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Original Article

Comparison of clinical characteristics, immunophenotype and prognosis between primary gastrointestinal and primary nodal diffuse large B-cell lymphomas

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Abstract: Objective: This study aims to investigate the clinical and biological characteristics of primary gastrointestinal and primary nodal diffuse large B-cell lymphoma (DLBCL), and compare the prognosis between these two. Methods: The clinical data of 224 DLBCL patients were retrospectively analyzed. Among these patients, 145 patients had primary tumors in the lymph nodes and 79 patients had primary tumors in the gastrointestinal tract. All patients were further followed-up for 2-107 months. Immunohistochemical staining was performed using a Dako EnVision detection kit. The expression of BCL-2, BCL-6 and MUM1 proteins was detected. Data were analyzed using SPSS 19.0 statistical software, and were compared using X^2-test. Survival analysis was conducted using the log-linear model, Cox's proportional hazards regression model and Life Table. Results: For primary nodal DLBCL patients, the 3-year survival rate of was 43.1% and 5-year survival rate was 38.2%; while for primary gastrointestinal DLBCL patients, the 3-year survival rate was 63.6% and 5-year survival rate was 60.9%. Univariate analysis revealed that age >60 years, elevated LDH, and elevated international prognostic index (IPI) grade were associated with adverse outcomes in patients with primary nodal and gastrointestinal DLBCL. The expression of BCL-2 protein was associated with poor prognosis of primary nodal DLBCL patients, the expression of BCL-6 protein was the favorable prognostic factor of primary nodal DLBCL, and the expression of BCL-2, BCL-6 and MUM1 proteins was not correlated with the prognosis of patients with primary gastrointestinal DLBCL. Further multivariate COX regression analysis revealed that the expression of BCL-2 protein and the increase in IPI grade were independent and adverse prognostic factors of primary nodal DLBCL, while the comprehensive treatment of surgery, radiotherapy and chemotherapy was an independent favorable prognostic factor of primary nodal DLBCL. Increased IPI grade was an independent and adverse prognostic factor of primary gastrointestinal DLBCL. Conclusion: The overall prognosis of primary gastrointestinal DLBCL was better than that of primary nodal DLBCL, and increased IPI grade was an independent and adverse prognostic factor of primary nodal and primary gastrointestinal DLBCLs.

Keywords: Diffuse large B cell lymphoma, gastrointestinal tract, prognosis

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin's lymphoma (NHL), accounting for 30-40% of adult NHL cases in Western countries [1]. Data from the China Lymphoma Pathology Collaborative Group show that the proportion in China is as high as 50-60% [2]. The disease is a moderate to high malignant tumor with obvious heterogeneity in clinical features, immunophenotype and cytogenetics, as well as invasion [3]. Extranodal DLBCL mainly occurs in the gastrointestinal tract. In addition, DLBCL is the most common pathological type of gastrointestinal malignant lymphoma, and its incidence has increased [4, 5]. Furthermore, it was reported in foreign literatures that intranodal and extranodal DLBCLs have different biological behaviors and prognoses [6]. At present, the difference between the pathogeneses of intranodal and extranodal DLBCLs remains unknown. Gastrointestinal DLBCL (GI-DLBCL) in the early clinical stage is most common, in which the international prognostic index (IPI) was at low or moderate risk, elevated serum LDH and bone

marrow infiltration are rare, and the 5-year cumulative survival rate was relatively high [7]. In this study, the clinical pathology of 224 DLBCL patients was studied to analyze the prognostic factors of primary nodal and primary GI-DLBCL.

Patients and methods

Patients

The data of 224 patients diagnosed with intranodal and GI-DLBCL were collected. These patients had paraffin blocks and complete clinical and follow-up data from January 2004 to December 2011. These data were collated and analyzed according to the World Health Organization (WHO) Classification of Tumors of the Hematopoietic and Lymphoid Tissues 2008.

Immunohistochemical detection method, antibody source, and result determination

EnVision two-step immunohistochemical staining was conducted in this study. The first antibodies (CD4, CD20, CD79a and MUM1 antibodies) were obtained from Dako (Denmark), and CD138, Vs38e, Bcl-2, Bcl-6 and Ki-67 antibodies were obtained from ZSGB-BIO (Beijing, China). The positive marker was tan or brownish yellow granules with clear position in the tumor cells in DLBCL specimens. The known markers Bcl-2, Bcl-6 and mum13 were determined using qualitative identification, the positive indicator of Bcl-2 was the specific staining of more than 30% of the cell membrane and cytoplasm; and the positive indicator of Bcl-6 and MUM1 was the staining of more than 30% of nucleus.

Grouping criteria for patients

Primary nodal DLBCL (N-DLBCL) refers to a patient that was first found to have an enlarged lymph node without lesions in other parts, with histological findings consistent with the DLBCL criteria, with disease progression, and with or without the involvement of the bone marrow or other sites. In addition, these histological findings must meet the DLBCL criteria, and the diagnosis of primary GI-DLBCL must be consistent with the diagnostic criteria of primary gastrointestinal lymphoma proposed in related literatures, that is: (1) no enlargement of superficial lymph nodes; (2) no enlargement of mediastinal lymph nodes; (3) count and subsets of peripheral blood leukocytes are normal; (4) the lesions are mainly distributed in the digestive tract or with local lymph node involvement; (5) no primary lesions in the liver and spleen.

Follow-up for patients

In-patient follow-up information was collected by the Follow-up Department of our hospital, while outpatient and consultation patients were followed-up by telephone call or letter. The diagnosis time was the start time of follow-up, and the time of last contact with the patient or family member was the deadline. Furthermore, reasons for termination of the follow-up of a patient who terminated the follow-up were recorded (e.g. death due to illness, loss of visit, or death from other unrelated causes). Finally, complete follow-up data were obtained from 224 patients.

Statistics processing

Data were analyzed using SPSS 19.0 statistical software, and were compared using X^2-test. Survival analysis was conducted using log-linear model analysis, multivariate COX proportional hazards regression analysis and Life Table. Different survival curves were compared using the log-rank test. $P<0.05$ was considered statistically significant.

Results

General clinical features

Clinical results: Lesion sites: 145 patients had primary tumors in the lymph nodes and 79 patients had primary tumors outside of the lymph nodes (gastrointestinal tract). In this study, among these 224 patients, 151 patients were male (100 patients had primary N-DLBCL and 51 patients had GI-DLBCL) and 73 patients were female (45 patients had primary N-DLBCL and 28 patients had GI-DLBCL). The median onset age was 40-50 years old, wherein, 38 patients had an onset age of <40 years old (25 patients had primary N-DLBCL and 13 patients had GI-DLBCL), 38 patients had an onset age of within 40-60 years old (67 patients had primary N-DLBCL and 47 patients has GI-DLBCL), and 72 patients had an onset age of >60 years

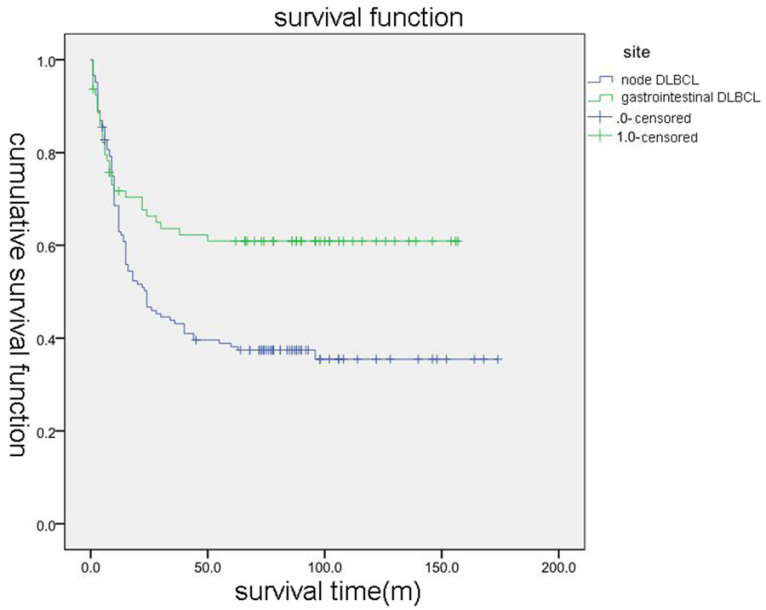

Figure 1. Overall survival curve of primay gastrointestinal tract DLBCL and primay node DLBCL patients.

old (53 patients had primary N-DLBCL and 19 patients had GI-DLBCL). Among these 224 patients with complete clinical data, LDH was normal in 97 patients (60-245 U/L, primary N-DLBCL in 63 patients and GI-DLBCL in 34 patients), while LDH increased in 127 patients (primary N-DLBCL in 82 patients and GI-DLBCL in 51 patients). The international prognostic index (IPI) score: 129 patients had 0-1 points (primary N-DLBCL in 68 patients and GI-DLBCL in 41 patients); 89 patients had 2-3 points (primary N-DLBCL in 57 patients and GI-DLBCL in 32 patients), and 26 patients had 4-5 points (primary N-DLBCL in 20 patients and GI-DLBCL in six patients). Treatment regimens included chemotherapy (CHOP regimen: cyclophosphamide, doxorubicin, vincristine, prednisone; R-CHOP regimen: rituximab + CHOP regimen), radical surgery, and local radiotherapy (local enhanced radiotherapy, the dose was within 25-40 Gy, no serious radiation injury occurred). Among them, 49 patients underwent chemotherapy alone, (chemotherapeutic course ≥4 times, GI-DLBCL in eight patients and N-DCBCL in 41 patients), 27 patients underwent surgery alone (GI-DLBCL in 19 patients and N-DCBCL in nine patients), 117 patients underwent comprehensive treatment (including surgery + chemotherapy + radiotherapy; surgery + chemotherapy; surgery + radiotherapy; and radiotherapy + chemotherapy). The chemotherapeutic course was ≥4 times, in which 51 patients had GI-DLBCL, 66 patients had N-DCBCL. Furthermore, 31 patients underwent other treatments (chemotherapeutic course <4 times or no treatment, GI-DLBCL in two patients, and N-DCBCL in 29 patients). All patients had complete follow-up data, and the overall median survival time was 30 months. Moreover, the median survival time of patients with GI-DLBCL was 67 months, and median survival time of patients with N-DLBCL was 22 months.

Comparison of prognosis between primary GI- and N-DLBCL patients

The 3- and 5-year survival rate was 43.1% and 38.2%, respectively, for patients with N-DLBCL; and 63.6% and 60.9%, respectively, for patients with GI-DLBCL. The prognosis of primary GI-DLBCL was better than that of primary N-DLBCL (**Figure 1**; log-rank test, P=0.021).

Univariate comparison analysis

The survival analysis of primary nodal and primary GI-DLBCL revealed that elevated LDH, IPI score, treatment, and age >60 years were associated with the survival rate of patients with nodal and GI-DLBCL (P<0.05 for all). However, the expression of BCL-2, BCL-6 and MUM1 proteins, and its source of cells (according to the expression of CD10, BCL-6 and MUM1 protein, they are divided into germinal center source [GCB] and non-germinal center source [non-GCB] subtypes) were related to the survival rates of patients with N-DLBCL and GI-DLBCL to different extents. The 3- and 5-yearsurvival rates of patients with negative BCL-2 protein were 56.0% and 54.0%, respectively; while of patients with positive BCL-2 were 45% and 44%, respectively. DLBCL patients with BCL2 protein expression has poor overall prognosis (**Figure 2**; log-rank test, P=0.021). In patients with N-DLBCL, the 3- and 5-year survival rate of patients with positive BCL-2 protein was 38.1% and 30.9%, respectively; while the survival rate

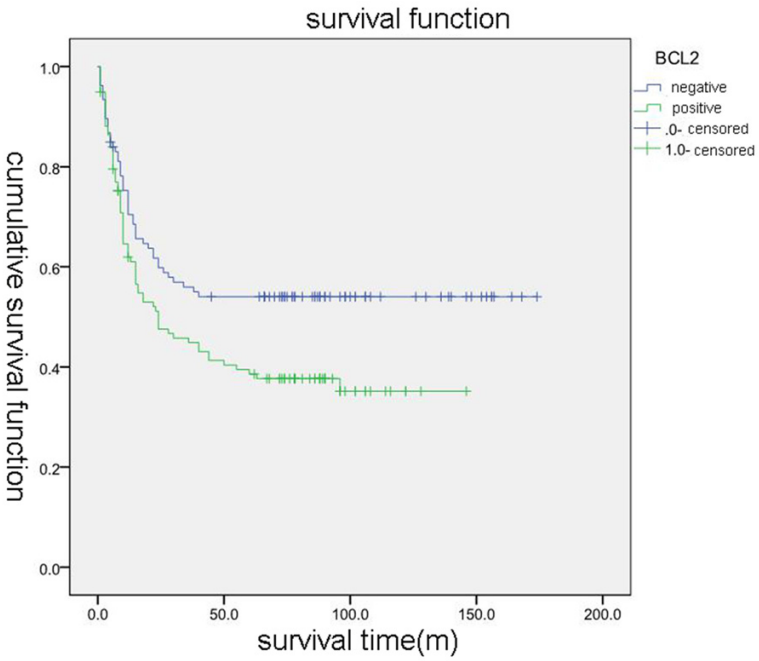

Figure 2. Corelation between BCL2 protein expression and DLBCL prognosis.

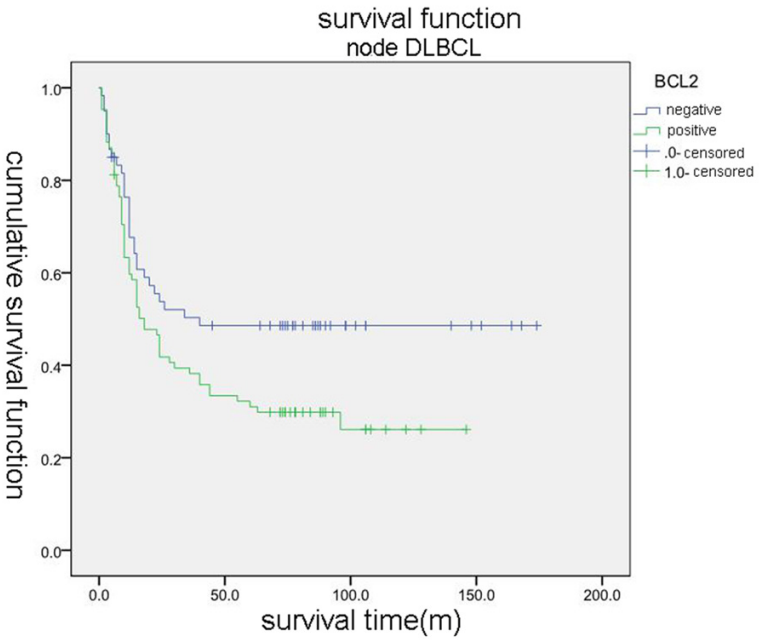

Figure 3. Corelation between BCL2 protein expression and primay node DLBCL prognosis.

of patients with negative BCL-2 protein were 50.0% and 44.8%, respectively. This shows that the prognosis of patients with negative BCL2 was better than that of patients with positive BCL2, and the difference was statistically significant (**Figure 3**; log-rank test, *P*=0.037). In patients with GI-DLBCL, the 3- and 5-year survival rate of patients with positive BCL-2 were 62.1% and 57.1%, respectively; while the survival rate of patients with negative BCL-2 protein were 60.9% and 58.7%, respectively. The difference in survival time between patients with negative and positive was not statistically significant. Among all patients, the 3- and 5-year survival rates of patients with negative BCL-6 protein were 45.1% and 37.6%, respectively, while the survival rates of patients with positive BCL-6 protein were 60.0% and 54.2%, respectively. Survival analysis revealed that the difference in overall prognosis between DLBCL patients with negative and positive Bcl-6 was not statistically significant. For patients with N-DLBCL, the 3- and 5-year survival rates of patients with negative Bcl-6 protein were 35.4% and 29.6%, respectively, while the survival rates of patients with positive Bcl-6 protein were 49.4% and 47.4%, respectively; and the difference between these two was statistically significant (**Figure 4**, log-rank test, *P*=0.017). In patients with GI-DLBCL, the 3- and 5-year survival rates of patients with negative Bcl-6 were 59.5% and 58.3%, respectively, while the survival rates of patients with positive Bcl-6 were 63.2% and 59.5%, respectively; and the difference between these two was not statistically significant (log-rank test, *P*=0.969). The 3- and 5-year survival rates of patients with negative MUM1 protein were 52.7% and 49.6%, respectively, while the survival rates of patients with positive MUM1 protein were 48.1% and 43.0%, respec-

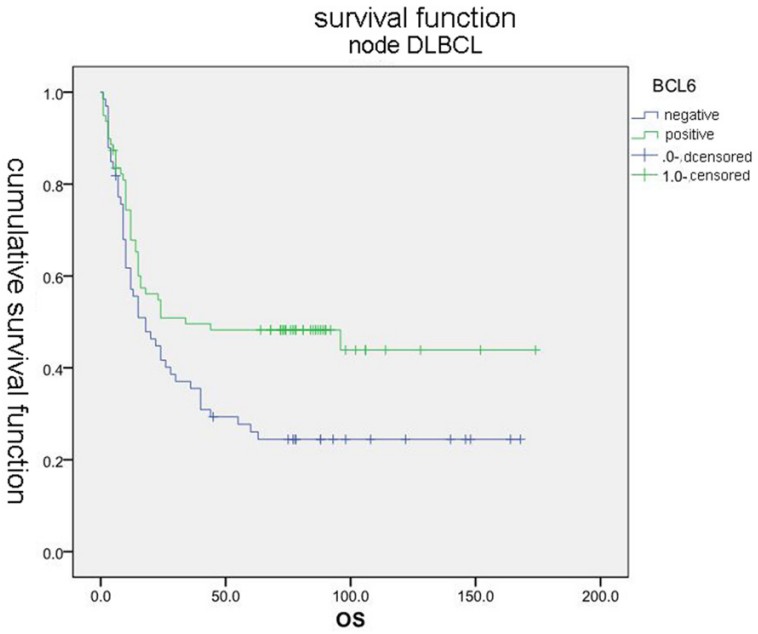

Figure 4. Corelation between BCL6 protein expression and primay node DLBCL prognosis.

tively. Survival analysis revealed that MUM1 protein expression had no effect on the overall prognosis of DLBCL (log-rank test, *P*=0.066). In patients with N-DLBCL, the 3- and 5-year survival rates of patients with positive MUM1 protein were 41.8% and 35.0%, respectively; while the survival rates of patients with negative MUM1 protein were 42.3% and 37.6%, respectively; and the difference between these two was not statistically significant (log-rank test, *P*=0.773). In patients with GI-DLBCL, the 3- and 5-year survival rates of patients with positive MUM1 protein were 57.9% and 55.3%, respectively; while the survival rates of patients with negative MUM1 protein were 73.8% and 71.7%, respectively; and the difference between these two was not statistically significant (log-rank test, *P*=0.224). Survival analysis revealed that the 3- and 5-year survival rates of patients with GCB tumor type were 51.0% and 46.9%, respectively; while the survival rates of patients with non-GCB tumor type were 48.4% and 40.0%, respectively; and the difference between these two was not statistically significant (log-rank test, *P*=0.616). The 3- and 5-year survival rates of patients with primary nodal GCB tumor were 40.4% and 34.7%, respectively; while the survival rates of patients with primary nodal non-GCB were 48.8% and 42.3%, respectively; and the difference between these two was not statistically significant (log-rank test, *P*=0.334). The 3- and 5-year survival rates of patients with primary gastrointestinal GCB tumor were 69.4% and 68.8%, respectively, while the survival rates of patients with primary gastrointestinal non-GCB tumor were 46.2% and 40.0%, respectively; and the difference between these two was statistically significant (log-rank test, *P*=0.018; **Table 1**).

Multivariate regression analysis

The results of Cox's proportional hazards regression model revealed that IPI score (HR=0.632, 95% CI: 1.300-2.724, *P*<0.01) and BCL-2 (HR=0.494, 95% CI: 1.135-2.366, *P*<0.01) were independent adverse prognostic factors of DLBCL. Treatment (HR=-0.201, 95% CI: 0.712-0.941, *P*<0.01) was an independent and favorable prognostic factor of DLBCL (**Table 2**). However, the results of the Cox's proportional hazard regression model revealed that for patients with primary GI-DLBCL, IPI score (HR=0.741, 95% CI: 1.652-2.665, *P*<0.01) was an independent adverse prognostic factor (**Table 3**). The results of the Cox's proportional hazard regression model revealed that for patients with primary N-DLBCL, IPI score (HR=0.681, 95% CI: 1.548-2.522, *P*<0.01) was an independent adverse prognostic factor; and treatment (HR=-0.151, 95% CI: 0.747-0.989, *P*<0.05) was an independent and favorable prognostic factor (**Table 4**). The X^2-test revealed that differences in the 3- and 5-year survival rates among patients with low, medium and high IPI grades were statistically significant (*P*<0.01). Risk factor analysis revealed that a IPI score >2 points was an independent prognostic risk factor for primary N-DLBCL and primary GI-DLBCL. The analysis of different treatment regimens (surgery alone, chemotherapy alone, comprehensive treatment and other treatments) revealed that comprehensive treatment is an independent and favorable factor for DLBCL.

Table 1. Univariate comparison analysis of prognostic factors of node and the gastrointestinal tract diffuse large B cell lymphoma patients

		Node DLBCL survival rate (%)		*P* value	Gastrointestinal tract DLBCL survival rate (%)		*p* value
		3 years	5 years		3 years	5 years	
Sex	Female	48.9	44.4	0.392	66.7	65.4	0.485
	Male	40.2	33.7		58.3	55.3	
Age (years)	<40	48.0	36.0	0.024	66.7	58.3	0.022
	40~60	50.0	46.3		68.2	67.4	
	>60	32.1	25.0		42.2	38.9	
LDH	Normal	53.2	51.6	0.014	75.0	74.2	0.028
	Rise	35.0	29.1		51.2	47.6	
IPI	Low-risk group	65.2	57.6	0.000	79.5	78.9	0.000
	Middle-risk group	25.0	18.2		46.7	41.4	
	High-risk group	20.0	11.1	0.783	16.7	0	0.117
BCL2	Positive	38.1	30.9	0.037	62.1	57.1	0.993
	Negative	50.0	44.8		60.9	57.7	
BCL6	Positive	49.4	47.4	0.117	63.2	59.5	0.996
	Negative	35.4	29.6		59.5	58.3	
MUM1	Positive	41.8	35.0	0.773	57.9	55.3	0.224
	Negative	42.3	37.6		73.8	71.7	
Treatment	Chemotherapy	38.5	34.2	0.000	37.5	28.6	0.000
	Operation	11.1	0		29.4	23.5	
	Other therapy	24.1	25.0		0	0	
	Comprehensive treatment	59.4	51.0		79.2	76.6	
Cell derived	GCB	40.4	34.7	0.334	69.4	68.8	0.018
	NON-GCB	48.8	42.3		46.2	40.0	

Table 2. COX risk proportional regression model multivariate analysis of prognostic factors of node and gastrointestinal tract DLBCL patients

Estimate of parameter	Standard error	χ^2 value	*P* value	Risk ratio (95% credibility interval)
0.632	0.182	11.219	0.000	1.882 (1.300~2.724)
0.494	0.187	6.943	0.008	1.639 (1.135~2.366)
-0.201	0.071	7.957	0.005	0.818 (0.712~0.941)

Discussion

DLBCL is the most common NHL, which accounts for approximately 30% of primary NHL cases each year. The mortality rate of DLBCL is relatively high. Current researches have focused on seeking factors associated with disease prognosis from various aspects, and stratified the disease as carefully and comprehensively as possible, in order to provide standardized treatment and carry out individualized and stratified therapy on the basis of different risk factors for different patients. In the pathological diagnosis, screening out a group of effective and simple markers for DLBCL prognosis has important significance for the selection of chemotherapy regimens and the determination of prognosis. The gastrointestinal tract is the most common extranodal vulnerable site of DLBCL, in which GI-DLBCL cases account for approximately 30-40% of extranodal DLBCL cases. A related study revealed that [8] the overall prognosis of primary GI-DLBCL was better than that of primary N-DLBCL. The analysis of this study revealed that the 3- and 5-year survival rates of GI-DLBCL were 63.6% and 60.9%, respectively, while the survival rates of N-DLBCL were 43.1% and 38.2%, respectively; and the differences between these two were statistically significant (log-rank test, *P*=0.005). These were consistent with the results reported in a recent literature [9]. At present, the common treatment regimens of DLBCL are CHOP and R-CHOP regimens.

Table 3. COX risk proportional regression model multivariate analysis of prognostic factors of primary gastrointestinal DLBCL patients

Influence factor	Estimate of parameter	Standard error	χ^2 value	*P* value	Risk ratio (95% credibility interval)
IPI	0.741	0.122	36.853	0.000	2.098 (1.652~2.665)

Table 4. COX risk proportional regression model multivariate analysis of prognostic factors of primary node DLBCL patients

Influence factor	Estimate of parameter	Standard error	χ^2 value	*P* value	Risk ratio (95% credibility interval)
IPI	0.681	0.124	29.933	0.000	1.976 (1.548~2.522)
Treatment	-0.151	0.071	4.483	0.034	0.870 (0.747~0.989)

In this study, COX's regression model analysis revealed that comprehensive treatment (combined treatment of surgery, radiotherapy and chemotherapy) was a favorable prognostic factor for DLBCL and primary N-DLBCL overall, but its prognostic significance for primary GI-DLBCL remains unestablished. The optimal treatment mode of primary GI-DLBCL remains in exploration and debate at present [10]. In history, for a long time, the treatment of gastrointestinal lymphoma has been based on surgery, and supplemented with postoperative radiotherapy or chemotherapy. In this study, univariate survival analysis revealed that comprehensive treatment was associated with good prognosis of patients. It should be pointed out that in this study, 75.9% of GI-DLBCL patients underwent gastric cancer radical surgery. This may play a certain role in the satisfactory prognosis of primary GI-DLBCL.

IPI is an important evaluation index to guide the treatment and prognosis evaluation of DLBCL. Its clinical information is easy to obtain, and many studies have confirmed the reliability of this evaluation [11]. In this study, patients were grouped according to IPI score. Univariate survival analysis revealed that the 5-year survival rate of patients in each group was 67.4%, 40.9%, 17.5%, respectively; and the differences among different IPI grades were statistically significant. The results of further multivariate COX regression analysis also revealed that a IPI score >2 points was an independent risk factor for the prognosis of overall DLBCL, primary N-DLBCL and primary GI-DLBCL.

Bcl-2 protein is an apoptosis-related protein. Its overexpression can lead to the inhibition of cell apoptosis, and confer the survival advantage to lymphocytes; playing an important role in the occurrence of lymphoma and the sensitivity of lymphoma cells to radiotherapy and radiotherapy [12, 13]. The expression rate of Bcl-2 protein was 40-60% in primary DLBCL, and BCL-2 protein expression is an adverse prognostic factor in patients with DLBCL [14]. The follow-up analysis of this study revealed that the prognosis of patients with negative Bcl-2 was significantly better than in patients with positive Bcl-2, and the 3- and 5-year survival rates of patients with negative Bcl-2 were significantly longer than those of patients with positive Bcl-2; suggesting that Bcl-2 protein expression is a adverse prognostic factor of DLBCL [14]. Therefore, in the daily diagnosis, the detection of BCL-2 protein expression in DLBCL patients has an important significance. However, interestingly, in primary GI-DLBCL patients, the protein expression of BCL2 has no significance in predicting prognosis. This suggests that the pathogenesis or the Bcl2 expression mechanism of GI-DLBCL may be different from those of N-DLBCL. Primary GI-DLBCL can be divided into simple DLBCL and DLBCL containing MALT from pathological types. The latter is considered to arise from the transformation of large cell from MALT lymphoma. Studies have revealed that the BCL-10/MALT1 complex and API1/MALT1 fusion protein in MALT lymphoma could activate the NF-κB protein, induce tumor cells to express BCL-2 protein, and prevent apoptosis; leading to the neoplastic proliferation of cells [15, 16]. In addition, in 2008, WHO established a strict diagnostic criteria for extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissues (MALT lymphoma); and the high-grade MALT lymphoma case was directly classified into GI-DLBCL, thereby increasing the heterogeneity of GI-DLBCL. Therefore, the role of BCL-2 protein in the pathogenesis of GI-DLBCL is more complicated, affecting the indicating role of this protein in the prognosis of GI-DLBCL.

BCL-6 is a nuclear transcriptional inhibiting factor that mainly participates in regulating the

activation and differentiation of lymphocytes. In normal conditions, its role is to express germinal center B-cells. After these B-cells experiencing maturation in the germinal center, its expression gradually decreases. Therefore, the BCL-6 gene is not expressed in memory B-cells or plasma cells, and is not expressed in mantle cells, marginal zone cells and bone marrow precursor B-cells; and its low expression is an important factor for tumorigenesis [17]. The follow-up analysis of this study revealed that the prognosis of patients with positive BCL-6 was significantly better than that of patients with negative BCL-6, and the 3- and 5-year survival rates of patients with positive BCL-6 were significantly better than those with negative BCL-6; suggesting that a high expression of BCL-6 protein is a marker of better prognosis. This is consistent with the results in literatures [18-20]. However, in patients with primary GI-DLBCL, the expression of BCL-6 protein has no value in suggesting the prognosis. This suggests that the pathogenesis of DLBCL or the mechanism of BCL-6 expression in GI-DLBCL may be different from those of N-DLBCL. Mum-1 is a transcriptional regulatory factor that mainly regulates the differentiation of B-cells. Under normal conditions, it is expressed in B-cells at the terminal stage of differentiation, and differentiates into plasma cells in the germinal center, which is a marker of germinal center-derived cells [21]. Related studies have revealed that Mum-1 expression indicates poor prognosis, and is a prognostic marker independent of other biomarkers [22]. Follow-up data of this study revealed that the difference in the-expression of MUM1 protein between N-DLBCL and primary GI-DLBCL was not statistically significant.

In summary, the pathologic types of DLBCL are numerous and disorderly, and the treatment methods and prognoses of primary nodal and primary gastrointestinal DLBCL are also different. Therefore, it is necessary to distinguish between different primary sites and pathological types, study related prognostic factors, and seek for an optimal treatment method in depth. IPI >2 points and the expression of BCL-2 protein are independent risk prognostic factors for DLBCL and N-DLBCL. Chemotherapy combined with surgery plus radiotherapy is an independent favorable factor for DLBCL and primary N-DLBCL. The overall prognosis of primary GI-DLBCL is better than that of primary N-DLBCL. IPI score >2 points is an independent risk prognostic factor. The application of radical operation for primary GI-DLBCL treatment requires the verification of large-scale prospective studies.

Disclosure of conflict of interest

None.

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