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ORIGINAL ARTICLE

Clinical Characteristics and Prognostic Factors for Adult HIV-Negative Burkitt Lymphoma: a Single-Center Retrospective Study

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SUMMARY

Background: **We performed a retrospective cohort study to examine the clinical characteristics, prognosis factors, and survival outcomes of HIV-negative adult Burkitt's lymphoma.**
Methods: **The retrospective study was conducted on adult patients, who were diagnosed with HIV-negative Burkitt lymphoma at our center between 2014 and 2022. Univariate and multivariate Cox regression analyses were conducted to identify potential risk factors for mortality. Survival rates were estimated, using the Kaplan-Meier curve and the log-rank test.**
Results: **A total of 23 patients were identified, with male patients making up the majority (69.6%). Over half (56.5%) of the patients had bone marrow involvement, while a third (30.4%) had central nervous system involvement. More than half of the patients (13/23) were given R-hyper CVAD as their first-line therapy. The median PFS and OS were 11 and 12 months, respectively. In multivariate analysis, central CNS involvement was found to be an independent predictor of worse OS among patients with BL, with a hazard ratio of 15.53 (95% CI: 1.09 - 22.5). We also found that patients with CNS involvement were more likely to have higher LDH (p = 0.045) and ECOG scores (p = 0.002).**
Conclusions: **Our research revealed that CNS is an important predictor of OS and DFS. LDH > 3ULN levels were associated with worse PSF. This study is valuable, because it shows the characteristics of a population that is currently poorly studied and has a lower incidence in China.**
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INTRODUCTION

Burkitt lymphoma (BL) is a rare and highly aggressive B-cell lymphoma; one of the fastest-growing human malignancies [1]. Sporadic BL is a common occurrence throughout the world, with the majority of cases happening in Western Europe and the United States [2], but it occurs less frequently in China. It is more common in children and adolescents and accounts for only 1 to 2% of non-Hodgkin's lymphoma in adults [3]. Sporadic BL usually occurs in the jawbone, craniofacial bone, abdominal organs, and in the central nervous system.

Often, it appears in the form of exordial or acute leukemia [4]. The tumor comprises of single, medium-sized B cells with basophilic cytoplasmic and mitotic images. Cancer grows at a fast pace, and the disease progresses rapidly due to its short doubling time [5]. As it often progresses quickly and is prone to spreading to sites beyond the nodes, including internal abdominal organs and the central nervous system (CNS), immediate diagnostic evaluations and therapy are required.

In adult BL patients, the conventional R-CHOP chemotherapy regimen alone is not enough. Currently, short-term and intensive multi-drug chemotherapy that includes central nervous system preventive therapy is the preferred treatment option [6]. With appropriate treatment, lasting remission can be achieved in 60 - 90% of the children and young adults with BL, and many patients can even be cured. However, elderly BL patients have a poor overall survival rate. It is important to provide active and supportive treatment along with chemotherapy. For refractory or recurrent (R/R) patients, autologous hematopoietic stem cell transplantation can prolong survival, while radiotherapy has limited effect. Unfortunately, there is no specific protocol recommended for the treatment of HIV-negative BL/ALL in adults due to the lack of comparative randomized trials.

There has been limited research conducted on Burkitt lymphoma in individuals who are HIV-negative. Hence, to better understand HIV-negative Burkitt lymphoma and enhance its diagnostic and treatment protocols, this study retrospectively analyzed clinical characteristics and prognostic factors in adult HIV-negative BL patients.

MATERIALS AND METHODS

Study population

A retrospective analysis was conducted on 23 HIV-negative adult BL patients initially treated at our medical center between January 2014 and December 2022. We excluded HIV-associated Burkitt lymphoma and patients younger than 18 years. Patients with unclear pathologic diagnoses and patients with missing data were also excluded. All patients were confirmed by using World Health Organization (WHO) classification criteria of tumors of hematopoietic and lymphoid tissues, 2022 (5th edition) [7], which included pathology, morphology, immunology, cytogenetics, and molecular biology. Written informed consent was obtained from the patients before the study started.

Clinical data analysis

We collected demographic data (gender, age) of the study population, work status of the Eastern Oncology Cooperative Group (ECOG), serum LDH levels, Ann Arbor stage, extranodal involvement, bone marrow involvement, CNS involvement, and Epstein-Barr virus (EBV) infection. When lymphoma was diagnosed, white blood cell, hemoglobin, and platelet counts were measured. Serum lactate dehydrogenase (LDH) levels were standardized according to the nationally prescribed upper limit of normal (ULN).

Treatment regimens

The R-Hyper-CVAD regimen combines rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone. The R-DA (dose-adjusted) EPOCH regimen is a chemotherapy regimen that includes rituximab, etoposide, doxorubicin, vincristine, prednisone, and cyclophosphamide. The R-CHOP regimen is a combination of rituximab and four chemotherapy drugs: cyclophosphamide, doxorubicin, vincristine, and prednisone. The VICP regimen is a combination of four drugs: vinorelbine, idarubicin, cyclophosphamide, and dexamethasone. Clinicians at each site used PET-CT or whole-body CT scans to determine treatment response.

Statistical analysis

The study followed patients through hospitalization or telephone interviews to evaluate overall survival (OS) and progression-free survival (PFS). OS is defined as the time from the diagnosis of BL to the final follow-up or death from any cause. PFS is the period after BL diagnosis until disease progression, recurrence, or death from any cause. Univariate and multivariate Cox regression analyses were conducted to identify potential risk factors for mortality. Statistical analyses were performed using SPSS version 25.0. After estimating them with the Kaplan-Meier curve, survival rates were compared by using the log-rank test. Statistical significance was defined for a p-value of less than 0.05.

RESULTS

Clinical features

In this retrospective study, we collected data on 23 adult BL patients who tested negative for HIV. All patients were at the advanced stage, with male patients making up the majority (69.6%). Over half (56.5%) of the patients had bone marrow involvement, while a third (30.4%) had central nervous system involvement. Additionally, 73.9% (17/23) of the patients had extranodal involvement. We observed three times higher serum lactate dehydrogenase (LDH) levels in 26.1% (6/23) of the patients. Furthermore, 47.8% (11/23) of the patients had more than 500 copies/uL of EBV-DNA. Only one patient did not receive rituximab treatment. You can find detailed clinical characteristics in Table 1.

Treatment and response

In this study, all patients received standardized therapy. Three patients underwent hematopoietic stem cell transplantation, while only one received cART. Thirteen patients underwent R-hyper CVAD, five received R-CHOP, four were treated with RDA-EPOCH, and one was given VICP. Out of those treated, 52.17% (12/23)

Table 1. Clinical characteristics of Burkitt lymphoma in adults at baseline (n = 23).

Characteristics	n (%)
Gender	
Male	16 (69.6)
Female	7 (30.4)
Age	
< 40	9 (39.1)
≥ 40	14 (60.9)
Primary site	
Nodal	6 (26.1)
Extra-nodal	17 (73.9)
Ann Arbor stage	
III	10 (43.5)
IV	13 (56.5)
ECOG PS	
0 - 1	15 (65.2)
≥ 2	8 (34.8)
BM involvement	
No	10 (43.5)
Yes	13 (56.5)
CNS involvement	
No	16 (69.6)
Yes	7 (30.4)
EBV DNA	
< 500	12 (52.2)
≥ 500	11 (47.8)
First-line treatment	
R-hyper CVAD	13 (56.5)
R-CHOP	5 (21.7)
RDA-EPOCH	4 (17.4)
VICP	1 (4.3)
Rituximab	
With	22 (95.6)
Without	1 (4.4)
LDH level	
≤ 3 × ULN	17 (73.9)
> 3 × ULN	6 (26.1)
Hemoglobin, mean ± SD	107.9 ± 30.9
WBC, median (IQR)	5.5 (4.2, 7.7)
PLT, median (IQR)	206.0 (103.0, 351.0)

ECOG PS - Eastern Cooperative Oncology Group performance status, BM - bone marrow, CNS - central nervous system, LDH - lactate dehydrogenase, ULN - upper limit of normal, R-Hyper-CVAD - rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, R-CHOP - rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, R-DAEPOCH - rituximab, etoposide, doxorubicin, vincristine, prednisone, and cyclophosphamide, VICP - vinorelbine, idarubicin, cyclophosphamide, and dexamethasone, WBC - white blood cell, PLT - platelet.

Table 2. Risk factors for survival of patients with Burkitt lymphoma.

	Overall survival				Progression-free survival			
Variables	**Univariate**	**Multivariate**			**Univariate**	**Multivariate**		
	p-value	**HR**	**95%**	**p-value ***	**p-value**	**HR**	**95%**	**p-value ***
Male	**0.123**				**0.137**			
Age > 40	**0.391**				**0.473**			
Ann Arbor stage IV	**0.045**				**0.037**			
Primary site	**0.826**				**0.704**			
ECOG > 1	**0.99**				**0.003**			
BM involvement	**0.397**				**0.085**			
CNS involvement	**0.004**	**15.53**	**1.09 - 22.5**	**0.043**	**0.002**	**10.04**	**1.6 - 63.5**	**0.014**
Evaluated LDH	**0.63**				**0.463**			
LDH > 3ULN	**0.13**	**9.22**	**0.97 - 87.63**	**0.053**	**0.021**	**6.83**	**1.41 - 33.13**	**0.017**
EBV DNA > 500	**0.616**				**0.714**			
Marrow transplantation	**0.999**				**0.332**			
CART	**0.274**				**0.585**			
First-line treatment	**0.812**				**0.851**			
R-Hyper CVAD								
RCHOP								
R-DA-EPOCH								

received more than four cycles of chemotherapy. At the last follow-up, 6 out of the 23 patients (26.1%) had passed away following treatment, while 17 patients (73.9%) were still alive.

Twenty patients were given central nervous system prophylaxis through intrathecal administration of cytarabine (50 mg), DXM (5 mg), and methotrexate (12.5 mg). One patient with central nervous system tumor involvement had a poor response to treatment and died two months later. Furthermore, eight patients underwent disease progression.

Survival and prognostic factors

The median PFS and OS for patients with BL were 11 and 12 months, respectively. Univariate analysis showed that Ann Arbor stage IV ($p = 0.045$) and CNS involvement ($p = 0.004$) were associated with shorter OS. Univariate analysis revealed that several factors were associated with shorter PFS, including Ann Arbor stage IV ($p = 0.037$), ECOG PS 2 to 4 ($p = 0.003$), CNS involvement ($p = 0.002$), and LDH > 3 × ULN ($p = 0.021$). In multivariate analysis, only CNS involvement was found to be an independent predictor of worse OS among patients with BL, with a hazard ratio of 15.53 (95% CI: 1.09 - 22.5). Besides, CNS involvement (HR = 10.04; 95% CI, 1.6 - 63.5) and LDH levels greater than three times the ULN (HR = 6.83; 95% CI, 1.41 - 33.13) were found to be independent prognostic factors of DFS (Table 2). Both univariate and multivariate analyses indicated a significant association between LDH levels greater than three times the ULN, CNS involvement, and survival.

Patients with CNS involvement had a better OS than those without (Figure 1A, $p = 0.00044$). Also, a significant distinction was discovered between CNS involvement and PFS (Figure 1B, $p = 0.00046$). When analyzing the link between 3 × ULN and clinical outcomes, it was observed that patients with higher than 3 × ULN had worse PFS (Figure 1D, $p = 0.011$). At the same time, no statistical difference was calculated among 3 × ULN and OS (Figure 1D, $p = 0.1$).

CNS involvement

During the follow-up period, seven patients were identified to have CNS involvement, and four of them died. Subsequently, we analyzed the clinical characteristics of patients with CNS involvement. We found that patients with CNS involvement were more likely to have higher LDH ($p = 0.045$) and higher ECOG scores ($p = 0.002$). The clinical characteristics of patients with CNS involvement were compared to those without. Table 3 provides a detailed comparison of the two subgroups.

Table 3. Clinical features of adult patients with HIV-negative Burkitt lymphoma with or without central nervous system involvement.

Features	Without CNS-involvement n = 16	With CNS-involvement n = 7	p-value
Gender			
Female	4 (25)	3 (42.9)	0.626
Male	12 (75)	4 (57.1)	
Age			
< 40	5 (31.2)	4 (57.1)	0.363
≥ 40	11 (68.8)	3 (42.9)	
Primary site			
Nodal	4 (25)	2 (28.6)	1
Extra-nodal	12 (75)	5 (71.4)	
Ann Arbor stage			
III	9 (56.2)	1 (14.3)	0.089
IV	7 (43.8)	6 (85.7)	
ECOG PS			
0 - 1	14 (87.5)	1 (14.3)	0.002
≥ 2	2 (12.5)	6 (85.7)	
BM involvement			
No	7 (43.8)	3 (42.9)	1
Yes	9 (56.2)	4 (57.1)	
EBV DNA			
< 500	8 (50)	4 (57.1)	1
≥ 500	8 (50)	3 (42.9)	
First-line treatment			
VICP	1 (6.2)	0 (0)	0.778
R-Hyper CVAD	9 (56.2)	4 (57.1)	
RCHOP	4 (25)	1 (14.3)	
R-DA-EPOCH	2 (12.5)	2 (28.6)	
Elevated LDH			
No	6 (37.5)	2 (28.6)	1
Yes	10 (62.5)	5 (71.4)	
3 × ULN			
No	14 (87.5)	3 (42.9)	0.045
Yes	2 (12.5)	4 (57.1)	

DISCUSSION

Our research is a real-world study of the clinical characteristics and prognosis of HIV-negative Burkitt lymphoma in adults from a single center in China. The study analyzed the clinical characteristics of 23 cases of HIV-negative BL, the outcomes of specific treatment regimens, and the factors that affect the prognosis of BL patients. In our study, CNS involvement emerged as the most significant predictor of OS and DFS.

In adults, sporadic BL rarely occurs [8]. Sporadic Burkitt lymphoma is also more common in men, with more than twice the incidence than in women [8,9], which is consistent with our results. Previous research indicated that EBV infection is typically less common in endemic Burkitt's lymphoma cases, with a detection rate of 20% to 30% [10]. In the present study, we found 47.8% (11/23) EBV DNA ≥ 500 copies/uL. BL frequently affects extranodal areas, particularly the central nervous system (CNS) and bone marrow. In a recent retrospect-

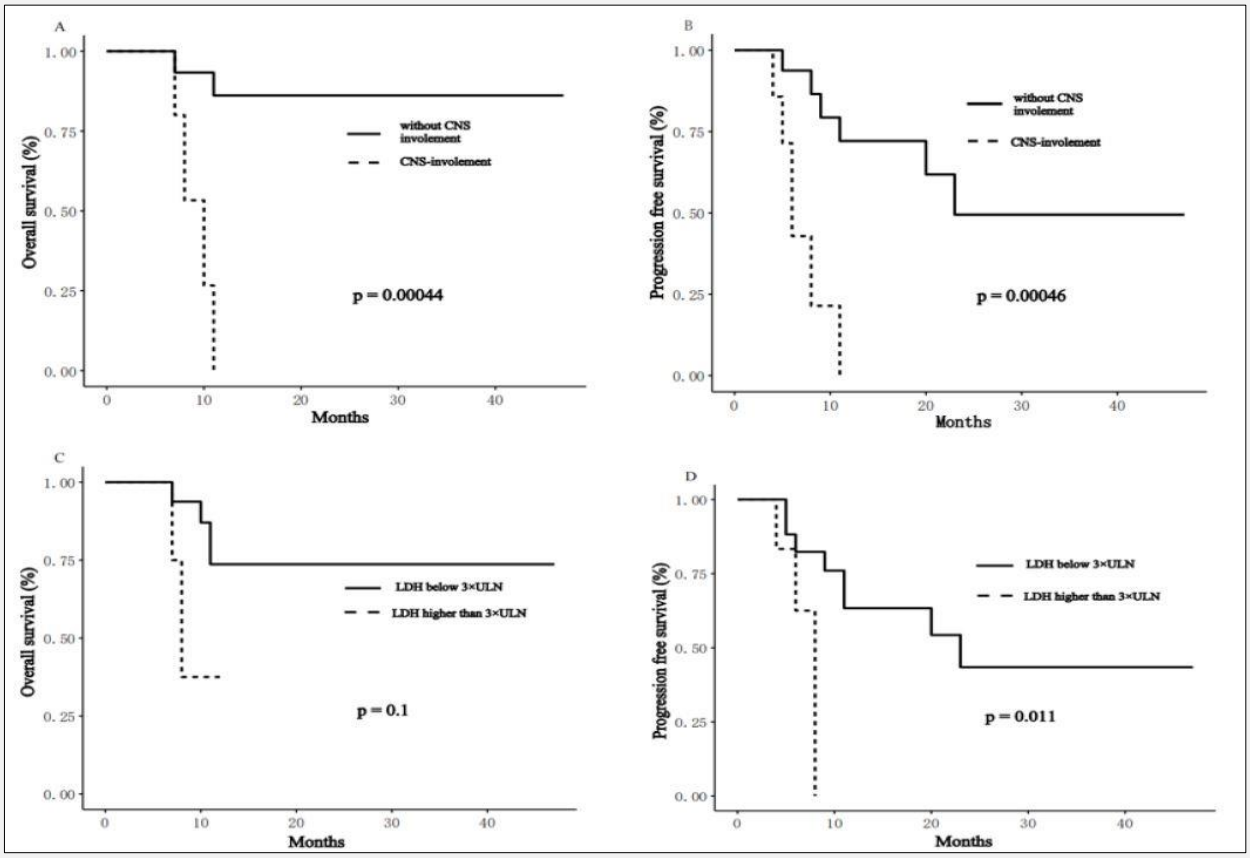

Figure 1. The prognosis of patients with HIV-negative Burkitt lymphoma in adults.

The overall survival (A) and progression-free survival (B) of central nervous system involvement. The overall survival (C) and progression-free survival (D) of patients with LDH higher than 3 x ULN. ULN, upper limit of normal.

tive study of US adults with BL, 19% of the patients experienced CNS involvement before diagnosis [11]. In addition, before introducing intensive treatment regimens with central nervous system prophylaxis, 30% to 50% of the patients with Burkitt lymphoma relapsed in the central nervous system [12]. Seven patients in our study experienced central nervous system recurrence, and five of them received prophylactic intrathecal chemotherapy in tandem with a high dose of methotrexate or cytarabine.

Rituximab has been widely used in BL regimens due to the improvement in outcomes with its use in aggressive lymphoma. Regarding historical controls, the inclusion of rituximab has been shown to improve outcomes of CODOX-M/IVAC and hyper-CVAD regimens [13,14]. As demonstrated by a meta-analysis of 646 patients, the use of rituximab improved overall survival even though the difference was not significant in most clinical trials [15]. Additionally, a retrospective analysis of 30 centers in the USA found no significant difference in outcomes between the most frequently used regimens, which were CODOX-M/IVAC, hyper-CVAD, and R-EPOCH [11]. Other retrospective studies have shown no significant differences in overall PFS or OS between the first-line regimen used in BL [16,17]. Only one patient in our study did not receive rituximab, and there was no substantial difference in OS or DFS between the four treatment regimens. The effectiveness of existing treatment options is limited for patients, and we need more clinical trials to explore more suitable treatment strategies. Several studies have found that CNS involvement is an unfavorable prognostic factor in BL [11,18]. In the recent multi-center study from Western China, patients with CNS involvement showed poorer OS and DFS, although the sample size of this study was small [19]. Several studies indicate that the low survival rate following central nervous system recurrence is consistent with the poor overall prognosis of recurrent BL [20-23].

In our study, patients with central nervous system involvement had higher ECOG scores and a greater likelihood of LDH levels that were three times higher than normal compared to those without involvement. We found that CNS infiltration was an independent indicator of survival in patients with BL in univariate and multivariate analyses. One of the important research goals for the future is to find more suitable strategies for treating CNS involvement.

Elevated serum LDH has been considered a poor prognostic indicator for hematological and solid malignancies for an extended period. LDH is a component of the BL International Prognostic Index (BL-IPI) scoring system [24]. A retrospective study indicated that serum LDH could serve as a reliable indicator of patient tumor burden in high-grade aggressive B-cell lymphomas [25]. Similarly, the correlation between LDH biomarkers that exceed the upper limit of normal value and DFS was also observed in our study. LDH is closely associated with tumor invasion and burden due to rapid growth and hypoxia in the microenvironment.

We recognize that the current study has certain shortcomings. To begin with, this is a retrospective study conducted at a single center. Second, the small sample size caused a lower statistical power due to the rarity of the disease. Finally, the limited follow-up period prevented the observation of outcomes in all patients. Although it has shortcomings, this study is valuable because it reveals the characteristics of a population that currently needs to be better studied and has a lower incidence. The results of this study need to be validated in a larger patient population.

CONCLUSION

According to this study, CNS involvement is associated with OS and DFS in the case of HIV-negative adult BL patients. Clinical trials for adult patients with BL have been challenging due to its rare and aggressive nature.

Declaration of Interest:

The authors state that there are no conflicts of interest.

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