et al. and Moulignier et al., PLWH with PCNSL receiving cART and front-line HDMTX achieved 5-year OS rates of 60% and 48%, respectively.[33,34] The OS of PLWH with PCNSL in this study was consistent with the findings of these two studies.

Barta et al. analyzed 1546 PLWH with lymphomas before and after cART in the pre- and post-rituximab eras. They reported that rituximab treatment was associated with higher CR rates as well as improved progression-free

Table 4 Univariate and multivariate analyses of prognostic factors for overall survival in people living with HIV who had diffuse large B-cell lymphoma.

Variables	Univariate analysis	*p* value	Multivariate analysis	*p* value	Multivariate analysis	*p* value
	Hazard ratio (95% Cl)		Adjusted hazard ratio (95% Cl)		Adjusted hazard ratio (95% Cl)	
CD4+ T cell count <200 cells/mm^3 at lymphoma diagnosis	1.595 (0.704–3.613)	0.263				
PVL > 10^5 copies/mm^3 at lymphoma diagnosis	1.025 (0.427–2.462)	0.957				
cART >6 months before lymphoma diagnosis	2.320 (1.060–5.077)	**0.035**[a]	3.257 (1.448–7.324)	**0.004**[a]		
aaIPI 2–3	2.985 (1.255–7.104)	**0.013**[a]	2.403 (0.898–6.433)	0.081	1.642 (0.636–4.239)	0.306
CNS involvement	3.022 (1.400–6.523)	**0.005**[a]	2.461 (1.035–5.850)	**0.042**[a]	0.573 (0.245–1.338)	0.198
Front-line rituximab	0.793 (0.355–1.772)	0.572				
CR to front-line treatments	0.010 (0.001–0.079)	**<0.001**[a]			0.009 (0.001–0.070)	**<0.001**[a]

[a] Bold represents $p < 0.05$ (statistically significant).

Abbreviations. Cl: confidential interval; PVL: plasma viral load; cART: combination antiretroviral therapy; aaIPI: age-adjusted international prognostic index; CNS: central nervous system; CR: complete response.

survival and higher OS rates.[35] In the study conducted by Schommers et al., CR to front-line therapy was associated with long-term durable survival in PLWH with lymphomas.[36] In our cohort, PLWH with DLBCL receiving front-line rituximab-based treatments had a higher CR rate than those receiving non-rituximab treatments (57% vs. 53%). The PLWH with BL receiving front-line rituximab-based treatments had even higher CR rates than those not receiving rituximab (69% vs. 17%). Achieving CR after front-line therapy was strongly associated with durable survival in PLWH with DLBCL and BL, and very few individuals had disease relapse. On the contrary, PLWH with DLBCL and BL who did not achieve CR to front-line therapies had frequent disease relapses and poor short-term survival, despite intensive salvage chemotherapy treatments. Intensifying the induction chemotherapy might be considered as a strategy to improve outcomes. On the other hand, the extremely poor salvage efficacy suggests that primary refractoriness to chemotherapy might be a crucial characteristic of the disease etiology. There may be underlying molecular differences between lymphomas in PLWH who achieve CR and those who fail to achieve CR. In-depth molecular analyses are warranted to optimize new treatment strategies.

Very low CD4+ T-cell counts at lymphoma diagnosis tended to have more treatment-related complications and worse survival, especially during rituximab use.[12,13,37] In the study conducted by Gopal et al., PLWH on cART at lymphoma diagnosis had increased mortality. For that study, the authors defined lymphoma development on cART as PLWH receiving any antiretroviral medication between 4 and 24 weeks prior to lymphoma diagnosis.[4] The authors speculated PLWH on cART at lymphoma diagnosis may not benefit from positive effects of cART on survival in addition to lymphoma treatment. In another study conducted by the Collaboration of Observational HIV Epidemiological Research Europe study group, PLWH receiving cART for longer than 90 days at lymphoma diagnosis had worse survival than those receiving cART for less than 90 days or no cART at lymphoma diagnosis.[38] Similarly, our data showed that PLWH receiving cART for longer than 6 months before diagnosis had worse OS rates than PLWH receiving shorter durations of cART, and the cART duration before lymphoma development was associated with CD4+ T-cell count distribution and treatment response to front-line therapies. These differences were also most apparent in the DLBCL subgroup. Since current supportive care can minimize the risk of fatality due to opportunistic infections, such an outcome difference might also suggest underlying molecular differences in the lymphoma cells and an interaction with immunity in PLWH.

This study has several limitations, including its retrospective design and the diversity in chemotherapy dosages, cycles, and imaging follow-up intervals, which can potentially impact the rates of CR to front-line treatments. Additionally, since the study data covered the period between 2000 and 2019, recent advances in clinical care and new drug development may have resulted in improved outcomes. Nevertheless, this study comprehensively illustrates the clinicopathological features, treatment modalities, long-term outcomes, and prognostic factors in PLWH with lymphomas, especially DLBCL. Our findings suggest that physicians should provide PLWH with lymphomas multidisciplinary care to cure them or maximize their long-term survival. Further studies should be conducted to investigate molecular prognostic factors of lymphoma and develop new treatment strategies for PLWH without CR after front-line therapies.

Ethics approval and consent to participate

The National Taiwan University Hospital Research Ethics Committee (NTUHREC) approved this retrospective study and waived the need for informed consent (NTUHREC No. 201907063RINC). The medical charts were retrospectively reviewed, and all procedures were carried out in accordance with the Declaration of Helsinki.

Availability of data and material

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Author contributions

WL Ma and WD Liu were responsible for literature collection, data management and interpretation, statistical analysis, and manuscript writing. WD Liu, HY Sun, WH Sheng, SM Hsieh, CC Hung and SJ Wu contributed to patient care and clinical data collection. SJ Wu treated patients; planned, designed, and coordinated the study throughout the study period; and wrote the manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

The authors have no conflicts of interest to declare.

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References

1. Spano JP, Costagliola D, Katlama C, Mounier N, Oksenhendler E, Khayat D. AIDS-related malignancies: state of the art and therapeutic challenges. *J Clin Oncol* 2008;**26**:4834—42.
2. Hleyhel M, Belot A, Bouvier AM, Tattevin P, Pacanowski J, Genet P, et al. Risk of AIDS-defining cancers among HIV-1-infected patients in France between 1992 and 2009: results from the FHDH-ANRS CO4 cohort. *Clin Infect Dis* 2013;**57**:1638—47.
3. Liu WD, Tsai WC, Hsu WT, Shih MC, Chen MY, Sun HY, et al. Impact of initiation of combination antiretroviral therapy according to the WHO recommendations on the survival of HIV-positive patients in Taiwan. *J Microbiol Immunol Infect* 2020;**53**:936—45.
4. Gopal S, Patel MR, Yanik EL, Cole SR, Achenbach CJ, Napravnik S, et al. Temporal trends in presentation and survival for HIV-associated lymphoma in the antiretroviral therapy era. *J Natl Cancer Inst* 2013;**105**:1221—9.
5. Guillet S, Gérard L, Meignin V, Agbalika F, Cuccini W, Denis B, et al. Classic and extracavitary primary effusion lymphoma in 51 HIV-infected patients from a single institution. *Am J Hematol* 2016;**91**:233—7.
6. Barta SK, Lee JY, Kaplan LD, Noy A, Sparano JA. Pooled analysis of AIDS malignancy consortium trials evaluating rituximab plus CHOP or infusional EPOCH chemotherapy in HIV-associated non-Hodgkin lymphoma. *Cancer* 2012;**118**:3977—83.
7. Ramos JC, Sparano JA, Rudek MA, Moore PC, Cesarman E, Reid EG, et al. Safety and preliminary efficacy of vorinostat with R-EPOCH in high-risk HIV-associated non-Hodgkin's lymphoma (AMC-075). *Clin Lymphoma Myeloma Leuk* 2018;**18**:180—90.
8. Besson C, Goubar A, Gabarre J, Rozenbaum W, Pialoux G, Châtelet FP, et al. Changes in AIDS-related lymphoma since the era of highly active antiretroviral therapy. *Blood* 2001;**98**:2339—44.
9. Besson C, Lancar R, Prevot S, Algarte-Genin M, Delobel P, Bonnet F, et al. Outcomes for HIV-associated diffuse large B-cell lymphoma in the modern combined antiretroviral therapy era. *AIDS* 2017;**31**:2493—501.
10. Alderuccio JP, Olszewski AJ, Evens AM, Collins GP, Danilov AV, Bower M, et al. HIV-associated Burkitt lymphoma: outcomes from a US-UK collaborative analysis. *Blood Adv* 2021;**5**:2852—62.
11. Shepherd L, Ryom L, Law M, Hatleberg CI, de Wit S, Monforte AD, et al. Differences in virological and immunological risk factors for non-Hodgkin and Hodgkin lymphoma. *J Natl Cancer Inst* 2018;**110**:598—607.
12. Mounier N, Spina M, Gabarre J, Raphael M, Rizzardini G, Golfier JB, et al. AIDS-related non-Hodgkin lymphoma: final analysis of 485 patients treated with risk-adapted intensive chemotherapy. *Blood* 2006;**107**:3832—40.
13. Kaplan LD, Lee JY, Ambinder RF, Sparano JA, Cesarman E, Chadburn A, et al. Rituximab does not improve clinical outcome in a randomized phase 3 trial of CHOP with or without rituximab in patients with HIV-associated non-Hodgkin lymphoma: AIDS-Malignancies Consortium Trial 010. *Blood* 2005;**106**:1538—43.
14. Yang CJ, Chen MY, Hsieh SM, Sheng WH, Sun HY, Hung CC, et al. Non-Hodgkin's lymphoma in patients with human immunodeficiency virus infection in Taiwan. *J Microbiol Immunol Infect* 2010;**43**:278—84.
15. Chuang SS, Chen SW, Chang ST, Kuo YT. Lymphoma in Taiwan: review of 1347 neoplasms from a single institution according to the 2016 revision of the world Health Organization classification. *J Formos Med Assoc* 2017;**116**:620—5.
16. Wu SJ, Chiang CJ, Lin CT, Tien HF, Lai MS. A nationwide population-based cross-sectional comparison of hematological malignancies incidences between Taiwan and the United States of America. *Ann Hematol* 2016;**95**:165—7.
17. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* 2016;**127**:2375—90.
18. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *J Clin Oncol* 2014;**32**:3059—68.
19. Ribera JM, Oriol A, Morgades M, González-Barca E, Miralles P, López-Guillermo A, et al. Safety and efficacy of cyclophosphamide, adriamycin, vincristine, prednisone and rituximab in patients with human immunodeficiency virus-associated diffuse large B-cell lymphoma: results of a phase II trial. *Br J Haematol* 2008;**140**:411—9.
20. Boué F, Gabarre J, Gisselbrecht C, Reynes J, Cheret A, Bonnet F, et al. Phase II trial of CHOP plus rituximab in patients with HIV-associated non-Hodgkin's lymphoma. *J Clin Oncol* 2006;**24**:4123. 28.
21. Little RF, Pittaluga S, Grant N, Steinberg SM, Kavlick MF, Mitsuya H, et al. Highly effective treatment of acquired immunodeficiency syndrome-related lymphoma with dose-adjusted EPOCH: impact of antiretroviral therapy suspension and tumor biology. *Blood* 2003;**101**:4653—9.

22. Cortes J, Thomas D, Rios A, Koller C, O'Brien S, Jeha S, et al. Hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone and highly active antiretroviral therapy for patients with acquired immunodeficiency syndrome-related Burkitt lymphoma/leukemia. *Cancer* 2002;**94**:1492—9.
23. Batchelor T, Carson K, O'Neill A, Grossman SA, Alavi J, New P, et al. Treatment of primary CNS lymphoma with methotrexate and deferred radiotherapy: a report of NABTT 96-07. *J Clin Oncol* 2003;**21**:1044—9.
24. Hoskin PJ, Lowry L, Horwich A, Jack A, Mead B, Hancock BW, et al. Randomized comparison of the stanford V regimen and ABVD in the treatment of advanced Hodgkin's lymphoma: United Kingdom National cancer Research Institute lymphoma group study ISRCTN 64141244. *J Clin Oncol* 2009;**27**:5390—6.
25. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Department of Health and Human Services. Available at: https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv. C10—C11.
26. Hagiwara S, Nagai H, Tanaka J, Okada S. The current state of human immunodeficiency virus-associated lymphoma in Japan: a nationwide retrospective study of the Japanese Society of Hematology Blood Disease Registry. *Int J Hematol* 2019;**110**:244—9.
27. Pei SN, Wang MC, Ma MC, Kuo CY, Liao CK, Qiu H, et al. A comprehensive retrospective cohort study of the journey of B-cell lymphoma in Taiwan. *Sci Rep* 2021;**11**:10069.
28. Ma WL, Hou HA, Hsu YJ, Chen YK, Tang JL, Tsay W, et al. Clinical outcomes of primary intraocular lymphoma patients treated with front-line systemic high-dose methotrexate and intravitreal methotrexate injection. *Ann Hematol* 2016;**95**:593—601.
29. Bashir R, McManus B, Cunningham C, Weisenburger D, Hochberg F. Detection of Eber-1 RNA in primary brain lymphomas in immunocompetent and immunocompromised patients. *J Neuro Oncol* 1994;**20**:47—53.
30. Kasamon YL, Ambinder RF. AIDS-related primary central nervous system lymphoma. *Hematol Oncol Clin North Am* 2005;**19**:665—87.
31. Singer EJ, Valdes-Sueiras M, Commins D, Levine A. Neurologic presentations of AIDS. *Neurol Clin* 2010;**28**:253—75.
32. Raez LE, Patel P, Feun L, Restrepo A, Raub Jr WA, Cassileth PA. Natural history and prognostic factors for survival in patients with acquired immune deficiency syndrome (AIDS)-related primary central nervous system lymphoma (PCNSL). *Crit Rev Oncog* 1998;**9**:199—208.
33. Gupta NK, Nolan A, Omuro A, Reid EG, Wang CC, Mannis G, et al. Long-term survival in AIDS-related primary central nervous system lymphoma. *Neuro Oncol* 2017;**19**:99—108.
34. Moulignier A, Lamirel C, Picard H, Lebrette MG, Amiel C, Hamidi M, et al. Long-term AIDS-related PCNSL outcomes with HD-MTX and combined antiretroviral therapy. *Neurology* 2017;**89**:796—804.
35. Barta SK, Xue X, Wang D, Tamari R, Lee JY, Mounier N, et al. Treatment factors affecting outcomes in HIV-associated non-Hodgkin lymphomas: a pooled analysis of 1546 patients. *Blood* 2013;**122**:3251—62.
36. Schommers P, Gillor D, Hentrich M, Wyen C, Wolf T, Oette M, et al. Incidence and risk factors for relapses in HIV-associated non-Hodgkin lymphoma as observed in the German HIV-related lymphoma cohort study. *Haematologica* 2018;**103**:857—64.
37. Sparano JA, Lee JY, Kaplan LD, Levine AM, Ramos JC, Ambinder RF, et al. Rituximab plus concurrent infusional EPOCH chemotherapy is highly effective in HIV-associated B-cell non-Hodgkin lymphoma. *Blood* 2010;**115**:3008—16.
38. Bohlius J, Schmidlin K, Costagliola D, Fätkenheuer G, May M, Caro Murillo AM, et al. Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study group, Prognosis of HIV-associated non-Hodgkin lymphoma in patients starting combination antiretroviral therapy. *AIDS* 2009;**23**:2029—37.

Appendix A. Supplementary data

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