

# Immunophenotypic Analysis of AIDS-Related Diffuse Large B-Cell Lymphoma and Clinical Implications in Patients

**qiying li**

chongqing university cancer hospital

**wenjun zhang**

chongqing university cancer hospital

**yang shi**

chongqing university cancer hospital

**zhenqi kong**

chongqing university cancer hospital

**dehong huang**

chongqing university cancer hospital

**bingling guo**

chongqing university cancer hospital

**chunyan xiao**

chongqing university cancer hospital

**ying xiang** (✉ [xiangying0331@sina.com](mailto:xiangying0331@sina.com))

Chongqing University Cancer Hospital <https://orcid.org/0000-0002-3500-6539>

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## Research Article

**Keywords:** DLBCL, AIDS, BCL-2

**DOI:** <https://doi.org/10.21203/rs.3.rs-315653/v1>

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# Abstract

Diffuse large B-cell lymphoma (DLBCL) represents a clinically heterogeneous disease. Models based on immunohistochemistry predict clinical outcomes. However, whether these immunophenotypes could be applied as a predictive indicator in AIDS-Related DLBCL remains unclear. To explore predictive immunophenotypes and their clinical implications in AIDS-related DLBCL, we analyzed patient samples treated 2008–2019 with R-CHOP/CHOP-like and central nervous system (CNS) prevention treatment for DLBCL with HIV infection in Chongqing cancer hospital. c-MYC, CD4 count, and co-expression of BCL-2 and c-MYC presented the potential of being predictive markers in the prognosis of AIDS-related DLBCL, while absolute lymphocyte count did not show any effects in clinical outcomes. Surprisingly, we found that BCL-2 and the germinal center b-cell (GCB) subtype also could predict the prognosis of AIDS-related DLBCL, which against previous studies. Thus, the specific mechanism of BCL-2 and GCB subtype in AIDS-related DLBCL still requires to be explored.

## Introduction

Diffuse Large B-cell lymphoma (DLBCL) is one of the most common types of non-Hodgkin lymphoma (NHL), making up 30 to 40 percent of all lymphoma(1). According to the survey, the incidence rate of DLBCL in western countries accounts for 20% ~ 30% of NHL, while in Asian countries, the incidence rate is even higher, up to about 40% (2). At present, cell origin analysis based on immunohistochemistry is widely used in clinical practice. CD10, Bcl-6, and MUM1 can be easily detected by immunohistochemistry (Hans) for regional diffuse large B-cell lymphoma of origin in the germinal center. DLBCL typical immunophenotypes: CD20+, CD45+, CD13-; GCB subtype – DLBCL: CD10 + or CD10- BCL6 + and MUM1-. In some patients, LDH and  $\beta$ 2-MG were significantly increased before treatment, and the remission serum LDH and  $\beta$ 2-MG were significantly decreased after treatment, suggesting that LDH and  $\beta$ 2-MG levels can be used as auxiliary indicators for the prognosis and efficacy judgment of NHL. The degree of malignancy, systemic symptoms, clinical-stage, serum LDH level, age, extravascular infiltration, and performance status (PS) were all factors influencing the prognosis (3).

In recent years, epidemiological data show that AIDS-related lymphoma has gradually replaced Kaposi's sarcoma as the most common AIDS-related malignant tumor, and 90% of the pathological types of the former are diffuse large B-cell lymphoma. Compared with non-HIV-infected lymphoma patients, the treatment of HIV/AIDS-DLBCL is faced with increased chemotherapy-related risks caused by severe immunosuppression, leading to the termination of chemotherapy and even the death of the patients. At present, chemotherapy + highly active antiretroviral therapy (HAART) has become the standard regimen for the treatment of AIDS lymphoma. The mechanism is that CD4 + cell count of patients receiving HAART can recover quickly after the end of chemotherapy, making sufficient and standardized chemotherapy possible. Commonly used immunohistochemical markers may not be clinically relevant for HIV-infected DLBCL patients with current treatment strategies for lymphoma and HIV infection control. The only predictive immunohistochemical marker was ki-67, in which a higher proliferation index was associated with better survival, suggesting that patients with a higher proliferation rate of tumor had

a better response to treatment. In the era of HAART, the increase of CD4 + T lymphocytes in patients reduces the impact of AIDS-related opportunistic infections on prognosis, enabling most NHL patients to receive standardized chemotherapy. Studies have shown that starting HAART early can reduce cancer risk by 64 percent. The benefits of HAART not only inhibit HIV (4) but also may inhibit cancer-causing virus infection and reduce inflammation through other mechanisms. At the same time, in B-cell-derived NHL, CHOP - based regimen can be used as a first-line chemotherapy regimen. Studies have shown that CD20 monoclonal antibody (rituximab) combined with CHOP regimen and HAART treatment can improve the remission rate and survival rate of AIDS-related DLBCL. The survival rate is close to that of HIV-negative lymphoma patients, with a 1-year survival rate of 66% and a 5-year survival rate of 55% (5).

We aimed to examine any different molecular pathogenic mechanisms of DLBCL in HIV-infected and uninfected patients diagnosed and treated in the HAART era. To further assess the value of BCL-2 and c-MYC expression profiles on the short-term prognosis and long-term prognosis of AIDS-related DLBCL, respectively.

## **Materials And Methods**

### **Study design, population, and setting**

We included HIV-infected DLBCL patients (n = 27) and matched HIV-uninfected DLBCL patients (n = 27) who were admitted to Chongqing Cancer Hospital between 2008 and 2019. All patients were treated with R-CHOP/CHOP-like and CNS prevention treatment. The diagnosis of DLBCL and HIV status is based on the previous medical history of the patients and the admission examination. All HIV-infected adult patients ( $\geq 18$  years) diagnosed with DLBCL were eligible to participate in the study. Because tumor biology may vary by age and, in HIV-infected patients, DLBCL is often diagnosed at a younger age, to ensure comparability between HIV-uninfected DLBCL patients and HIV-infected DLBCL patients, we matched subjects 1:1 by age group (i.e., < 40 years, 40–60 years, and > 60 years) and gender.

This study was approved by local Ethics Committee.

### **Pathology review and tissue microarray construction**

The study pathologists (QY. Li and WJ. Xiang) reviewed hematoxylin and eosin (H&E)-stained slides to confirm the DLBCL diagnosis and identify representative tumor blocks for tissue microarray (TMA) construction. Three 1.2 mm cores from different areas of the donor block were obtained from each patient and inserted in a grid pattern into a recipient paraffin block using a tissue arrayer (Beecher Instruments).

### **Immunohistochemistry**

3–4  $\mu\text{m}$  thick sections were placed on slides covered with poly-L-lysine out of the blocks of cHL-diagnosed formalin-fixed paraffin-embedded biopsy samples for immunohistochemical studies. The standard protocol was applied by the Benchmark GX IHC/ISH (Ventana) automatic staining device for the

anticors of c-Myc (clone Y69, Ventana) and Bcl-2 (clone 2/100/05, Novocastra). For BCL-2 cytoplasmic staining, a 30% cutoff was selected according to Hans et al. (6) and their algorithm was used to define the germinal center B-cell-like (GCB) versus non-GCB phenotype. For c-Myc staining, a cutoff value of 40% was chosen.

## Outcome measures

Two-year mortality was selected as the primary outcome (long-term prognosis) because most deaths in HIV-infected patients (48% in our study) occur within two years of DLBCL diagnosis. Mortality was ascertained for all subjects through regular follow-up visits and telephone follow-up. As such, there was no loss-to-follow-up for the mortality outcome. Response after 6 cycles of chemotherapy was selected as a secondary outcome (short-term prognosis). A complete response (CR) was defined as the complete disappearance of all clinically detectable diseases. A partial response (PR) was defined as a > 50% decrease in tumor size without an increase in the size of any other known lesion or the appearance of a new lesion. The product of the maximum diameter and the length perpendicular to the maximum diameter were used to determine tumor size. Static disease (SD) was defined as the absence of any significant change in measurable lesions. Progressive disease (PD) was defined as the appearance of a new lesion or a > 25% increase in tumor size. The standard International Prognostic Index (IPI) was calculated based on age, clinical stage, extranodal involvement, serum lactose dehydrogenase (LDH), and Eastern Cooperative Oncology Group (ECOG) performance status (Supplemental Table 1). Stage at diagnosis and extranodal involvement were collected from hospital cancer registries. Absolute Lymphocyte Count (ALC) and CD4 cell counts were obtained from hospital laboratory databases. Among HIV-infected DLBCL patients, we also collected HIV disease factors from hospital HIV registries, including prior AIDS diagnosis, use of ART, and duration of known HIV infection. Information on the receipt of chemotherapy was collected from hospital cancer registries.

## Statistical analysis

The demographic and DLBCL characteristics were compared between patients who were HIV infected versus uninfected. Tumor marker expression was also considered as "positive" or "negative" based on previously published cutoff values for each marker, and compared using the Fisher exact test. Because of the small sample size in the analytical subcohort, P-value < 0.10 was used as the cutoff for statistical significance in this study.

For markers differentially expressed due to HIV status, the relationship between short-term prognosis and long-term prognosis and the expression of these markers was further investigated in hiv-infected patients. Bonferroni method was used to adjust for multiple comparisons. Kaplan–Meier survival curves for each of these markers were generated. All analyses were performed with SPSS Version 27.0 (P < 0.05 was statistically significant).

## Results

## Patient characteristics

The characteristics of the 27 HIV-infected and the 27 matched HIV-uninfected DLBCL patients are presented in Supplemental Table 2. The mean age at DLBCL diagnosis was similar by HIV status (48 years) due to matching and the majority of the patients were male (> 90%). HIV-infected patients had a mean CD4 cell count of 225.9 cells/mm<sup>3</sup> at DLBCL diagnosis while HIV-uninfected patients were 227.8 cells/mm<sup>3</sup> at DLBCL diagnosis. Among the HIV-infected DLBCL patients, a total of 8 deaths (29.6%) occurred during the 1-year follow-up. In contrast, only 2 (7.4%) deaths occurred in the 1 year among the 27 matched HIV-uninfected DLBCL patients.

## GC subtype of AIDS-Related DLBCL predicts a better prognosis

In this study, eighteen cases (67%) were subclassified as GCB DLBCL and 9 cases (33%) were classified as non-GCB DLBCL. This contrasts with the inverse proportion reported in the HIV-negative setting using this classification: 41% for GCB DLBCL and 60% for non-GCB DLBCL.

Overall survival is time to death regardless of cause. Two phenotypes of AIDS-Related DLBCL presented a similar one-year survival (Table 1). However, GCB-DLBCL showed a prolonged median survival and higher complete response (CR) (Table 1). Additionally, cumulative survival at 10 years of follow-up by phenotype also revealed a better prognosis of GCB-DLBCL (Fig. 1), which suggested prognostic prediction of AIDS-Related DLBCL based on GCB and non-GCB phenotypes is feasible.

## BCL-2 expression, c-MYC expression, and their co-expression showed potential as predictive indicators in AIDS-related DLBCL

Previous study has already proven that higher expression level of c-MYC predicts a poorer prognosis of AIDS-related DLBCL, while BCL-2 expression level does not affect prognosis of this disease. Surprisingly, overexpression of BCL-2 was associated with better outcomes in our study, which contradicts previous conclusions(7, 8). Comparing BCL-2 expression level in HIV-uninfected DLBCL (70%), only one-fourth of AIDS-related DLBCL is BCL-2 positive. Meanwhile, BCL-2 expression level is higher in GCB subtype of AIDS-related DLBCL, which might take responsibility for the favorable clinical outcomes of GCB DLBCL (Table 2).

Recent researches indicated that co-expression of c-MYC and BCL-2 is considering as a predictive biomarker for outcomes of patients with DLBCL. To demonstrate whether it could be used as a prognosis-related factor in HIV-infected DLBCL, we explored the expression of c-MYC/BCL-2 and clinical outcomes in the cohorts of patients with HIV-infected DLBCL (Table 2). Comparing with patients with c-MYC (-)/BCL-2 (-) and c-MYC (-)/BCL-2 (+), c-MYC (+)/BCL-2 (+) did present a poor prognosis. However, the group that presented the worst outcomes turned out to be patients with c-MYC (+)/BCL-2 (-) (Fig. 2).

Considering the result mentioned above that higher expression of BCL-2 is related to a better prognosis, this result seemed to be acceptable. Thus, co-expression of c-MYC and BCL-2 has the potential as a predictor for the prognosis of AIDS-Related DLBCL.

On the other hand, all cases of c-MYC (+)/BCL-2 (+) are GCB DLBCL in a cohort of HIV-infected DLBCL, which might explain the better prognosis of GCB DLBCL. Although the limited sample size is not statistically significant, it still demonstrated that this phenotype might be AIDS-related DLBCL specific.

## High CD4 count Predicts a Better Clinical Outcome in AIDS-Related DLBCL

According to CD4 count, we stratified the cases into three different categories: high amount (CD4 count > 200), intermediate (100 < CD4 count < 200), and low (CD4 count < 100)(9). No significant difference was found among the three groups whether with long-term clinical outcome or short-term clinical outcome (Table 3); however, there was a significant difference in overall survival among the three groups (P = 0.026, Fig. 3). One-year survival rate for high CD4 was 75%, for intermediate was 43% and for low was 50%.

Table 3  
Clinical outcomes of two phenotypes for HIV-infected patients

Phenotype	Median Survival (month)	One-Year Survival	CR <sup>a</sup>	PR <sup>a</sup>	PD <sup>a</sup>
GCB DLBCL <sup>b</sup> (n = 18)	25.1	0.67 (0.41–0.87)	11	5	2
Non-GCB DLBCL (n = 9)	11.3	0.56 (0.30–0.93)	2	5	2
P			0.076		
a. CR: complete response; PR: partial response; PD: progressive disease;					
b. GCB DLBCL: Germinal center b-cell Diffuse large lymphoma					

## Low absolute lymphocyte count Does Not Predict Worse Clinical Outcome

Previously, the low absolute lymphocyte count of non-AIDS DLBCL patients has already been approved to be an important prognostic factor associated with poorer survival and a higher risk of relapse in several settings (10). However, there was no difference in both long-term and short-term clinical outcomes between normal ALC ( $\geq 1$ ) (11) and low ALC (< 1) (Table 4). No difference in overall survival was found

between ALC ( $\geq 1$ ) and low ALC ( $< 1$ ) cases ( $P = 0.344$ , Fig. 4). One-year survival rate for normal ALC ( $\geq 1$ ) was 67% and for ALC ( $< 1$ ) was 60%.

Table 4  
Clinical outcomes of HIV-infected DLBCL

Bcl-2	c-MYC	GCB <sup>a</sup>	Non-GCB	One-Year Survival	Median Survival (months)	CR <sup>b</sup>	PR	PD
Positive	Positive	4	0	50%	5.9	50%	0	50%
Positive	Negative	1	2	100%	26.1	100%	0	0
Negative	Positive	4	2	33%	11.3	17%	50%	33%
Negative	Negative	9	5	71%	14.5	50%	50%	0
a. GCB: germinal center B-cell-like lymphoma;								
b. CR: complete response; PR: partial response; PD: progressive disease								

Table 5  
Clinical outcome by CD4 count for HIV-infected patients

CD4 count	Median Survival (months)	One-Year Survival	CR <sup>a</sup>	PR	PD
High amount (n = 16)	25.1	0.75	56.3%	31.2%	12.5%
Intermediate amount (n = 7)	9.7	0.43	42.8%	42.8%	14.4%
Low amount (n = 4)	8.6	0.50	25%	50%	25%
P			0.570		
a. CR: complete response; PR: partial response; PD: progressive disease					

Table 6  
Clinical outcome by absolute lymphocyte count for HIV-infected patients

Absolute Lymphocyte Count	Median Survival (months)	One-Year Survival	CR <sup>a</sup>	PR	PD
$\geq 1$ (n = 12)	20.7	0.67	50%	50%	
$< 1$ (n = 15)	13.3	0.60	46.8%	26.6%	26.6%
P			0.450		
a. CR: complete response; PR: partial response; PD: progressive disease					
Abbreviations: GC = Germinal center; Non-GC = Non-germinal center					

## Discussion

The distinct clinical features and aggressive behavior of AIDS-related DLBCL beg the question of whether the prognostic indicators applicable to DLBCL could continue to be used in AIDS-related DLBCL patients. This knowledge is critical to improving outcomes of HIV-infected patients with DLBCL. Previous researches demonstrated that some frequent prognostic indicators of DLBCL, for instance, BCL-2, cannot be directly applied to AIDS-related DLBCL.

Currently, the prognostic implication of GCB and non-GCB subtypes of DLBCL remains inconclusive, and it has been reported that GCB and non-GCB subtypes of AIDS-related DLBCL would not affect clinical outcomes(12). However, our results indicated GCB subtype of AIDS-Related DLBCL is related to a better prognosis. Considering the high frequency of GCB subtype in AIDS-Related DLBCL, if this conclusion could be confirmed, it would have significant prognostic value. Furthermore, as expression of CD10p, MUM1 and BCL6 are common parameters for determination of GCB subtype, it is worth exploring their implication in AIDS-related DLBCL again.

Meanwhile, BCL-2 is shown to be a favorable prognostic indicator in AIDS-related DLBCL. It has been proven that a higher expression level of BCL-2 predicts a poor prognosis in non-AIDS DLBCL(13). Considering the anti-apoptosis function, BCL-2 should show a similar role in AIDS-related DLBCL. However, whether other mechanisms that would affect BCL-2 function are involved in AIDS-related DLBCL remains undetected. Because of the limited patient numbers, whether this conclusion is true still requires future verification. Instead, c-MYC is determined to be another effective prognosis biomarker in AIDS-related DLBCL. Also, co-expression of BCL-2 and c-MYC presents the potential to be a predictive biomarker in patients with AIDS-related DLBCL. However, clinical outcomes of patients with BCL-2(-)/c-MYC (+) and BCL-2(-)/c-MYC (-) suggests that c-MYC may play a more vital role than BCL-2.

According to previous research, the immunosuppressive effect of R-CHOP, which is the first-line treatment of DLBCL, in newly diagnosed cases of lymphoma tends to persist for > 2 years, having an impact on CD4 count decreasing(14). That would be an attack on patients with AIDS, for their precarious immune system. Thus, whether the AIDS-related DLBCL patients with low CD4 are good for chemotherapy should be discussed. In our study, we did not find that the low CD4 group was associated with poor clinical outcomes, suggesting that AIDS-related DLBCL should be treated with chemotherapy with or without a low CD4 count.

A potential limitation of this study was the limited sample size for certain subgroup comparisons. This may explain the lack of statistical significance of low absolute lymphocyte count and high absolute lymphocyte count in AIDS-related DLBCL patients, which in contrast with recent researches(15–17).

## Conclusion

These data indicate that with current treatment strategies for lymphoma and control of HIV infection, some immunohistochemical markers may not be clinically relevant in patients with AIDS-related DLBCL.

All of BCL-2, c-MYC, co-expression of c-MYC and BCL-2, and GCB subtype show the potential to immunohistochemical marker in prognosis of patients with AIDS-related DLBCL. However, specific mechanisms of BCL-2 and GCB subtype still require to be investigated. Besides, future studies should examine the relevance of gene rearrangement and co-expression of c-MYC and BCL-2 in HIV-infected DLBCL, which may further inform patient risk stratification and treatment.

## **Declarations**

### **Authors' contributions**

Y.X provided the originating concept, oversaw data collection, and performed the analysis. ZQ.K was responsible for patient care and assisted with study implementation in the field. DH.H participated in the study design. BL.G and CY.X participated in study design, literature review, data interpretation. QY.L was responsible for study design and writing. WJ.Z and Y.S participated in the writing of the article. All authors made important intellectual contributions to the work and have agreed on the final draft for submission.

### **Funding**

Sponsored by Natural Science Foundation of Chongqing, China (cstc2019jcyj-msxmX079)

### **Availability of data and material**

Data and material will be available upon request to the corresponding author.

### **Ethics approval and consent to participate**

The study was approved by the Chongqing University Cancer Hospital. The approved study was registered. Each participant's guardian will be provided with information regarding the study. Written informed consent will be obtained from each participant's guardian. The privacy of all participants will be protected. Personal medical records will be reviewed by investigators, who will promise to keep the content confidential. It will be performed in accordance with the standards of the International Committee on Harmonization on Good Clinical Practice and the revised version of the Declaration of Helsinki principles.

### **Consent for publication**

The participants' guardians provided written informed consent for the publication of their data and associated images.

### **Competing interests**

The authors declare that they have no competing interests.

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## Figures

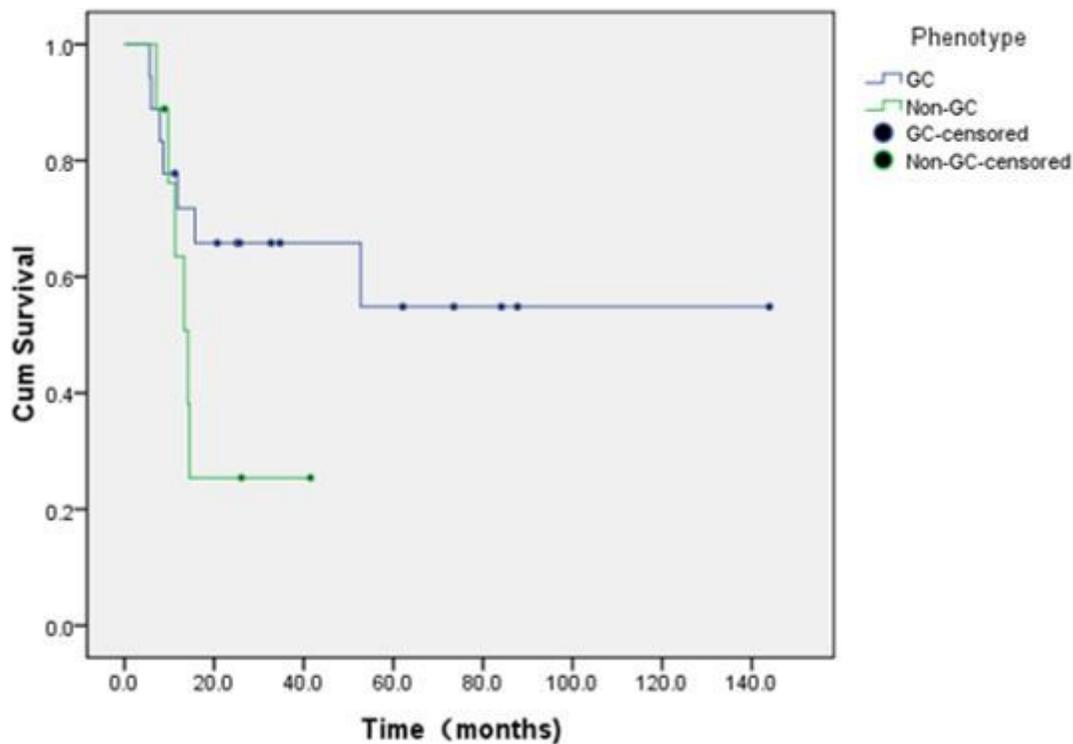


Figure 1

Kaplan-Meier plots showing cumulative survival at 10 years of follow-up by phenotype. Abbreviations: GC=Germinal center; Non-GC=Non-germinal center

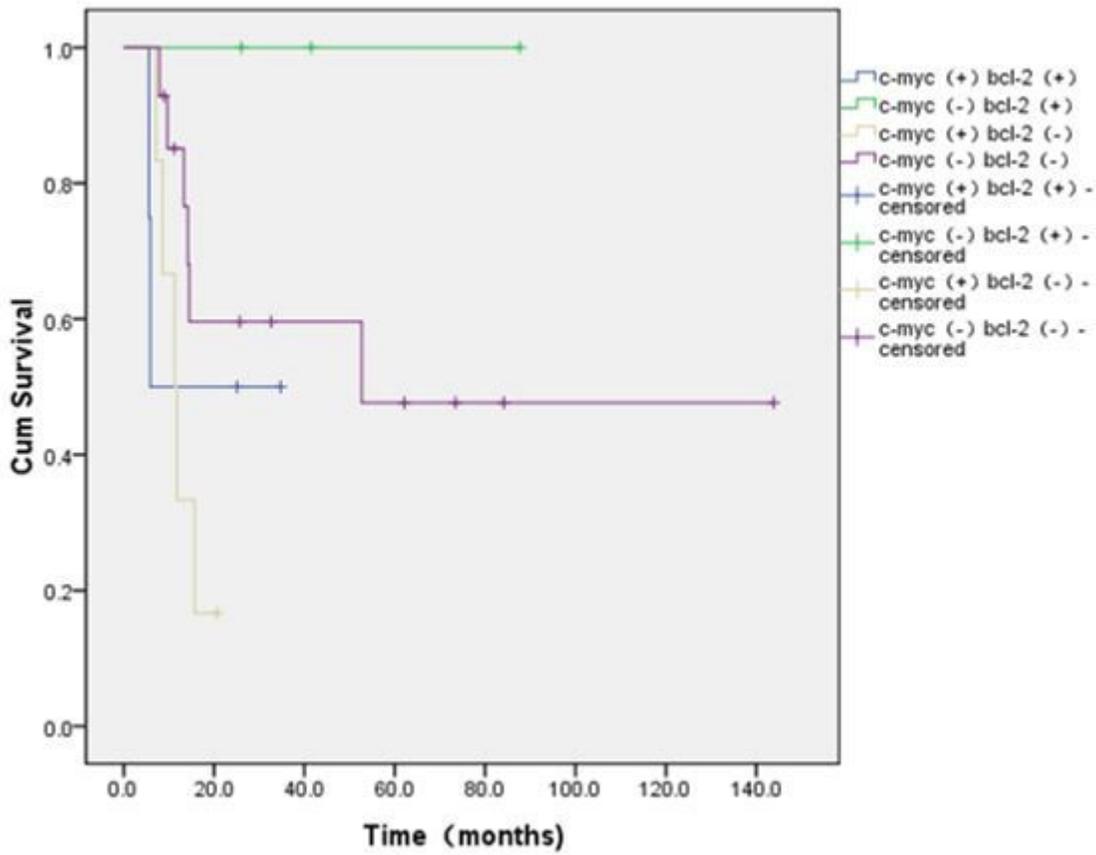


Figure 2

Kaplan-Meier plots showing cumulative survival at 10 years of follow-up by c-MYC/BCL-2 dual expression.

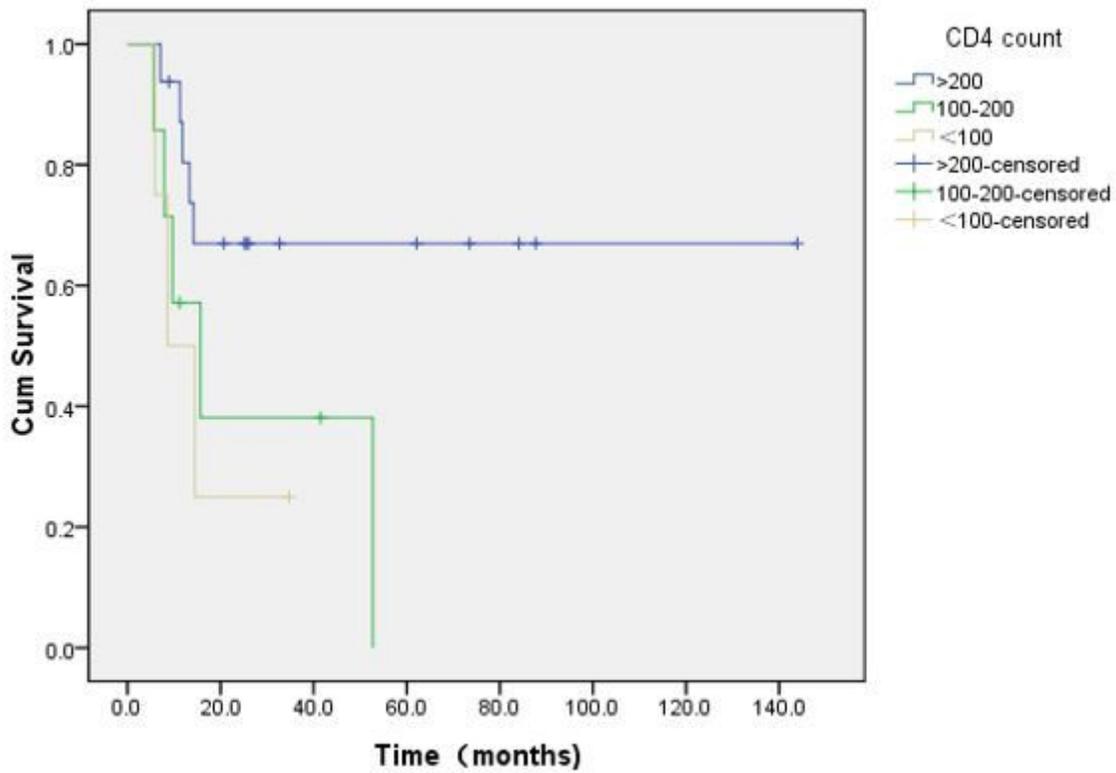
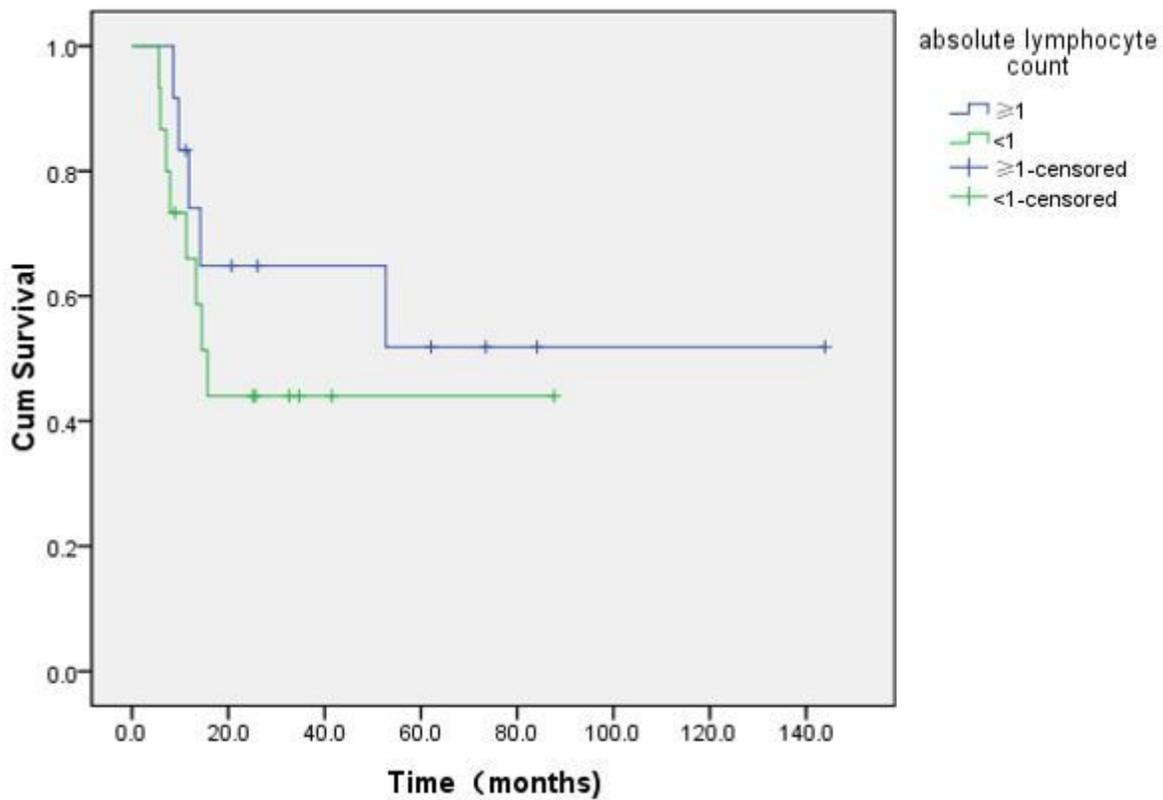


Figure 3

Kaplan-Meier plots showing cumulative survival at 10 years of follow-up by CD4 count.



## Figure 4

Kaplan-Meier plots showing cumulative survival at 10 years of follow-up by absolute lymphocyte count.

## Supplementary Files

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