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Serum β2-microglobulin level is associated with the survival of HIV-associated diffuse large B-cell lymphoma: a retrospective study from China

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HIV-associated diffuse large B-cell lymphoma (DLBCL) is a rare type of lymphoma with poor prognosis. β2-microglobulin (β2-M) is elevated in people living with HIV, but its prognostic significance in HIV-associated DLBCL remains unclear. We retrospectively analyzed 89 HIV-associated DLBCL patients treated at Chongqing University Cancer Hospital between October 2012 and December 2023. The primary outcome was the clinical overall survival (OS) rate. The optimal cut-off value of β2-M was determined to be 5 mg/L. Compared to the low serum β2-M group (< 5 mg/L), patients in the high serum β2-M group (≥ 5 mg/L) had a higher International Prognostic Index (IPI)/ age adjusted IPI (aaIPI) score, more B symptoms, lower $CD4^+$T cell counts, and higher lactate dehydrogenase (LDH) level. Patients in high group exhibited poorer OS, with 1-, 3-, and 5-year OS rates of 33.4%, 22.8%, and 18.2%, respectively. Multivariate Cox regression analysis identified serum β2-M ≥ 5 mg/L as an independent risk factor influencing OS of this patient group. Moreover, $CD8^+$T cell count < 392 cells/μL, LDH ≥ 375 U/L, and non-receipt of standard treatment were also independent risk factors. Receiver operating characteristic curve analysis demonstrated that these four independent risk factors accurately predicted survival in HIV-associated DLBCL. 5 mg/L threshold for serum β2-M was associated with poor OS in HIV-associated DLBCL, indicating it could serve as a novel biomarker for assessing their prognosis.

Keywords β2-M, HIV, DLBCL, Overall survival

Abbreviations

β2-M	Beta-2 microglobulin
IPI	International prognostic index
aaIPI	Age adjusted IPI
CNS	Central nervous system
NLR	Neutrophil to lymphocyte ratio
LMR	Lymphocyte to monocyte ratio
PLR	Platelet to lymphocyte ratio
LDH	Lactate dehydrogenase

Individuals infected with human immunodeficiency virus (HIV) have a high risk of developing malignant tumors, which significantly contributes to the elevated mortality observed in this group[1]. Lymphoma is the most prevalent malignancy among people living with HIV (PLWH), even in those receiving antiretroviral therapy (ART)[2]. Despite advancements in the treatment of HIV-associated lymphomas, they remain an important cause of high mortality in PLWH[3]. With widespread use of ART, the incidence of HIV-associated non-Hodgkin's

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lymphoma (NHL) surpassed that of Kaposi sarcoma, becoming the predominant malignancy among HIV-associated cancers[4]. The relative risk of NHL in PLWH is estimated to be 10–20 times more than in the general population, with an incidence rate of approximately 85–193 per 100,000 person-years[3]. Among HIV-associated NHL subtypes, diffuse large B cell lymphoma (DLBCL) accounts for approximately 60–70% of cases[5]. DLBCL patients with HIV exhibit significantly worse survival outcomes compared to those without HIV[6]. Although combination ART has improved DLBCL survival rates and decreased the incidence of HIV-associated NHL, the overall prognosis for HIV-associated DLBCL remains poor[7]. Therefore, it is necessary to identify new biomarkers for predicting survival in HIV-associated DLBCL patients.

β2-microglobulin (β2-M), a crucial light chain subunit for assembling major histocompatibility complex class-I antigens, is primarily produced by polymorphonuclear leukocytes and lymphocytes. It is distributed in various bodily fluids, including plasma, urine, cerebrospinal fluid, saliva, and colostrum[8]. β2-M exists in two main forms: cell membrane surface β2-M and soluble β2-M with a low molecular weight of 11.8 kD[8,9]. Viral infections, including HIV, increase the synthesis of β2-M[10]. β2-M plays significant roles in immune control and tumorigenesis, including regulation of the survival, growth, apoptosis, and metastasis of cancer cells[11].

Previous studies have demonstrated that elevated serum β2-M levels are poor prognostic factors for various lymphomas, including DLBCL (β2-M ≥ 3.2 mg/L), angioimmunoblastic T-cell lymphoma(β2-M ≥ 4.0 mg/L), NK/T-cell lymphoma (β2-M ≥ 2.5 mg/L), and Hodgkin's lymphoma (β2-M ≥ 2.5 mg/L)[12–16]. However, HIV-associated DLBCL differs from common DLBCL due to the chronic inflammatory state induced by HIV co-infection. The prognostic significance of serum β2-M levels in this specific population, as well as the optimal threshold, remains unclear. Therefore, further investigation into the association between β2-M levels and survival outcomes in HIV-associated DLBCL is clinically important.

Due to the low incidence of HIV-associated DLBCL, studies on this subject are limited. This retrospective study investigated the impact of serum β2-M level on the survival of HIV-associated DLBCL patients. The findings could aid in clinical diagnosis, treatment, and prognostic assessment of HIV-associated DLBCL.

Methods

Study design and population

We conducted a retrospective analysis of demographic data, clinical manifestations, laboratory test results, and treatments for 89 patients diagnosed with HIV-associated DLBCL. These patients were admitted to Chongqing University Cancer Hospital in China between October 2012 and December 2023. The inclusion criteria were age > 18 years; PLWH meeting the diagnostic criteria outlined in the Chinese AIDS Diagnosis and Treatment Guidelines (2021 edition), confirmed through a positive HIV antibody screening test and a positive antibody confirmation test; and a definitive diagnosis of DLBCL according to the World Health Organization Classification of Tumors of Hematopoietic and Lymphoid Tissues. The exclusion criteria were patients with concurrent malignant tumors; those with significantly missing or incomplete clinical data; and individuals lacking clinical outcome and survival data. The study adhered to the principles of the Declaration of Helsinki. The data are anonymous, and the requirement for informed consent was therefore waived. Informed consent was waived by the Affiliated Chongqing University Cancer Hospital Ethics Committee (approval no. CZLS2023085-A-100).

Observation indicators

We collected demographic features, clinical manifestations, and laboratory test results, which included the serum β2-M level, age, sex, Ann Arbor stage, International Prognostic Index (IPI)/ age adjusted IPI (aaIPI) score, presence of B symptoms (fever, night sweats, and unexplained weight loss), extranodal involvement, bone marrow involvement, central nervous system involvement, Ki67 index, neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), $CD4^+$ T cell count, $CD8^+$ T cell count, natural killer (NK) cell count, serum lactate dehydrogenase (LDH) level, and whether or not patients received standard treatment.

Definition of standard treatment

Standard treatment defined as tumor chemotherapy combined with ART. ART included two nucleoside reverse transcriptase inhibitors and one nonnucleoside reverse transcriptase inhibitor. The chemotherapy cohort included patients who received any of the following regimens: rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP); Rituximab combined with etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (R-EPOCH). According to the NCCN guidelines (Version 2.2025), both R-CHOP and R-EPOCH are recommended treatment regimens for HIV-associated DLBCL.

Definition of overall survival

The primary outcome of this study was overall survival (OS), defined as the time between HIV-associated DLBCL diagnosis and death from any cause or the last follow-up (31 December 2023).

Statistical analysis

Optimal cut-off values for the β2-M level were determined using X-tile software (version 3.6.1, https://medicine.yale.edu/lab/rimm/research/software/). According to the optimal cut-off value, β2-M level was divided into high level group and low level group. And determined the optimal cutoff value for the Ki67 index, NLR, LMR, PLR, $CD4^+$ T cell count, $CD8^+$ T cell count, NK cell count, and LDH level by using X-tile software. Continuous variables with a normal distribution were analyzed using Student's *t*-test and expressed as means ± standard deviation, while those with a non-normal distribution were analyzed using the Mann-Whitney U test and expressed as medians [interquartile range (IQR)]. Categorical variables were analyzed using the χ^2 test or Fisher's exact test and are presented as numbers (percentages). The Kaplan-Meier method and log-rank test were used to

compare survival rates among groups. Cox proportional hazards regression was used to identify risk factors for OS in HIV-associated DLBCL patients. Multivariate Cox regression analyses were performed on variables that were significant ($p < 0.2$) in univariate analyses. Differences were considered statistically significant at $p < 0.05$. Independent risk factors and IPI/aaIPI score were selected to predict 1-, 3-, and 5-year survival, and Receiver Operating Characteristic (ROC) curves were plotted to analysis the area under curve (AUC). Statistical analyses were performed using R (version 4.2.1, https://cran.r-project.org/bin/windows/base/old/4.2.1/) and SPSS (version 25.0, https://www.ibm.com/spss).

Results

Baseline clinical characteristics of patients

β2-M exhibited an optimal cut-off value of 5 mg/L (Fig. 1). Based on this, we conducted a clinical data analysis in the cohort. The 89 HIV-associated DLBCL patients in this study had a mean age of 51.94 ± 13.10 years old (range: 26–87 years). Of these patients, 82 (92.1%) were male and 7 (7.9%) were female. A total of 72 (80.9%) patients presented with Ann Arbor stage III–IV. Additionally, 29 (32.6%) patients had low or low-intermediate disease risk, while 60 (67.4%) showed high-intermediate or high disease risk. B symptoms were observed in 30 (33.7%) patients, and 41 (46.1%) had extranodal involvement. Bone marrow and central nervous system (CNS) involvement were present in 14.6% and 12.4% of patients, respectively. Other clinical characteristics are summarized in Table 1.

In this study, the optimal cut-off serum β2-M level was determined to be 5 mg/L. Consequently, patients were stratified into two groups: the high β2-M group (≥ 5 mg/L) and the low β2-M group (< 5 mg/L). Compared to

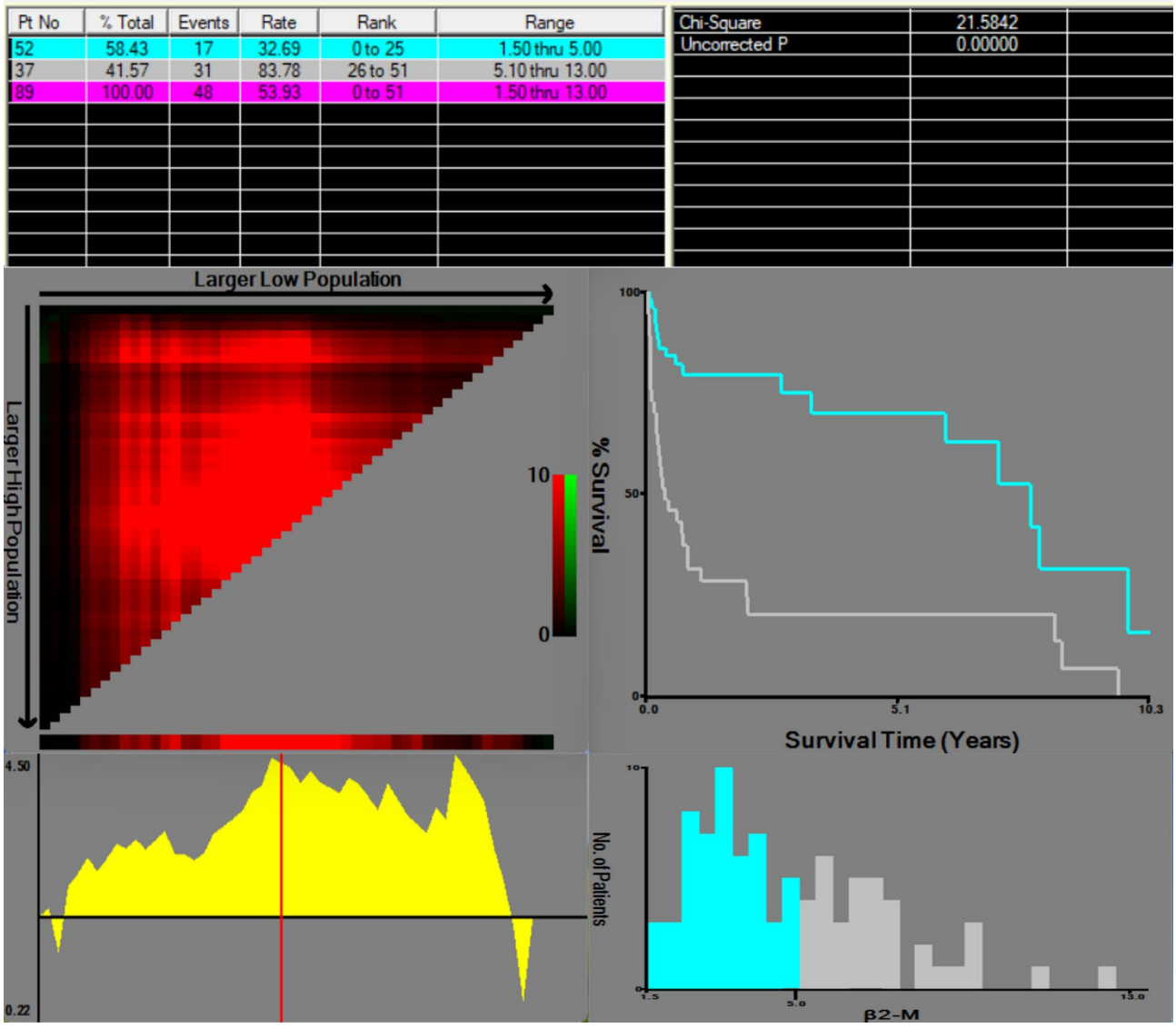

Fig. 1. X-Tile analysis of survival data based on HIV-associated DLBCL patients revealed a continuous distribution based on β2-M. The plots show the χ^2 log-rank values produced when dividing the patients with two cut-points, producing high and low subsets. β2-M, beta-2 microglobulin.

Characteristics	*n* (%)	β2-M, *n* (%)		*p*
		< 5 mg/L	≥ 5 mg/L	
Age (years)				0.845
< 60	67 (75.3)	38 (74.5)	29 (76.3)	
≥ 60	22 (24.7)	13 (25.5)	9 (23.7)	
Sex				0.421
Female	7 (7.9)	3 (5.9)	4 (10.5)	
Male	82 (92.1)	48 (94.1)	34 (89.5)	
Ann-Arbor				0.493
I-II	17 (19.1)	11 (21.6)	6 (15.8)	
III-IV	72(80.9)	40 (78.4)	32 (84.2)	
IPI/aaIPI				0.014
Low/Low-intermediate	29 (32.6)	22 (43.1)	7 (18.4)	
High-intermediate/High	60 (67.4)	29 (56.9)	31 (81.6)	
B symptoms				0.019
NO	59 (66.3)	39 (76.5)	20 (52.6)	
YES	30 (33.7)	12 (23.5)	26 (47.4)	
Extranodal involvement				0.828
NO	48 (53.9)	27 (52.9)	21 (55.3)	
YES	41 (46.1)	24 (47.1)	17 (44.7)	
Bone marrow involvement				0.379
NO	76 (85.4)	45 (88.2)	31 (81.6)	
YES	13 (14.6)	6 (11.8)	7 (18.4)	
CNS involvement				0.134
NO	78 (87.6)	47 (92.2)	31 (81.6)	
YES	11 (12.4)	4 (7.8)	7 (18.4)	
Ki67				0.867
< 0.6	18 (20.2)	10 (19.6)	8 (21.1)	
≥ 0.6	71 (79.8)	41 (80.4)	30 (78.9)	
NLR				0.071
< 2.77	45 (50.6)	30 (58.8)	15 (39.5)	
≥ 2.77	44 (49.4)	21 (41.2)	23 (60.5)	
LMR				0.164
< 2.14	37 (41.6)	18 (35.3)	19 (50.0)	
≥ 2.14	52 (58.4)	33 (64.7)	19 (50.0)	
PLR				0.305
< 306.52	68 (76.4)	41 (80.4)	27 (71.1)	
≥ 306.52	21 (23.6)	10 (19.6)	11 (28.9)	
$CD4^+$ T cell (cells/μL)				0.041
< 117	23 (25.8)	9 (17.6)	14 (36.8)	
≥ 117	66 (74.2)	42 (82.4)	24 (63.2)	
$CD8^+$ T cell (cells/μL)				0.731
< 392	31 (34.8)	17 (33.3)	14 (36.8)	
≥ 392	58 (65.2)	34 (66.7)	24 (63.2)	
NK cell (cells/μL)				0.240
< 280	79 (88.8)	47 (92.2)	32 (84.2)	
≥ 280	10 (11.2)	4 (7.8)	6 (15.8)	
LDH (U/L)				0.000
Continued				

Characteristics	*n* (%)	β2-M, *n* (%)		*p*
		< 5 mg/L	≥ 5 mg/L	
< 375	52 (58.4)	39 (76.5)	13 (34.2)	
≥ 375	37 (41.6)	12 (23.5)	25 (65.8)	
Standard treatment				0.005
NO	20 (22.5)	6 (11.8)	14 (36.8)	
YES	69 (77.5)	45 (88.2)	24 (63.2)	

Table 1. Clinical characteristics of HIV-associated DLBCL patients. Categorical variables, including β2-M, age, Ki67 index, NLR, LMR, PLR, $CD4^+$ T cell count, $CD8^+$ T cell count, NK cell count, and LDH levels, were determined using X-Tile software. β2-M, beta-2 microglobulin, IPI, international prognostic index, aaIPI, age adjusted IPI, CNS, central nervous system, NLR, neutrophil to lymphocyte ratio, LMR, lymphocyte to monocyte ratio, PLR, platelet to lymphocyte ratio, LDH, lactate dehydrogenase.

Time	OS (%)	95% CI
One-year	64.3	0.570 ~ 0.724
Three-year	56.5	0. 480 ~ 0.663
Five-year	51.7	0. 422 ~ 0.633

Table 2. The OS of HIV-associated DLBCL patients.

the low β2-M group, the high β2-M group exhibited more significant adverse clinical features, including a higher IPI/aaIPI score, more B symptoms, elevated LDH level, and decreased $CD4^+$ T cell count (Table 1). However, no significant differences were observed between the high and low β2-M groups in age, sex, Ann Arbor stage, extranodal involvement, bone marrow involvement, CNS involvement, Ki67 index, NLR, LMR, PLR, $CD8^+$ T cell count, or NK cell count (Table 1).

Survival outcomes

In this study, 47 patients (52.8%) died during follow-up. Based on our follow-up data, the causes of death were as follows: (1) tumor progression involving vital organs ($n = 30$, 63.83%), (2) severe infections in the later stage of AIDS ($n = 8$, 17.02%), (3) cardiovascular diseases ($n = 4$, 8.5%), and (4) complications from other diseases ($n = 5$, 10.64%). The median survival time was 40.1 months, and the median follow-up time was 29.7 months. The 1-, 3-, and 5-year OS rates were 64.3%, 56.5%, and 51.7%, respectively (Table 2; Fig. 2).

Impact of serum β2-M level on survival

The Kaplan-Meier method and log-rank test indicated that the high β2-M group had worse OS rates compared to the low β2-M group (Fig. 3, $p < 0.0001$). The 1-, 3-, and 5-year OS rates for the low β2-M group were 79.2%, 74.3%, and 74.3%, while those for the high β2-M group were 33.4%, 22.8%, and 18.2%, respectively (Fig. 3).

Prognostic factors associated with survival

Univariate Cox regression analysis identified several factors related to OS in HIV-associated DLBCL patients ($p < 0.2$), including serum β2-M level (hazard ratio [HR] = 4.28, 95% CI: 2.28–8.06, $p < 0.001$), IPI/aaIPI score (HR = 2.16, 95% CI: 1.07–4.36, $p = 0.031$), NLR (HR = 2.42, 95% CI: 1.32–4.42, $p = 0.004$), LMR (HR = 2.22, 95% CI: 1.23–4.00, $p = 0.008$), PLR (HR = 1.77, 95% CI: 0.92–3.39, $p = 0.087$), $CD4^+$ T cell count (HR = 1.80, 95% CI: 0.98–3.32, $p = 0.059$), $CD8^+$ T cell count (HR = 0.34, 95% CI: 0.18–0.64, $p = 0.001$), NK cell count (HR = 0.48, 95% CI: 0.22–1.05, $p = 0.065$), serum LDH level (HR = 3.28, 95% CI: 1.80–5.96, $p < 0.001$), and whether they received standard treatment (HR = 3.37, 95% CI: 1.85–6.17, $p < 0.001$) (Table 3).

Variables with p-values < 0.2 in the univariate Cox regression analysis were included in the multivariate Cox regression analysis. Among these, β2-M ≥ 5 mg/L stood out as a particularly strong independent risk factor (HR = 2.39, 95% CI: 1.05–5.47, $p = 0.038$), highlighting its significant impact on the OS of HIV-associated DLBCL patients. In addition, $CD8^+$ T cell count < 392 cells/μL (HR = 2.89, 95% CI: 1.18–7.07, $p = 0.020$), LDH ≥ 375 U/L (HR = 2.04, 95% CI: 1.03–4.02, $p = 0.041$), and non-receipt of standard treatment (HR = 3.08, 95% CI: 1.41–6.69, $p = 0.005$) were also identified as independent risk factors for OS in HIV-associated DLBCL patients (Table 4; Fig. 4). It's concluded that β2-M significantly influences the OS in HIV-associated DLBCL patients and can serve as a novel prognostic indicator for this patient group.

Predictive value of independent risk factors for survival

The ROC analysis (Fig. 5) showed that when used as individual predictors, the AUC values for β2-M level, $CD8^+$ T cell count, LDH, and non-receipt of standard treatment were used as individual predictors of HIV-associated DLBCL prognosis, their AUC values were 0.737, 0.637, 0.770, and 0.644 for 1-year survival; 0.752, 0.646, 0.746, and 0.642 for 3-year survival; and 0.771, 0.638, 0.735, and 0.636 for 5-year survival. When the four factors were combined, the AUC values improved to 0.868, 0.872, and 0.868 for predicting 1-, 3-, and 5-year survival, respectively (Table S1). Contrastingly, the AUC values for the established IPI/aaIPI score in

Variables	HR (95% CI)	*p*
β2-M (≥5 vs. < 5 mg/L)	4.28 (2.28–8.06)	< 0.001
Age (≥60 vs. < 60 years)	1.45 (0.75–2.80)	0.264
Sex (Male vs. Female)	1.26(0.44–3.60)	0.672
Ann-Arbor (III-IV vs. I-II)	0.94 (0.45–1.96)	0.866
IPI/aaIPI (High-intermediate/High vs. Low/Low-intermediate)	2.16 (1.07–4.36)	0.031
B symptoms (YES vs. NO)	1.32 (0.72–2.43)	0.362
Extranodal involvement (YES vs. NO)	0.90(0.51–1.60)	0.717
Bone marrow involvement (YES vs. NO)	1.58 (0.76–3.28)	0.222
CNS involvement (YES v s NO)	0.98 (0.39–2.50)	0.972
Ki67 (≥0.6 vs. < 0.6)	1.14 (0.56–2.30)	0.716
NLR (≥2.77 vs. < 2.77)	2.42 (1.32–4.42)	0.004
LMR (< 2.14 vs. ≥2.14)	2.22 (1.23-4.00)	0.008
PLR (≥306.52 vs. < 306.52)	1.77 (0.92–3.39)	0.087
$CD4^+$ T cell (< 117 vs. ≥117 cells/μL)	1.80 (0.98–3.32)	0.059
$CD8^+$ T cell (< 392 vs. ≥392 cells/μL)	2.92 (1.56–5.45)	0.001
NK cell (< 280 vs. ≥280 cells/μL)	0.48 (0.22–1.05)	0.065
LDH (≥375 vs. < 375 U/L)	3.28 (1.80–5.96)	< 0.001
Standard treatment (NO vs. YES)	3.37 (1.85–6.17)	< 0.001

Table 3. Univariate analysis of the prognosis of HIV-associated DLBCL patients. *HR*, hazard ratio, *β2-M*, beta-2 microglobulin, *IPI*, international prognostic index, *aaIPI*, age adjusted IPI, *CNS*, central nervous system, *NLR*, neutrophil to lymphocyte ratio, *LMR*, lymphocyte to monocyte ratio, *PLR*, platelet to lymphocyte ratio, *LDH*, lactate dehydrogenase.

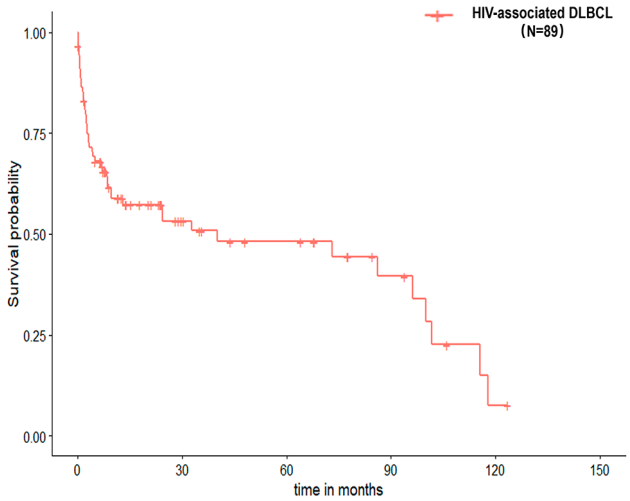

Fig. 2. OS of HIV-associated DLBCL patients.

predicting 1-, 3-, and 5-year survival were only 0.604, 0.630, and 0.614, respectively (Table S1). These findings suggested that the four independent risk factors identified in this study provide a more accurate prediction of HIV-associated DLBCL's survival, both individually and in combination, and outperform the conventional IPI/aaIPI score.

Discussion

The effect of serum β2-M level on the OS of HIV-associated DLBCL patients in the Chinese population remains uncertain. This study provided evidence that β2-M ≥ 5 mg/L is a significant prognostic factor for OS in HIV-associated DLBCL patients.

Serum β2-M is a small protein synthesized and released by various cells, making it detectable in normal individuals and frequently utilized in clinical tests. Its small size enables glomerular filtration[17]. Consequently, both impaired renal function and excessive production of β2-M could contribute to elevated serum levels[17]. Moreover, as serum β2-M predominantly originates from leukocytes, increased levels are associated with inflammatory responses, and inflammatory responses are commonly observed in tumors and viral infections[16,18,19].

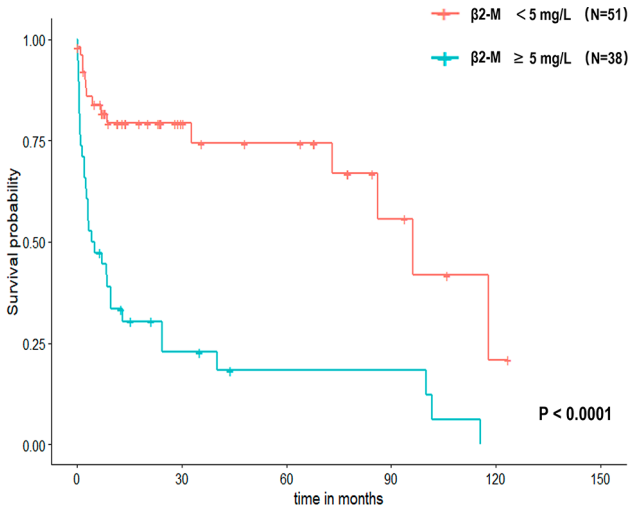

Fig. 3. Overall survival of HIV-associated DLBCL patients grouped according to β2-M level. β2-M, beta-2 microglobulin.

Variables	HR (95%CI)	*P*
β2-M (≥ 5 vs. < 5 mg/L)	2.39 (1.05–5.47)	0.038
IPI/aaIPI (High-intermediate/High vs. Low/Low-intermediate)	1.29 (0.54–3.08)	0.562
NLR (≥ 2.77 vs. < 2.77)	1.32 (0.61–2.86)	0.488
LMR (< 2.14 vs. ≥ 2.14)	1.30 (0.50–3.34)	0.587
PLR (≥ 306.52 vs. < 306.52)	0.54 (0.24–1.19)	0.127
$CD4^+$ T cell (< 117 vs. ≥ 117 cells/μL)	1.19 (0.54–2.63)	0.663
$CD8^+$ T cell (< 392 vs. ≥ 392 cells/μL)	2.89 (1.18–7.07)	0.020
NK cell (< 280 vs. ≥ 280 cells/μL)	0.67 (0.25–1.81)	0.430
LDH (≥ 375 vs. < 375 U/L)	2.04 (1.03–4.02)	0.041
Standard treatment (NO vs. YES)	3.08 (1.41–6.69)	0.005

Table 4. Multivariate analysis of the prognosis of HIV-associated DLBCL patients. *HR*, hazard ratio, *β2-M*, beta-2 microglobulin, *IPI*, international prognostic index, *aaIPI*, age adjusted IPI, *NLR*, neutrophil to lymphocyte ratio, *LMR*, lymphocyte to monocyte ratio, *PLR*, platelet to lymphocyte ratio, *LDH*, lactate dehydrogenase.

Kanemasa et al. indicated that an elevated β2-M level was an unfavorable factor for the survival of DLBCL patients, compared with β2-M < 3.2 mg/L, β2-M level ≥ 3.2 mg/L had significantly lower OS, (3-year OS, 89.4% vs. 50.9%, $p < 0.001$)[16]. Another study also has demonstrated that β2-M is significantly associated with the clinical outcomes of DLBCL[20]. In PLWH, a prolonged state of hyperinflammation characterizes systemic chronic immune activation, which could result in elevated β2-M level[21,22]. Notably, increased β2-M correlates with poor survival in PLWH[22]. Despite the clinical significance of β2-M in various malignancies and viral infections, the relationship between β2-M levels and OS in patients with HIV-associated DLBCL has not been thoroughly investigated. Therefore, this study seeks to examine the association between β2-M levels and survival outcomes in HIV-associated DLBCL patients, with the objective of identifying reliable prognostic biomarkers for this specific patient population.

This study demonstrated that serum β2-M level is an independent risk factor associated with the OS of HIV-associated DLBCL patients, the 3-year OS of HIV-associated DLBCL patients was only 56.5% at high level of β2-M. However, the biological mechanisms underlying this association remain poorly understood. Several studies have provided evidence that serum β2-M level correlate with specific biological and tumor microenvironmental features in malignant lymphomas, influencing their growth, survival, and apoptosis regulation[11]. Animal experiments have demonstrated that heightened expression of β2-M fosters the growth and invasion of prostate, breast, lung, and renal cancer cells both in vitro and in vivo, ultimately leading to mortality in mice[23]. Research demonstrated that when serum β2-M levels are elevated, the 3-year OS rate of HIV-associated DLBCL patients is significantly lower than that of HIV-negative DLBCL patients[14]. In contrast to HIV-negative DLBCL, HIV-associated DLBCL exhibits more pronounced translocations involving *MYC* and *BCL6*, coupled with a higher likelihood of a proliferation index > 80%. These molecular features contribute to increased aggressiveness[24,25]. The results furtherly revealed that patients with HIV-associated DLBCL exhibited more aggressive. Consequently, we

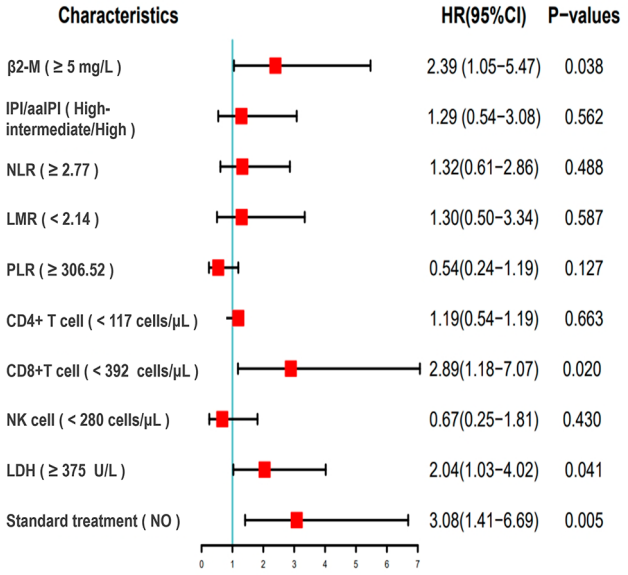

Fig. 4. Multiforest analysis of the survival of HIV-associated DLBCL patients. HR, hazard ratio; β2-M, beta-2 microglobulin; IPI, international prognostic index; aaIPI, age adjusted IPI; NLR, neutrophil to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; PLR, platelet to lymphocyte ratio; LDH, lactate dehydrogenase.

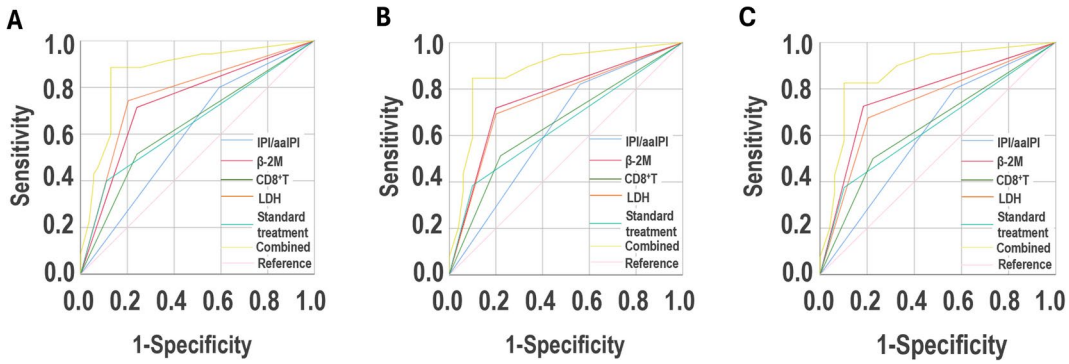

Fig. 5. ROC curve analysis of independent risk factors and IPI/aaIPI score for predicting survival in HIV-associated DLBCL patients. The ROC curves illustrate the predictive performance of β2-M level, $CD8^+$ T cell count, LDH, and non-receipt of standard treatment for 1-year (**A**), 3-year (**B**), and 5-year (**C**) survival. ROC, Receiver Operating Characteristic; β2-M, beta-2 microglobulin; IPI, international prognostic index; aaIPI, age adjusted IPI; LDH, lactate dehydrogenase.

hypothesized that elevated serum β2-M level may promote the growth of HIV-associated DLBCL tumor cells, increasing the aggressiveness of these cells and resulting in poorer survival outcomes. However, the specific underlying mechanism requires further investigation.

This was the first study to reveal an association between the β2-M level and survival of HIV-associated DLBCL patients. This study also offers a novel indicator for prognostic assessment in HIV-associated DLBCL patients. In addition to serum β2-M level, our study revealed that the $CD8^+$ T cell count < 392 cells/μL, LDH level ≥ 375 U/L, and non-receipt of standard therapy were also independent risk factors for the OS of HIV-associated DLBCL patients. $CD8^+$ T cells play a crucial role in recognizing and eliminating HIV-infected cells, helping to control the replication and spread of the virus[26]. DLBCL is infiltrated with activated $CD8^+$ T cells[27]. The proportion of $CD8^+$ T cells significantly increase among newly diagnosed DLBCL patients who receive effective rituximab-based immunochemotherapy[28], suggesting that $CD8^+$ T cells may be a useful prognostic marker for DLBCL. Furthermore, traditional risk factors within the IPI/aaIPI score, such as LDH level, were found to be predictors of the survival of HIV-associated DLBCL patients. Our previous study indicated that an elevated LDH level is an independent risk factor for adverse prognosis of newly diagnosed HIV-associated aggressive B-cell NHL patients[29]. Another study also demonstrated that an elevated LDH level is associated with poorer OS, consistent with our results[30]. In this study, HIV-associated DLBCL patients with an LDH level ≥ 375 U/L exhibited lower 3- and 5-year OS rates, indicating a correlation between LDH level and survival in these patients. Additionally, our data demonstrated that 22.5% of HIV-associated DLBCL patients did not receive standard treatment, likely

due to psychological factors such as fear of discrimination, along with financial difficulties. Consequently, the 3-year OS rate of patients who did not receive standard treatment was only 20%, ultimately lowering the OS rate of HIV-associated DLBCL patients.

IPI/aaIPI score is the most widely used prognostic assessment system for NHL, including HIV-associated lymphoma. However, studies have shown that IPI/aaIPI score has significant limitations in predicting the prognosis of HIV-associated DLBCL[30]. In this study, we identified four independent risk factors—β2-M level, $CD8^+$ T cell count, LDH, and non-receipt of standard treatment. Both individual and combined predictions of HIV-associated DLBCL survival outperformed IPI/aaIPI score. Moreover, the combined prediction was significantly more accurate than any single factor. This study further confirms the limited prognostic value of IPI/aaIPI score for HIV-associated DLBCL patients and provides a more reliable foundation for developing a prognostic assessment system for HIV-associated DLBCL.

Limitations

This study had several limitations. First, as a single-center retrospective study, its case representation is inherently limited, and the restricted patient source may affect the generalizability of our findings. Additionally, the retrospective design introduces potential selection bias, which, despite our rigorous methodology, cannot be entirely eliminated. Multi-center studies are needed to validate our results. Multi-center studies should be performed in future. Second, the sample size was relatively small. And some confounding factors were not accounted for due to data limitations and study scope. Third, other survival indices, including progression-free survival, were not investigated. Lastly, since this was a retrospective study and patient samples were not preserved, we could not further investigate how β2-M influences the aggressiveness of HIV-associated DLBCL.

Conclusions

In conclusion, this study demonstrated a correlation between β2-M level and the OS of HIV-associated DLBCL patients. A β2-M threshold of 5 mg/L was identified. Patients with HIV-associated DLBCL who had serum β2-M level ≥ 5 mg/L demonstrated a significantly reduced 3-year OS rate. Importantly, the serum β2-M level could serve as a readily measurable biological marker. Therefore, the integration of serum β2-M level into routine clinical tests for HIV-associated DLBCL patients is recommended. Furthermore, we identified four independent risk factors—β2-M level, $CD8^+$ T cell count, LDH, and non-receipt of standard treatment—that, both individually and in combination, provide more accurate survival predictions than the current IPI/aaIPI score. While the predictive power of these risk factors is promising, considering the highly heterogeneous and aggressive nature of HIV-associated DLBCL, as well as the limited number of cases in this study, further validation through prospective cohort studies is required. In the future, we aim to establish a new prognostic evaluation system for HIV-associated DLBCL by combining β2-M with other new indicators.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Author contributions

T carried out the design of the experiment and the writing of the article. J conducted data analysis and contributed to the writing of the article. G, L and W were involved in the data collection. Z, C and P carried out the quality control of the patients' data. Z and L took charge of the quality control of data analysis and the writing of the article, L took charge of the writing of the article, and Y was responsible for the design of the experiment, the quality control of data analysis, and the writing of the article.

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the Affiliated Chongqing University Cancer Hospital Ethics Committee (approval no. CZLS2023085-A-100).

Competing interests

The authors declare no competing interests.

Statements

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