Original Article

Relationship between the absolute lymphocyte count/absolute monocyte count ratio, soluble interleukin 2 receptor level, serum programmed cell death 1 level, and the prognosis of patients with diffuse large B-cell lymphoma

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Background: To analyze the relationship between the peripheral blood absolute lymphocyte count (ALC)/absolute monocyte count (AMC) ratio, soluble interleukin 2 receptor (sIL-2R) level, serum programmed cell death 1 (PD-1) level, and the prognosis of patients with diffuse large B-cell lymphoma (DLBCL).

Methods: A total of 78 patients with DLBCL admitted to hospital and 30 healthy controls were enrolled as the case group and control group between August 2019 and June 2020, respectively. The ALC/AMC ratio and the levels of sIL-2R and serum PD-1 between the 2 groups and among patients with different prognoses were compared. The evaluation efficiency of these 3 factors for the prognosis of DLBCL patients was analyzed by receiver operating characteristic (ROC) curves. The risk factors affecting the 1-year survival rate were analyzed by the Cox hazard model.

Results: The levels of sIL-2R, AMC, and PD-1 in the case group were significantly higher than those in the control group, while the ALC/AMC ratio was lower than that in the control group (P<0.05). The levels of sIL-2R and PD-1 in the poor prognosis group were significantly higher than those in the good prognosis group, while the ALC/AMC ratio was lower than that in the good prognosis group (P<0.05). The areas under the ROC curve (AUCs) of sIL-2R level, serum PD-1 level, and the ALC/AMC ratio in evaluating the prognosis of DLBCL patients were 0.805 (95% CI: 0.700–0.886), 0.825 (95% CI: 0.722–0.902), 0.792 (95% CI: 0.685–0.876), respectively. The critical values were 474.80 μg/L, 206.85 pg/mL and 3.01, respectively. The differences in the 1-year survival rate among DLBCL patients with different tumor sizes, B symptoms, sIL-2R levels, and ALC/AMC ratios were statistically significant (P<0.05). B symptoms (RR =1.721) and ALC/AMC ratio lower than 3.01 (RR =1.484) were independent influencing factors of the 1-year survival rate in DLBCL patients (P<0.05).

Conclusions: The ALC/AMC ratio, sIL-2R level, and serum PD-1 level can effectively assess the prognosis of DLBCL patients. B symptoms and ALC/AMC ratio lower than 3.01 are risk factors affecting the 1-year survival rate of patients.

Keywords: Absolute lymphocyte count (ALC); absolute monocyte count (AMC); soluble interleukin 2 receptor (sIL-2R); serum programmed cell death 1 (PD-1); diffuse large B-cell lymphoma (DLBCL)

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is a common type of non-Hodgkin's lymphoma, and its incidence in Asia is higher than that in Europe and the United States (1). The clinical diagnosis of this disease depends on the relevant standards of "WHO classification of hematopoietic and lymphoid tumors", but it lacks specific clinical manifestations, and the pathological mechanism is complex, which poses great difficulty for clinical diagnosis. The current treatment regimens include doxorubicin chemotherapy and anti-B cell monoclonal antibody therapy, but most patients still relapse and die after treatment (2,3). Therefore, finding effective molecular markers and evaluating the prognosis of DLBCL patients are helpful for the clinical diagnosis and treatment of DLBCL. Absolute lymphocyte count (ALC) and absolute monocyte count (AMC) are common hematological indicators, the former is a typical representative of immune function, and the maturation and differentiation of T lymphocytes are related to monocytes. The decrease of lymphocytes or the increase of monocytes can be regarded as a sign of abnormal immune function. Recent studies have shown that the ratio of ALC/AMC can be used to evaluate the prognosis of DLBCL patients (4). As an important immunosuppressive molecule, programmed cell death protein 1 (PD-1) is mainly expressed in macrophages and interacts with programmed death ligand 1 (PD-L1) to inhibit T cell proliferation (5). PD-1/PD-L1 signaling pathway is also the main way of tumor immune escape. Drugs targeting PD-1/PD-L1 have been put into clinical treatment, and detection of PD-1 level is of great benefit to the treatment plan of DLBCL. Soluble interleukin 2 receptor (sIL-2R) has also been reported to be associated with the prognosis of patients with DLBCL (6). At present, there is no report on the analysis of DLBCL combined with the above 3 factors, and there is still no consensus on the quantitative study of ALC/AMC, PD-1 and sIL-2R on the prognosis evaluation of DLBCL. In view of this, this study aims to analyze the changes in the ALC/AMC ratio, sIL-2R level, and PD-1 level in patients with DLBCL, and to explore the relationship between these changes and prognosis. We present the following article in accordance with the STARD reporting checklist (available at https://dx.doi.org/10.21037/apm-21-2551).

Methods

Information

A total of 78 patients with DLBCL admitted to our hospital from August 2019 to June 2020 were selected as the case group, including 40 males and 38 females, with an average age of 60.27±8.51 years old. Tumor sites occurred within the lymph node in 26 cases and outside the lymph node in 52 cases. A total of 29 patients had B symptoms (body temperature >38 ℃ for 3 days, weight loss within half a year of 10%, and sweating). Another 30 healthy people were selected as the control group, including 19 males and 11 females, with an average age of 59.84±7.90 years old. There was no significant difference in the general data between the 2 groups (P>0.05), indicating that they were comparable. In addition, according to the efficacy standard after DLBCL treatment (7), the patients were divided into poor prognosis group and good prognosis group according to different prognosis.

The inclusion criteria were as follows: (I) patients met the clinical diagnostic criteria of DLBCL (8); (II) follow-up data was available. The exclusion criteria were as follows: (I) combined with other malignant tumors; (II) history of radiotherapy and chemotherapy; (III) patients with diseases that have a greater impact on ALC and AMC; (IV) severe infection; (V) organic lesions in important organs; (VI) incomplete clinical pathological data. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committee of Sichuan Provincial People's Hospital [Lunsheng (Research) No. 434, 2020] and informed consent was taken from all the patients.

Study methods

Treatment

Patients in the case group were treated with rituximab

Table 1 Comparison of hematological indexes between the 2 groups

Group	No. of cases	sIL-2R (μg/L)	ALC (×10^9/L)	AMC (×10^9/L)	ALC/AMC	PD-1 (pg/mL)
Case group	78	476.80±62.91	2.14±0.41	0.72±0.16	2.98±0.25	198.42±34.23
Control group	30	128.65±40.33	1.98±0.29	0.61±0.14	3.24±0.20	103.56±27.50
χ^2		28.125	1.955	3.308	5.099	13.575
P		0.000	0.053	0.001	0.000	0.000

sIL-2R, soluble interleukin 2 receptor; ALC, absolute lymphocyte count; AMC, absolute monocyte count; PD-1, programmed cell death 1.

combined with cyclophosphamide + doxorubicin + vincristine + prednisone (R-CHOP) chemotherapy regimen in our hospital (9). For the assessment of hematological indicators, routine blood examination was performed in all subjects. ALC and AMC were determined by automatic whole blood cell count, and the ALC/AMC ratio was calculated. At the same time, 4 mL elbow venous blood was extracted from the subjects the next morning after enrollment. Samples were centrifuged at 1,500 r/min for 20 min at room temperature using a low-speed centrifuge (SC-3616, USTC ZONKIA, Anhui). The supernatant was collected and stored at low temperature. The sIL-2R level was detected by the double antibody sandwich method, and the serum PD-1 level was detected using ELISA. The ELISA kits were provided by Wuhan Boster Biological Technology., Ltd. At the same time, blood routine examination was carried out, and 4 mL of venous blood of the subjects was placed in heparin anticoagulant tube. The density gradient centrifugation was performed using an automated whole blood cell counter. The number of ALC and AMC of the subjects was counted, and the ALC/AMC ratio was calculated using Excel software.

Follow-up

The follow-up time was 1 year through outpatient follow-up, and once a month after treatment. All DLBCL patients were followed up regularly until June 2021 or until the disease progressed. At the same time, the Kaplan-Meier method was used to analyze the median survival time and 1-year survival rate. The survival time was the date of admission to the last follow-up or death. The month was the unit, and the dead were regarded as complete data.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 24.0 software (SPSS, Illinois, USA). The measurement data with a skewed distribution were expressed as M (P25, P75) and the Mann-Whitney U test was used. The measurement data conforming to the normal distribution were expressed as means ± standard deviation and the independent t test was adopted. The enumeration data were expressed as percentage (%), and the comparison between groups was tested by χ^2. A receiver operating characteristic (ROC) curve was used to analyze the evaluation efficacy of the ALC/AMC ratio, sIL-2R level, and serum PD-1 level for the prognosis of patients with DLBCL. Cox regression was used to analyze the influencing factors of the 1-year survival rate of patients with DLBCL. P<0.05 indicated that the difference was statistically significant.

Results

Comparison of hematological indexes between the 2 groups

The results showed that the levels of sIL-2R, AMC, and PD-1 in the case group were significantly higher than those in the control group, and the ALC/AMC ratio was lower than that in the control group (P<0.05), as shown in *Table 1*.

Comparison of hematological indexes in DLBCL patients with different prognoses

The results showed that the levels of sIL-2R and PD-1 in the poor prognosis group were significantly higher than those in the good prognosis group, and the ALC/AMC ratio was lower than that in the good prognosis group (P<0.05), as shown in *Table 2*.

The prognostic value of the ALC/AMC ratio, sIL-2R level, and PD-1 level in DLBCL patients

The ROC curve was used to analyze the prognostic value of the ALC/AMC ratio, sIL-2R level, and serum PD-1 level in DLBCL patients. The areas under the ROC curve (AUCs) of sIL-2R, serum PD-1, and the ALC/AMC ratio

Table 2 Comparison of hematological indexes of DLBCL patients with different prognoses

Group	No. of cases	sIL-2R (μg/L)	ALC/AMC	PD-1 (pg/mL)
Poor prognosis group	32	610.59±84.22	2.85±0.22	255.40±40.84
Good prognosis group	46	383.72±48.08	3.07±0.27	158.78±29.63
χ^2		15.097	3.810	12.116
P		0.000	0.000	0.000

DLBCL, diffuse large B-cell lymphoma; sIL-2R, soluble interleukin 2 receptor; ALC, absolute lymphocyte count; AMC, absolute monocyte count; PD-1, programmed cell death 1.

Table 3 The prognostic value of the ALC/AMC ratio, sIL-2R level, and serum PD-1 level for evaluating the prognosis of DLBCL patients

Testing index	Critical value	Sensitivity	Specificity	AUC	95% CI	P
sIL-2R (μg/L)	474.80	81.25	86.96	0.805	0.700–0.886	0.000
PD-1 (pg/mL)	206.85	82.00	82.61	0.825	0.722–0.902	0.000
ALC/AMC	3.01	87.50	60.87	0.792	0.685–0.876	0.000

ALC, absolute lymphocyte count; AMC, absolute monocyte count; sIL-2R, soluble interleukin 2 receptor; PD-1, programmed cell death 1; DLBCL, diffuse large B-cell lymphoma; AUC, areas under the curve.

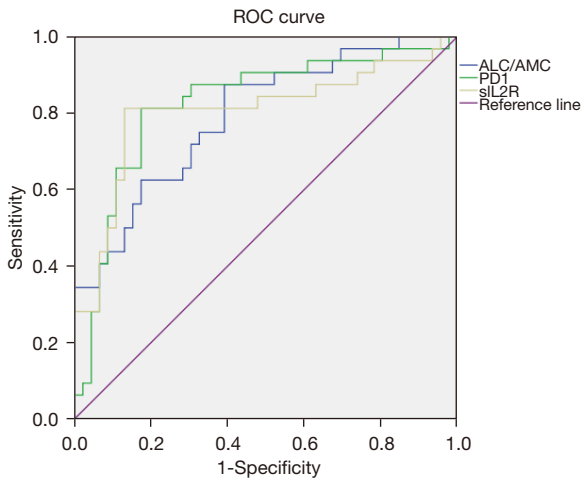

Figure 1 ROC curve of the ALC/AMC ratio, sIL-2R level, and serum PD-1 level in evaluating the prognosis of DLBCL patients. ROC, receiver operating characteristic; ALC, absolute lymphocyte count; AMC, absolute monocyte count; sIL-2R, soluble interleukin 2 receptor; PD-1, programmed cell death 1; DLBCL, diffuse large B-cell lymphoma.

in evaluating the prognosis of DLBCL patients were 0.805 (95% CI: 0.700–0.886), 0.825 (95% CI: 0.722–0.902), and 0.792 (95% CI: 0.685–0.876), respectively. The sensitivity was 81.25%, 82.00%, and 87.50%, and the specificity was 86.96%, 82.61%, and 60.87%, respectively. The critical values were 474.80 μg/L, 206.85 pg/mL, and 3.01, respectively (*Table 3*, *Figure 1*).

Univariate analysis of the 1-year survival rate of patients with DLBCL

During the follow-up period, 78 patients were followed up, 11 patients died, and 67 patients survived. The 1-year survival rate was 85.90%, and the median survival time was 9.21 months (95% CI: 5.727–11.335). Univariate analysis of clinicopathological features was performed using the Cox regression model. The results showed that there were statistically significant differences in the 1-year survival rate among DLBCL patients with different tumor size, B symptoms, sIL-2R level, and ALC/AMC ratio (P<0.05). There was no significant difference in the 1-year survival rate among DLBCL patients with different age, sex, TNM stage, tumor site, and PD-1 level (P>0.05), as shown in *Table 4*.

Multivariate analysis of the 1-year survival rate of DLBCL patients

The Cox regression model was used to conduct a multivariate analysis on the tumor size, B symptoms, sIL-2R level, and ALC/AMC ratio. The 1-year survival rate of patients with DLBCL was taken as the independent variable, and the above 4 factors were taken as the dependent

Table 4 Univariate analysis of the 1-year survival rate of DLBCL patients

Clinicopathological characteristics	No. of cases (%)	1-year survival (%)	Median survival period (months)	Log-rank χ^2	P
Age (years)				1.400	0.237
<60	48 (61.54)	89.58	9.36		
≥60	30 (38.46)	80.00	7.39		
Gender				0.782	0.376
Male	40 (51.28)	82.50	8.10		
Female	38 (48.72)	89.74	9.45		
TNM classification				2.088	0.148
I stage, II stage	37 (47.44)	91.89	10.16		
III stage, IV stage	41 (52.56)	80.49	7.87		
Tumor location				0.847	0.357
Extranodal	52 (66.67)	88.46	9.24		
Lymph nodes	26 (33.33)	80.77	8.01		
Tumor size (cm)				5.866	0.015
<4	53 (67.95)	92.45	10.35		
≥4	25 (32.05)	72.00	7.00		
B symptoms				10.925	0.001
None	49 (62.82)	95.92	11.05		
Yes	29 (37.18)	68.97	6.83		
sIL-2R (μg/L)				4.855	0.028
<474.80	45 (57.69)	93.33	10.67		
≥474.80	33 (42.31)	75.76	7.14		
PD-1 (pg/mL)				1.172	0.279
<206.85	47 (60.26)	89.36	9.27		
≥206.85	31 (39.74)	80.65	7.90		
ALC/AMC				11.735	0.001
≥3.01	50 (64.10)	96.00	11.20		
<3.01	28 (35.90)	67.86	6.28		

The levels of sIL-2R, PD-1, and ALC/AMC were distinguished by critical values. DLBCL, diffuse large B-cell lymphoma; sIL-2R, soluble interleukin 2 receptor; PD-1, programmed cell death 1; ALC, absolute lymphocyte count; AMC, absolute monocyte count.

variables. The assignment was as follows: tumor size (<4 cm =0, ≥4 cm =1), B symptoms (none =0, yes =1), sIL-2R level (<474.80 μg/L =0, ≥474.80 μg/L =1), and ALC/AMC ratio (≥3.01 =0, <3.01 =1). The results showed that B symptoms (RR =1.721) and ALC/AMC ratio <3.01 (RR =1.484) were independent factors affecting the 1-year survival rate of DLBCL patients, and the difference was statistically significant (P<0.05), as shown in *Table 5*.

Discussion

DLBCL is a type of malignant tumor with strong heterogeneity. At present, clinical CHOP or R-CHOP treatment has improved the prognosis of patients. The 'gold standard' international prognostic index (IPI) used to evaluate the prognosis of lymphoma has been unable to effectively distinguish high-risk groups, and new markers

Table 5 Multivariate analysis of the 1-year survival rate of DLBCL patients

Factor	β	SE	Wald χ^2	RR	95% CI	P
B symptoms	0.543	0.212	11.328	1.721	1.136–2.608	0.011
ALC/AMC ratio	0.395	0.182	7.564	1.484	1.039–2.121	0.031

ALC, absolute lymphocyte count; AMC, absolute monocyte count; DLBCL, diffuse large B-cell lymphoma; RR, risk ratio.

need to be identified to evaluate the prognosis of DLBCL patients (10,11). In the development of malignant tumors, tumor cells use various immune escape mechanisms to avoid being killed by the immune system. PD-1, as a negative costimulatory molecule which has attracted much attention in immunology, is often expressed in activated T cells, NK cells, and B cells, and can induce autoimmunity and play a negative regulatory role. After PD-L1 and PD-1 interact with each other, they can inhibit lymphocyte function and induce programmed death of tumor antigen-specific T cells, enabling tumor cell escape from immune monitoring (12,13). The level of sIL-2R in healthy serum is low. It can combine with the receptor to play an immunosuppressive role. Studies have shown that sIL-2R is significantly correlated with DLBCL (14). The ALC/AMC ratio, as a commonly used laboratory index, can reflect the host immune state. It has been used in the risk stratification of DLBCL (15). The purpose of this study was to analyze the value of above 3 indexes in the prognostic prediction of DLBCL.

In the comparison of hematological indexes between DLBCL patients and healthy controls, this study found that the levels of sIL-2R and PD-1 in the case group were higher than those in the control group, while the ALC/AMC ratio was lower than that in the control group, suggesting that DLBCL patients showed abnormal increases of sIL-2R and PD-1 and a decrease in the ALC/AMC ratio. At the same time, this study also showed that the levels of sIL-2R and PD-1 in patients with a poor prognosis were significantly higher than those in patients with a good prognosis, and the ALC/AMC ratio was lower than that in patients with a good prognosis, indicating that sIL-2R level, serum PD-1 level, and the ALC/AMC ratio could effectively evaluate the prognosis of patients with DLBCL. In previous studies, sIL-2R and serum PD-1 levels were also shown to have good predictive value for the prognosis of patients with DLBCL (16,17), which is basically consistent with the results of this study. The reason may be related to the immunosuppressive effect of sIL-2R and the development of tumors in patients with DLBCL. Serum PD-1 may affect the microenvironment of tumor cells through its negative regulation mechanism and immune escape function, but the specific mechanism in prognosis still needs to be further explored. In addition, when the ROC curve was used to analyze the prognostic value of sIL-2R level, serum PD-1 level, and the ALC/AMC ratio, it was found that all 3 factors had good evaluation efficiency. Lee *et al.* (18) found that a low ALC/AMC ratio indicated that the prognosis of patients with DLBCL was good. A recent study (19) showed that the expression of PD-1 in tumor cells of patients with DLBCL was related to high IPI score and mortality. Among them, patients with PD-1 positive expression in T cell subsets had a poor median survival time and survival rate, which was effectively consistent with the conclusion of this study.

Finally, univariate analysis found that tumor size, B symptoms, sIL-2R level, and ALC/AMC ratio were the factors affecting the 1-year survival rate of DLBCL patients, while multivariate analysis showed that B symptoms (RR =1.721) and ALC/AMC ratio <3.01 (RR =1.484) were the risk factors affecting the 1-year survival rate of DLBCL patients, suggesting that DLBCL patients with B symptoms and ALC/AMC ratio <3.01 had a high risk of disease progression. Zhang *et al.* (20) showed that the 3-year survival rate of patients with DLBCL whose ALC/AMC ratio was lower than 3.50 was only 50%, and patients with Hodgkin's lymphoma with a high ALC/AMC ratio had a longer survival time, with a critical value close to that of this study. Some researchers (21) have indicated that B symptoms are independent prognostic factors affecting progression-free survival in patients with DLBCL, so clinical attention should be paid to the 2 types of patients with B symptoms and ALC/AMC ratio <3.01, while developing effective programs to improve the survival rate of patients with DLBCL.

In summary, with the rapid development of immunohistochemistry and molecular biology, the methods for evaluating DLBCL are becoming more and more abundant. Most of the methods are expensive to operate. However, peripheral blood cell counts and the ALC/AMC

ratio are easy to obtain and inexpensive. At the same time, sIL-2R and serum PD-1 levels can effectively evaluate the prognosis of DLBCL, which is expected to make promising contributions to the clinical prognostic evaluation of DLBCL patients. It should be noted that the sample size of this study was small, and there were uncontrollable factors that caused selection bias. Some patients may be affected by dose and cycle when receiving chemotherapy, resulting in changes in survival time. However, this study can also provide better guidance for subsequent related studies.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-2551). Dr. WL, Dr. GX, Dr. MY reported that provision of study materials or patients from Sichuan Neo-life Stem Cell Biotech INC. Dr. WW reported that support for statistic analysis of data from Chengdu Neo-life Hope Medical Laboratory INC. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by ethics committee of Sichuan Provincial People's Hospital [Lunsheng (Research) No. 434, 2020] and informed consent was taken from all the patients.

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