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Prognostic Value of D-Dimer in Patients with Diffuse Large B-cell Lymphoma: A Retrospective Study*

Yu-di GENG[1†], Yi-ren CHEN[2†], Jin JIN[1], Xiao-di WANG[1], Shu ZHANG[1], Deng-ju LI[1#]
[1]*Department of Hematology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China*
[2]*College of Mathematics and Statistics, Shenzhen University, Shenzhen 518060, China*

Summary: This study evaluated the significance of serum D-Dimer for predicting survival of patients with diffuse large B-cell lymphoma (DLBCL). We analyzed the clinical data from 113 patients who were newly diagnosed with DLBCL at Tongji Hospital from January 2012 to January 2016. The results indicated that there were higher levels of D-Dimer in DLBCL patients with the following characteristics: stage Ⅲ/Ⅳ, lymphocyte monocyte ratio (LMR) <2.27, lactate dehydrogenase (LDH) > upper limit of normal (ULN), albumin (ALB) < 35 g/L, and anemia. After the first chemotherapeutic regimen, D-Dimer was significantly decreased concomitantly with LDH. Cox univariate regression analysis showed that the overall survival (OS) was negatively affected by the following factors: age > 60 years, stage Ⅲ/Ⅳ, LDH > ULN, LMR < 2.27, anemia and D-Dimer > 0.92. Multivariate analysis showed that only LDH > ULN (P=0.038) and age > 60 years (P=0.047) were independent adverse prognostic factors. However, it was suggested that D-Dimer could be regarded as a marker of high tumor burden and a potential prognostic screening tool for patients with DLBCL, not otherwise specified (NOS).
Key words: diffuse large B-cell lymphoma; D-Dimer; prognosis

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL) and accounts for approximately 31% of all NHL in Western countries and 37% of B-cell tumors worldwide[1, 2]. DLBCL is a heterogeneous entity with a wide range of outcomes[3]. The standard initial treatment of DLBCL is rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone on a 21-day schedule (RCHOP-21) for six cycles[1]. Although it is now a potentially curable malignancy, nearly 40% of patients with DLBCL die of either relapse or refractory disease[4].

The prognosis of DLBCL is a comprehensive result of host characteristics, tumor burden, tumor biology, tumor microenvironment and response to therapy[4]. The International Prognostic Index (IPI) for DLBCL includes five important factors: age, tumor stage, serum lactate dehydrogenase (LDH), performance status, and the number of extranodal disease sites. The revised IPI (R-IPI) is a better predictor of outcome than the IPI and it identifies 3 distinct prognostic groups with very good (94%), good (79%), and poor (55%) overall survival (OS) at 4 years, respectively, and the National Comprehensive Cancer Network IPI (NCCN-IPI)[5] further refines the categorization of age and LDH to better discriminate low- and high-risk subgroups[6]. Although diagnosis and treatment have improved dramatically with the use of several algorithms, approximately one-third of patients with advanced-stage DLBCL either remain refractory to therapy or suffer a relapse[7]. For this reason, other related factors should be evaluated to provide additional information for prognostic assessment.

Several potential factors have been proposed to predict the prognosis of DLBCL such as hemoglobin, C-reactive protein level, albumin, and lymphocyte/monocyte ratio, while further validation is needed[8–13]. Cancers often cause activation of the clotting system through humoral or mechanical effects, and cancer therapy is often accompanied with a hypercoagulable state[14]. The abnormal coagulation can cause serious complications, including venous thrombosis embolism (VTE) and disseminated intravascular coagulation (DIC), which lead to poor outcomes. Hemostatic markers vary dramatically with tumor evolution, and the extent of alteration in the coagulation and

Yu-di GENG, E-mail: gengyd1993@163.com; Yi-ren CHEN, E-mail: adavidcen@hotmail.com
†Both authors contributed equally to this work.
#Corresponding author, E-mail: lidengju@163.com
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fibrinolysis pathways has a great influence on the prognosis of cancer.

D-Dimer is a sensitive indicator of fibrin formation and degradation and thus of an ongoing thrombotic process[15]. It is also widely used to rule out deep venous thrombosis[16] as well as predict DIC and recurrent and future VTE[15, 17]. Tumor-related degradation products for coagulation and the fibrinolytic system such as D-Dimer may be utilized as predictors of tumor load and outcome. In fact, elevated D-Dimer has been found related to poor outcomes in several solid tumors such as colorectal cancer, melanoma and esophageal squamous cell carcinoma, as well as hematological neoplasms such as acute myeloid leukemia[18–20]. Based on previous studies, we intended to explore the potential relationship between D-Dimer and the prognosis of patients with DLBCL.

1 MATERIALS AND METHODS

1.1 Patients' Characteristics

Between January 2012 and January 2016, a total of 113 hospitalized patients with newly diagnosed DLBCL, not otherwise specified (NOS) were treated at Tongji Hospital in Wuhan, China. Patients with history of prior radiation therapy, cytotoxic chemotherapy, or any previous neoplasms or second primary malignancies were excluded. No pregnant patients or patients with prior coagulation instability, congenital coagulation disorders or thrombocytopenia were included. The Hans subtype classification showed that 40 cases were of germinal center B-cell (GCB) type and 42 cases of non-GCB type. Thrity-one cases had no enough information to determine the subtypes. Epstein-Barr virus (EBV)-DNA was detectable in 16 patients (14.16%). All patients received similar treatment regimens. The clinical characteristics obtained included age, sex, stage of disease, hemoglobin (HGB), albumin (ALB), lymphocyte monocyte ratio (LMR), HBsAg, serum D-Dimer and LDH. The study was reviewed and approved by the Institutional Review Board of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (IRB ID: TJ-C20160301) before the study began.

The immunoturbidimetry assay was used for detecting D-Dimer (Thermo Fisher Scientific, USA) and enzyme-linked immunosorbent assay for detecting LDH (Thermo Fisher Scientific, USA). Receiver operating characteristics curves (ROC) and the area under the curve (AUC) were used to determine the ideal cutoff value for survival as indicated by LMR and D-Dimer. The normal range for LDH measurement is 135–214 U/L. In accordance with World Health Organization guidelines, anemia is defined as an HGB < 120 g/L for females or < 130 g/L for males[6]. The diagnosis of DLBCL was based on the WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues[21].

1.2 Statistical Analysis

The Mann-Whitney *U* test was used to compare variables between groups. The Wilcoxon signed rank test was used to compare matched groups of LDH and D-Dimer values before and after each chemotherapy, respectively. OS from the initial diagnosis was estimated using Kaplan-Meier analysis. The log-rank test was used to compare the OS between two groups. The groups were divided by sex (male *vs.* female), age (< 60 *vs.* ≥ 60 years), staging (Ⅰ/Ⅱ *vs.* Ⅲ/Ⅳ), LMR (< 2.27 *vs.* ≥ 2.27), LDH value [≤ upper limit of normal (ULN) *vs.* > ULN], anemia status (Yes *vs.* No), ALB (< 35 *vs.* ≥ 35 g/L), and HBsAg status (positive *vs.* negative). A multivariate Cox proportional hazards regression model was used to analyze the data to assess the risk factors for OS. By binary logistic regression, we also assessed the synergistic effect of D-Dimer and age/LDH on prediction of the prognosis; the values of these functions were used as one marker and subjected to ROC analysis. A two-tailed $P<0.05$ was considered to be statistically significant.

2 RESULTS

2.1 Clinical Features

A total of 113 DLBCL cases diagnosed between January 2012 and January 2016 at Tongji Hospital were collected, including 60 males and 53 females, with an average age of 52 years (range, 17–82 years). The clinical characteristics are shown in table 1.

We selected the cutoff point of D-Dimer and LMR for predicting the survival outcomes based on the ROC curve analysis. The most discriminative cutoff value of LMR was 2.27 with an AUC value of 0.648 [95% confidence interval (CI), 0.543–0.754, $P=0.008$] and 0.92 for D-Dimer with an AUC value of 0.673 (95% CI, 0.572–0.773, $P=0.002$) (fig. 1).

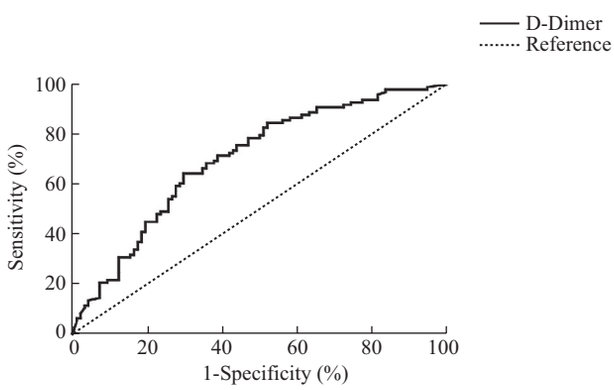

Fig. 1 The predictive value of D-Dimer for prognosis assessed by ROC curve analysis in 113 patients with DLBCL
Solid curve line represents a ROC curve of D-Dimer (AUC 0.673, 95%CI 0.572–0.773, sensitivity 84.4%, specificity 47.1%, $P=0.002$).

Table 1 Clinical characteristics and OS time of patients with DLBCL

Variables	Number (%)	D-Dimer		OS (month)	
		Mean±SD	*P* value	Mean±SD	*P* value
Sex			0.490		0.638
Male	60 (53.1%)	3.33±6.64		46.15±5.50	
Female	53 (46.9%)	1.67±1.18		41.03±4.18	
Age (year)			0.976		0.003
<60	76 (67.3%)	2.24±3.25		54.54±4.80	
≥60	37 (32.7%)	3.20±7.33		22.58±3.42	
Stage			<0.001		0.025
I/II	32 (28.3%)	1.06±0.89		45.54±4.10	
III/IV	81 (71.7%)	3.14±5.73		42.46±4.76	
LMR			<0.001		0.002
<2.27	53 (46.9%)	3.55±6.69		35.89±5.61	
≥2.27	60 (53.1%)	1.68±2.36		47.97±3.62	
LDH*			<0.001		<0.001
≤ULN	39 (38.2%)	1.14±1.19		66.39±5.35	
>ULN	63 (61.8%)	3.56±6.37		24.92±2.68	
ALB			<0.001		0.232
<35 g/L	41 (36.3%)	4.31±7.73		26.21±3.16	
≥35 g/L	72 (63.7%)	3.56±6.37		51.40±4.78	
HGB			<0.001		0.006
<LLN	72 (63.7%)	3.25±6.00		40.11±5.52	
≥LLN	41 (36.3%)	1.34±1.60		49.97±3.80	
HBsAg			0.122		0.102
Positive (+)	94 (83.2%)	2.18±4.55		37.97±2.84	
Negative (-)	19 (16.8%)	4.39±6.45		37.21±8.69	

LMR, lymphocyte monocyte ratio; LDH, lactate dehydrogenase; ULN, upper limit of normal; ALB, albumin; HGB, hemoglobin; LLN, lower limits of normal; HBsAg, hepatitis B surface antigen; SD, standard deviation; OS, overall survival

*LDH values for 11 patients were missing in the medical records.

The comparison results indicated that the D-Dimer values were higher in DLBCL patients with the following characteristics: stage Ⅲ or Ⅳ (3.14 *vs.* 1.06, *P*<0.001), LMR<2.27 (3.55 *vs.* 1.68, *P*<0.001), LDH value > ULN (3.56 *vs.* 1.14, *P*<0.001), ALB < 35 g/L (4.31 *vs.* 1.56, *P*<0.001), and HGB < 120 g/L for females and < 130 g/L for males (3.25 *vs.*1.34, *P*<0.001). However, there was no statistically significant difference in D-Dimer between the two groups divided in terms of age (<60 *vs.* ≥60 years), sex (male *vs.* female) or HBsAg (positive *vs.* negative).

2.2 Changes of D-Dimer after Chemotherapy

We collected the D-Dimer and LDH values before and after chemotherapy every time the patients returned to receive the next periodic chemotherapy until the third round. The comparison between the first chemotherapy indicated that D-Dimer decreased remarkably (2.23 *vs.* 0.89, *P*=0.017) together with LDH (442.02 *vs.* 227.11, *P*=0.008). However, rebounds of both LDH and D-dimer values were commonly seen during the intermission of chemotherapy. No significant decreases were discovered when we compared LDH and D-Dimer values in the subsequent two chemotherapy rounds. However, both LDH and D-Dimer values presented a declining trend after chemotherapy (table 2). More precisely, the percentage of patients with D-Dimer in the normal range was 20.4% at the beginning of chemotherapy and 33.3%, 46.3% and 47.4% after every subsequent round. The percentage of patients with LDH in the normal range was 38.2% at the beginning of chemotherapy and 52.1%, 65.8%, and 73.2% after every subsequent round.

2.3 Survival Analysis

All of the patients were followed up until June

Table 2 Variation of LDH and D-Dimer pre-chemotherapy and post-chemotherapy

Cycles	Detection marker	Actual cases	Prechemotherapy	Post-chemotherapy	*P* value
1st	LDH	44	442.02±449.43	227.11±90.46	0.008
2nd		32	223.38±83.03	188.51±67.68	0.054
3rd		28	228.00±48.34	202.00±48.34	0.096
1st	D-Dimer	48	2.23±3.78	0.89±0.70	0.017
2nd		32	0.77±0.57	0.68±0.53	0.108
3rd		29	0.84±0.65	0.79±0.54	0.952

30th 2016, and the median follow-up was 14 months (range: 1–82 months). The attrition rate of patients during follow-up was 1.8%. The 75th percentile of OS was 8 months. The 2-year OS rate was 60% and the 5-year OS rate was 52% (fig. 2). At the last follow-up, 66 patients were alive, 45 were dead, and 2 were lost to follow up. OS significantly decreased in patients with D-Dimer >0.92 (39.90 *vs.* 52.69, *P*=0.001). The univariate analysis shown in table 1 indicated that patients younger than 60 years old were predicted to have a longer survival time (54.54 *vs.* 22.58 months, *P*=0.003). Patients with LDH ≤ ULN lived relatively longer than those with LDH > ULN (66.39 *vs.* 24.92 months, *P*<0.001). Longer OS was also observed in patients with stage Ⅰ or Ⅱ disease (45.54 *vs.* 42.46 months, *P*=0.025). The difference in OS was remarkable between LMR < 2.27 and LMR ≥ 2.27, with latter value indicative of a longer survival time (47.97 *vs.* 35.89 months, *P*=0.002). In addition, patients who suffered from anemia (HGB < 120 g/L for females and < 130 g/L for males) were predicted to have a shorter survival time (40.11 *vs.* 49.97 months, *P*=0.006). However, sex, ALB < 35 g/L and a positive HBsAg status showed no correlations with OS in our study. Further multivariate analysis included all of the variables with *P*<0.05 mentioned above, but only LDH >ULN (*P*=0.038) and age > 60 years (*P*=0.047) were found to be independent prognostic predictors (table 3).

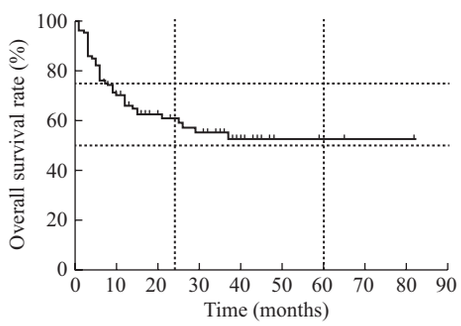

Fig. 2 The overall survival curve for all of the patients with newly diagnosed DLBCL
The 75th percentile of OS was 8 months. The 2-year OS rate was 60% and the 5-year OS rate was 52%.

Table 3 Multivariate analysis of factors influencing the OS of patients with DLBCL

Variables	OS	
	P value	HR (95% CI)
LDH (≤ ULN *vs.* > ULN)	0.039	0.389 (0.159–0.952)
Stage (Ⅰ/Ⅱ *vs.* Ⅲ/Ⅳ)	0.576	0.775 (0.318–1.890)
Age (≤ 60 *vs.* > 60 years)	0.042	0.507 (0.264–0.976)
LMR (< 2.27 *vs.* ≥ 2.27)	0.179	1.641 (0.796–3.380)
HGB (< LLN *vs.* ≥ LLN)	0.225	1.642 (0.737–3.662)
D-Dimer	0.442	1.017 (0.974–1.062)

LDH, lactate dehydrogenase; ULN, upper limit of normal; LMR, lymphocyte monocyte ratio; HGB, hemoglobin; LLN, lower limits of normal; OS, overall survival

To further investigate the predictive values of LDH and age, as well as other important potential factors including D-Dimer, ROC curves were generated to identify the sensitivity and specificity of these parameters. For age, ROC curves showed a sensitivity of 48.9% and a specificity of 77.9%, with an AUC of 0.663 (95% CI, 0.556–0.770, *P*=0.003). For LDH, ROC curve showed a sensitivity of 85.4% and a specificity of 52.5%, with an AUC of 0.722 (95% CI, 0.624–0.821, *P*<0.001). When age and D-Dimer were used in combination for optimum prediction of prognosis, ROC curve showed that they had a higher sensitivity (62.2%) than age and a slightly lower specificity (70.6%) (AUC 0.663, 95% CI, 0.556–0.770, *P*=0.003); When LDH and D-Dimer were used in combination for optimum prediction of prognosis, ROC curve showed the combination had a higher specificity (65.6%) than LDH and a slightly lower sensitivity (73.2%) (AUC 0.722, 95% CI, 0.624–0.821, *P*<0.001). Further studies on patients with LDH > ULN (*n*=63) indicated that D-Dimer predicted a higher specificity of 82.8% (AUC 0.680, 95% CI, 0.438–0.722, *P*<0.001) than age (65.5%) or LDH (65.5%). For patients aged > 60 years (*n*=37), ROC curve of D-Dimer also showed a higher specificity of 93.3% (AUC 0.626, 95% CI, 0.445–0.807, *P*<0.001) than age (80.0%) or LDH (84.6%) alone.

3 DISCUSSION

Of all the discussed potential prognostic factors, age at diagnosis, serum LDH levels and Ann Arbor stage have been previously recognized as independent predictors of DLBCL in IPI[22]. In fact, LDH has been observed to increase in many types of cancer, which is often associated with high tumor burden and poor outcome[23, 24]. Upregulation of LDH ensures substantial glycolytic metabolism to store energy for tumor growth since malignant cells utilize 5–10 times more glucose than cells in normal tissues and convert most of the glucose into lactate[23, 25]. In our study, D-Dimer was significantly higher in patients with abnormal LDH levels. The decreased trend of D-Dimer level was consistent with LDH changes after every chemotherapy. In particular, sharp decreases of both D-Dimer and LDH were found after the first round of chemotherapy. The reduced tumor burden after chemotherapy probably accounted for these results.

Malignant diseases are often accompanied by activated blood coagulation and the development of hypercoagulability during growth[26]. There is also evidence that anticoagulant therapy can reduce the incidence and mortality of cancer[27]. The extent of overactive coagulation has been reported to correlate with tumor stage and prognosis in some malignancies[28]. Malignant cells can also activate blood coagulation by

either releasing proinflammatory and proangiogenic cytokines or interacting directly with the native vasculature and blood cells to cause a disturbance of the coagulation system[26]. Fibrin formation and remodeling are involved in many steps of metastasis and play a crucial role in the formation of new vessels, which are associated with tumor angiogenesis, metastasis, and invasion[28]. D-Dimer is the unique degradation product of cross-linked fibrin and has been shown to be elevated in many types of cancer[29]. The alteration of hemostatic parameters, including D-Dimer, during the coagulation or fibrinolysis processes may increase thromboembolic complications resulting in morbidity and mortality[28]. A study showed that D-Dimer correlated well with tumor stage and IPI, which revealed specific interactions between angiogenic and coagulation-fibrinolysis system[30]. Patients with DLBCL frequently show comorbidity with coagulation disorders such as DIC and VTE[31]. A slight or serious imbalance in the coagulation system is associated with a relatively worse prognosis[32]. A study by Lekovic *et al* demonstrated that patients in the VTE subgroup had significantly higher D-Dimer and negatively influenced survival of patients with primary mediastinal large B-cell lymphoma[33].

Our results also showed that the OS of patients with DBLCL was negatively affected by D-Dimer based on the Cox univariate regression analysis. However, in the multivariable analysis, only age and LDH were identified as independent prognostic factors. The exclusion of D-Dimer may result from the dominant influence of age and serum LDH levels on the prognosis assessment. A latest study found D-Dimer as an independent predictor of worse OS in DLBLC patients[34]. The inconsistency may be the result of different cutoff values and analyzed population. Therefore, the significance of D-Dimer could be obscured by LDH and age in our study. However, we found that when D-Dimer was combined with either LDH or age, the sensitivity and specificity of prediction could be balanced to relatively high values. In addition, to predict the prognosis of patients with LDH > ULN or age > 60 years, D-Dimer alone could obtain a higher specificity than LDH or age alone. All the analysis above indicated that D-Dimer was still an important predictor in patients with DLBCL. Particularly, for aged people with abnormal LDH values, D-Dimer could predict the prognosis more accurately.

Our study also discussed several other routine blood parameters, including anemia and lower LMR, which were found to be associated with D-Dimer and the prognosis of patients with DLBCL apart from traditional prognostic models. In fact, anemia is observed frequently in lymphoproliferative disorders with a reported incidence of approximately 39% in patients with DLBCL[6]. Plenty of studies have recognized anemia as a significant prognostic factor in NHL[6, 8, 9]. Cancer-related anemia may result from bone marrow involvement, problems with iron reutilization and inhibition of erythropoiesis by inflammatory mediators[6]. LMR, which integrates absolute lymphocyte count (AMC)/absolute monocyte count (ALC), is a reflection of the tumor environment and host immunity, which plays an important role in lymphoma progression[10]. Several other studies supported LMR as an independent predictor of DLBCL, although the cutoff value of LMR varied from 2.0 to 4.0[10, 35–37].

The relatively small sample size, unbalanced grouping due to the retrospective nature, missing data and heterogeneity of patients should also be mentioned in the present study. Considering that D-Dimer as well as HGB and LMR are easily derived from a simple blood test, it is both technically and financially feasible to conveniently apply this protocol to routine clinical practice, and we believe that it is worth further exploration to validate these results in future prospective studies.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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