Prognostic value of albumin/lactate dehydrogenase ratio in AIDS-related lymphoma

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Abstract

Objective

This study aimed to explore the prognostic factors of patients with AIDS-related lymphoma.

Methods

The clinical data of 80 patients with AIDS-related lymphoma were retrospectively analyzed. According to the survival status of the patients, the patients were divided into a death group and a survival group. The factors affecting the prognosis of patients were analyzed by binary logistic regression.

Results

Binary logistic regression analysis showed that central metastasis and albumin/lactate dehydrogenase ratio (ALB/LDH) were the prognostic factors of ARL patients. The results showed that central metastasis ($P = 0.033$) was a risk factor, and ALB/LDH ($P = 0.001$) was a protective factor.

Conclusion

The albumin/lactate dehydrogenase ratio is a convenient, practical and inexpensive potential marker that can be used to predict the prognosis of patients with AIDS-related lymphoma and provide guidance for clinical treatment.

Introduction

AIDS-related lymphoma (acquired immunodeficiency syndrome-related lymphoma, ARL) is a group of heterogeneous lymphoid tumors associated with HIV infection, of which 85% of AIDS-related lymphomas are derived from B cells. The most common is diffuse large B cell lymphoma (DLBCL), accounting for about 80%-90%[1]. Studies have shown that 10% of deaths in HIV-infected patients on antiretroviral therapy are attributable to cancer, of which NHL-related deaths account for about 2%[2]. Therefore, it is necessary to improve the clinical diagnosis of ARL patients, and at the same time improve the identification of high-risk patients to improve the survival rate of patients. IPI score is the most commonly used prognostic system for lymphoma patients[3]. Not only does it need to combine multiple tests, but with the application of antiviral therapy, the survival of patients is significantly prolonged, and the ability of IPI score to screen for risk is limited. Patients with ARL have a higher risk of infection and a worse prognosis due to immunodeficiency. It is necessary to combine the immune status and nutritional status of the patients to comprehensively evaluate the prognosis of patients with AIDS-related lymphoma. In recent years, with the increase in the incidence of ARL, many prognostic molecules and immunohistochemical markers have been used as biomarkers for patient prognosis. Studies have shown

that cytidine deaminase, BCL-2, MYC[4, 5], human-related Transcription factor 3 (RUNX3) [6] RPS6KB1 and CDC2 amplified genes[7] are closely related to the prognosis of ARL patients. These markers are expensive, sophisticated and time-consuming to operate, and there is an urgent need for prognostic indicators with low clinical cost and easy access.

Some studies have shown that inflammatory response is an important factor in the occurrence and development of tumors and has potential prognostic value[8, 9]. Lactate dehydrogenase (LDH) is a type of glycolytic enzyme, which is mostly distributed in the kidney. High levels of LDH are markers of oxidative stress and inflammation, and are associated with tumor hypoxia, tumor angiogenesis and inflammation[10], high levels of LDH are closely associated with poor prognosis[11]. Albumin is a protein synthesized by the liver during inflammation. Serum albumin has protective properties, such as maintaining physiological homeostasis, antioxidant activity, anti-inflammatory effects, and preventing apoptosis[12]. Studies have shown that low serum albumin levels are closely related to poor prognosis in lymphoma patients[13, 14]. The predictive value of a single lactate dehydrogenase and albumin is limited, and comprehensive indicators are needed to conduct more accurate risk stratification and improve the predictive value.

Recent studies have found that lactate dehydrogenase/albumin ratio is associated with poor prognosis in cancer patients[15]. So far, the relationship between albumin/lactate dehydrogenase ratio and prognosis of patients with AIDS-related lymphoma has not been systematically reported. Therefore, this study retrospectively analyzed the relationship between ALB/LDH ratio and the prognosis of ARL patients.

Subjects And Methods

2.1 Subjects

Eighty patients with AIDS-related lymphoma in the First Affiliated Hospital of Zhejiang University School of Medicine from March 2013 to December 2021. Inclusion criteria: 1. All patients were diagnosed as AIDS patients by HIV antibody screening and confirmed by the Chinese Center for Disease Control and Prevention, and diagnosed as AIDS-related lymphoma by histopathology, immunohistochemistry and imaging. 2. Save complete information. Exclusion criteria: 1. Patients without histopathology and immunohistochemistry; 2. Patients with incomplete data in our hospital or patients with incomplete pathological and imaging data confirmed in other hospitals.

2.2 Data collection

The clinical diagnosis and treatment data of 80 ARL patients were collected based on clinical case data, including age, gender, HIV diagnosis time, transmission route, size of body surface mass, location and number of extranodal involvement, blood indexes, clinical stage, B symptoms, central metastasis, Bone marrow metastasis, pathological immunohistochemical results, whether antiviral therapy and plan, whether or not chemotherapy and plan, etc. ALB/LDH ratio calculation: the ratio of serum albumin and lactate dehydrogenase; PCT/ALB ratio calculation: procalcitonin and serum albumin ratio.

2.3 Statistical analysis

SPSS 26.0 software was used to analyze data, measurement data were expressed as ($\bar{x} \pm s$), and count data were expressed as composition ratio or incidence. Differences between groups were calculated by t test and chi-square (Fisher) test. The factors that may affect the prognosis of AIDS-related lymphoma patients were analyzed by binary logistic regression. The ROC curve was constructed for the factors affecting the prognosis of patients, and the AUC was calculated to estimate the prediction results and trends. Subgroup analysis was performed using Kaplan-Meier survival analysis, and survival curves were drawn using Graphpad Prism 9.0. All test results were considered statistically significant at $P < 0.05$.

Result

3.1 General characteristics

Among the 80 patients with AIDS-related lymphoma, the sex ratio of male to female was 71:9, and the average age was (47.3 ± 13.6) years old; 18 (22.5%) were sexually transmitted, 61 (76.2%) were unexplained, CD4+T lymphoma The number of cells was (207.3 ± 172.1), and the mean time to HIV diagnosis was (19.6 ± 34.9) months. 70 patients (87.5%) received regular antiviral therapy, 71 patients (88.7%) received chemotherapy, and 67 patients (83.8%) received antiviral therapy combined with chemotherapy, as shown in Table 1.

3.2 Clinical features and diagnosis

The first symptoms were unexplained surface mass in 38 cases (47.5%), body mass in 14 cases (17.5%) and fever in 11 cases (13.7%), as shown in Figure 1A. Clinical manifestations were B symptoms in 42 cases (52.5%), and 63 cases (78.7%) were in stage IV at the time of treatment. Eighty patients were pathologically diagnosed with lymphoma, including 44 cases of diffuse large B cell lymphoma (DLBCL) and 14 cases of Burkitt's lymphoma (BL), as shown in Figure 1B.

3.3 Univariate analysis and multivariate analysis

Univariate analysis showed D-dimer ($P = 0.005$), LDH ($P = 0.003$), Ki-67 ($P = 0.009$), ALB ($P = 0.001$), cholinesterase ($P = 0.014$), adenosine Deaminase ($P = 0.006$) and CRP ($P = 0.003$), PCT ($P = 0.038$), group ($P = 0.005$), central transfer ($P = 0.016$), ALB/LDH ratio ($P < 0.001$), PCT/ALB ratio ($P = 0.023$) and CRP/ALB ratio ($P = 0.001$) were associated with the prognosis of patients with AIDS-related lymphoma, as shown in Table 2. The binary logistic regression analysis showed that the prognostic factors of patients with AIDS-related lymphoma were central metastasis ($P = 0.033$), ALB/LDH ratio ($P = 0.001$), PCT/ALB ratio ($P = 0.176$). Central metastasis was risk factor and ALB/LDH was protective factor, as shown in Table 3.

3.4 Area under the ALB/LDH curve

The ability of ALB/LDH, PCT/ALB, ALB and LDH to identify patient survival was compared by AUC. The AUC of ALB/LDH ratio was 0.794 ($P < 0.001$, 95%CI: 0.69-0.90), which was higher than that of ALB and LDH. The Youden index was 0.48, the best cut-off value for the ALB/LDH ratio was 0.10, the sensitivity was 87%, and the specificity was 61%—as shown in Table 4 and Figure 2.

3.5 Subgroup analysis

In order to further study the relationship between ALB/LDH ratio and patient prognosis, 69 patients were divided into ALB/LDH ratio ≥ 0.10 group and ALB/LDH ratio < 0.10 group according to the best cutoff value of 0.10. Kaplan-Meier survival analysis indicated that the survival time of ALB/LDH ratio ≥ 0.10 group was significantly better than that of ALB/LDH ratio < 0.10 group. There was a significant difference in 1-year overall survival ($P = 0.010$), as shown in Figure 3.

Discussion

This study retrospectively analyzed the factors affecting the prognosis of patients with AIDS-related lymphoma. The results showed that central metastasis was a risk factor for poor prognosis in patients with ARL, and ALB/LDH was a protective factor. To our knowledge, this study is the first to identify ALB/LDH ratio levels as a biomarker for predicting prognosis in patients with AIDS-related lymphoma.

Early clinical studies have found that integrating central metastases into the CNS International Prognostic Index (CNS-IPI) risk model could improve identification of high-risk patients with secondary CNS disease[16]. AIDS-related lymphoma invades the central nervous system, indicating a high degree of malignancy, rapid progression, often complicated by multiple infections, and severe sepsis. This study found that ARL patients were more prone to pulmonary, intestinal and bloodstream infection, and 10% of patients developed sepsis or septic shock, which seriously affected the survival and prognosis of patients.

Study finds that high levels of LDH are closely associated with high tumor burden and aggressiveness in lymphoma patients, indicating poor prognosis[17]. LDH is a glycolytic enzyme released by necrotic cells. Due to the rapid growth of cancer cells, the tumor tissue is in a state of hypoxia for a long time, which inhibits the degradation of hypoxia-inducible factor-1 (hypoxia inducible factor-1, HIF-1 α)[10]. The accumulated high levels of HIF-1 again stimulate anaerobic glycolysis and LDH. LDH plays a key role in anaerobic glycolysis, catalyzing pyruvate into lactic acid. The large amount of lactic acid produced can lead to the death of healthy cells around the tumor, promote cancer cell metastasis, develop resistance to chemotherapy, inhibit anti-cancer immunity, providing conditions for tumor growth, invasion and metastasis[18, 19]. Multiple studies have demonstrated that elevated lactate dehydrogenase is involved in the pathogenesis of cancer through inflammation[20, 21]; in contrast, studies have found that lactate dehydrogenase inhibitors can reverse inflammation-induced changes in cancer cells[22]. Both suggest that high levels of LDH are associated with elevated cancer risk and poor prognosis. Combined with the immunodeficiency of AIDS patients and they are more vulnerable to tumor cell invasion. The tumor burden is heavier than that of HIV-negative patients, which further aggravates the patient's condition.

Serum albumin is an indicator of the nutritional status of cancer patients. Because of the coexistence of AIDS and lymphoma, ARL patients are wasting diseases. ARL patients have a higher risk of immunodeficiency and malnutrition. Studies have shown that low serum albumin levels are closely related to the poor prognosis of patients[13, 14]. Studies have found that hypoalbuminemia are closely related chronic inflammation and may be related to cytokines interleukin-6 and tumor necrosis factor. Inflammation and tumor interactions promote tumor progression[23]. It was early discovered that compared with patients with stage I/II or III non-Hodgkin lymphoma, patients with stage IV had higher levels of LDH and CRP, and significantly lower levels of albumin[24]. Recent studies have found that the ratio of lactate dehydrogenase/albumin is associated with poor prognosis in patients with esophageal squamous cell carcinoma, gastric cancer, colorectal cancer, and liver cancer[15, 25–27]. The lactate dehydrogenase/albumin ratio was also found to be associated with in-hospital mortality and as a prognostic factor in severely infected patients requiring intensive care[28]. All of the above indicated that the comprehensive indicators of lactate dehydrogenase and albumin have more predictive value than single indicators.

In this study, through subgroup analysis of 69 patients, it was found that there was a significant difference in the 1-year survival rate between the ALB/LDH ratio ≥ 0.10 group and the < 0.10 group, which further indicated that low ALB/LDH ratio was associated with poor prognosis. The ALB/LDH ratio combined with albumin and lactate dehydrogenase, is a prognostic indicator that incorporates tumor burden, hypoxia, nutritional status and inflammatory response into a comprehensive evaluation. Therefore, low levels of ALB/LDH indicate low albumin levels or high LDH or both. That suggest that ARL patients have poor nutritional status, heavy tumor burden, hypoxia, and high tumor resistance to chemoradiotherapy. Many studies have shown that low levels of albumin or high levels of LDH are associated with poor prognosis[11, 13, 14, 17]. ARL patients should also pay attention to the schedule and timing of antiviral therapy and chemotherapy. Because most AIDS patients do not seek medical treatment in time and are in critical condition when they are admitted to the hospital, it is necessary to strike a balance between antiretroviral therapy, chemotherapy and anti-infective therapy. It is necessary to play the role of the drug while reducing the adverse reactions of the drug. Otherwise, the treatment effect is not ideal, the disease progression is accelerated, and the survival rate of patients is reduced.

Therefore, it is necessary to comprehensively evaluate the condition of ARL patients with low levels of ALB/LDH, increase vigilance, and adjust chemotherapy and/or radiotherapy to provide guidance for improving the survival rate of patients. This study is a single-center retrospective study with a limited sample size. ARL patients have poor prognosis and complex disease. The conclusions need to be verified by further multi-center, large-sample, and prospective study cohorts.

Conclusion

Lymphoma is the most common malignant tumor and cause of death in AIDS patients. The clinical symptoms are not specific. Due to the neglect of patients, it is easy to miss the opportunity for early treatment, resulting in disease progression. This study found that the ALB/LDH ratio is associated with

the prognosis of ARL patients, provide a basis for patients to formulate individualized treatment, and is expected to become a biomarker for predicting the prognosis of patients with ARL. Therefore, early diagnosis and combined treatment can help improve the prognosis of patients, and anti-infective treatment is also the focus of clinical treatment. Our results are expected to be further validated by a multi-center, large-sample, prospective study cohort in the future, to improve the identification of high-risk patients, adjust treatment strategies in time, and provide guidance for clinical treatment.

Declarations

Declaration of Funding

1. AIDS functional cure strategy and clinical research (2017ZX10202102-002-002);
2. Quality control research on “large-scale field epidemiological investigation and intervention of major infectious diseases” in demonstration area (2018ZX10715104)

Conflict of Interest

The authors have no competing interests.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Jjiangjin Hui, Zzhikai Wan and Guanjing Lang. The first draft of the manuscript was written by Jjiangjin Hui and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval

This is an observational study. The First Affiliated Hospital of Zhejiang University School of Medicine Research Ethics Committee has confirmed that no ethical approval is required.

Informed consent

All participants obtained written informed consent.

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Tables

Table 1. Basic characters of 80 ARL patients

	Number	X±D/Composition ratio(%)
Gender		
male	71	88.7
female	9	11.2
Age		
Age (y)		47.3±13.6
<30	7	8.8
30-45	30	37.5
45-60	30	37.5
>60	15	18.8
Route of transmission		
sex	18	22.5
blood	1	1.2
unknown	61	76.2
Baseline CD4+ cell		
Baseline CD4+ cell/μl		207.3±172.1
<432	64	80.5
≥432	8	10.3
Time of diagnosis of HIV(month)		19.6±34.9
Antiretroviral therapy		
yes	70	87.5
no	10	12.5
Chemotherapy		
yes	71	88.7
no	9	11.2
Stage		
Ⅱ	5	6.2
Ⅲ	75	93.8

Group		
B symptoms	42	52.5
no	38	47.5
Co-infection		
Cryptococcus	5	6.3
Tuberculosis (TB)	9	11.2
Hepatitis	6	7.5
Syphilis	13	16.3
Herpes virus	16	20.0
Candida	12	15.0
Klebsiella pneumoniae	4	5.0
Fungal pneumonia	4	5.0
EBV infection	53	66.3
Intestinal infection	9	11.3
Sepsis	9	11.3

Table2. The Analysis of risk factors related to patients

Factors	Death (N=34)	Survival (N=46)	T/X ²	P
Age	47.64±14.77	47.06±12.88	0.04	0.852
Time of diagnosis of HIV	18.02±40.02	20.82±31.08	0.12	0.725
Maximum diameter of mass	3.95±3.32	4.82±2.54	1.31	0.258
Time of mass discovery	4.27±14.91	2.60±4.31	0.49	0.484
Neutrophils	5.43±12.57	2.73±1.51	2.08	0.153
Leukocyte	5.88±6.05	4.45±1.83	2.28	0.135
Red blood cells	3.56±0.83	3.95±0.79	4.45	0.038
Hemoglobin	107.61±25.30	118.30±23.94	3.71	0.058
Fibrinogen	3.55±1.22	3.10±1.23	2.55	0.114
D-dimer	2622.51±2913.75	1194.73±1400.64	8.38	0.005
LDH	1265.03±2099.81	291.02±132.00	9.69	0.003
Ki67	36.91±41.57	60.43±36.99	7.112	0.009
ALB/LDH	0.16±0.06	0.09±0.07	24.66	<0.001
PCT/ALB	0.001±0.003	0.01±0.03	5.39	0.023
FIB/ALB	0.13±0.17	0.08±0.03	4.56	0.036
CRP/ALB	1.16±1.49	0.35±0.55	11.45	0.001
LDH/ALB	37.39±71.33	7.45±4.48	8.09	0.006
ALB/Urea	7.18±2.87	8.92±2.82	7.15	0.009
Urea/LDH	0.01±0.01	0.02±0.02	14.25	<0.001
D-dimer/ALB	75.72±81.07	32.34±43.60	9.49	0.003
ALB/adenosine deaminase	2.13±1.24	2.94±1.15	7.68	0.007
Triglycerides	2.04±1.35	1.66±0.89	2.20	0.142
Phosphocreatine kinase	89.30±84.76	52.57±26.38	7.42	0.008
ALB	35.18±6.66	39.78±5.19	12.02	0.001
Cholinesterase	5431.78±2002.09	6500.30±1742.91	6.38	0.014
Glutamyl transpeptidase	100.30±148.66	51.20±42.42	4.44	0.038
Urea	5.97±3.97	4.85±1.46	3.08	0.083

Aspartate aminotransferase	51.41±62.58	28.56±30.67	4.64	0.034
Adenosine deaminase	24.75±19.68	15.32±5.57	7.92	0.006
CRP	37.01±44.05	14.02±21.19	9.34	0.003
Erythrocyte sedimentation rate	43.41±37.82	34.19±33.24	1.19	0.278
Procalcitonin	0.76±1.68	0.07±0.07	4.58	0.038
Microglobulin	4066.71±2965.78	2874.68±1461.62	2.72	0.108
CD4+	197.69±169.95	212.69±175.00	0.13	0.725
CD8+	1403.76±3382.69	639.35±340.35	2.33	0.131
CD4/CD8	0.31±0.23	0.39±0.39	0.88	0.352
IL-6	30.13±31.66	15.31±27.47	1.96	0.171
TNF-A	1.79±2.41	3.05±7.87	0.26	0.611
EBV DNA	1125137±3372591	48878±242284	3.97	0.051
Microglobulin	30(42.3)	41(57.7)	0.016	0.900
Antiretroviral therapy	27(38.6)	43(61.4)	3.529	0.060
Chemotherapy	27(38.0)	44(62.0)	3.67	0.056
B symptoms	24(57.1)	18(42.9)	7.76	0.005
Central nervous system metastases	10(71.4)	4(28.6)	5.81	0.016
Bone marrow involvement	15(51.7)	14(48.3)	$\chi^2=1.81$	0.179
Sepsis	5(55.6)	4(44.4)	$\chi^2=0.698$	0.403

LDH:lactate dehydrogenase; ALB:albumin; PCT:procalcitonin; FIB:fibrinogen; CRP:high-sensitivity C-reactive protein;

Table 3. Dichotomous logistic regression analysis of prognostic factors in patients with AIDS-related lymphoma

factors	Regression coefficients	WaldX2	P	OR(95%CI)
CNS involvement	2.29	4.53	0.033	9.89(1.20-81.63)
ALB/LDH	-17.84	11.86	0.001	1.79E-8(6.99E-13-4.59E-4)
PCT/ALB	48.48	1.84	0.176	1.14E+21(3.86E-10-3.33E+5)

OR: odd ratio; 95% CI: 95% Confidence interval; CNS:central nervous system; ALB:albumin; LDH:lactic dehydrogenase; PCT:procalcitonin.

Table 4. Comparison of the area under the curve

factors	AUC	P	95%CI
ALB/LDH	0.79	<0.001	0.69-0.90
PCT/ALB	0.42	0.216	0.28-0.55
ALB	0.73	0.001	0.62-0.84
LDH	0.24	<0.001	0.13-0.36

AUC: Area under the Curve; 95% CI: 95% Confidence interval; ALB:albumin; LDH:lactic dehydrogenase; PCT:procalcitonin.

Figures

Figure 1

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Figure 2

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Figure 3

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