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ORIGINAL RESEARCH

Contrast-Enhanced Ultrasound Parameters and D-Dimer: New Prognostic Parameters for Diffuse Large B-Cell Lymphoma

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Objective: To investigate the predictive role of contrast-enhanced ultrasonography (CEUS) plus D-dimer levels in the prognosis of patients with diffuse large B-cell lymphoma (DLBCL).

Methods: CEUS was applied to assess lymph nodes in 186 patients with confirmed DLBCL. The clinical data and laboratory indicators were collected from these patients, and a retrospective analysis was conducted on the relationship between the quantitative parameters of CEUS (TTP, PI, AUC, WOT), D-dimer levels, and clinical features of the DLBCL patients. The Cox regression model was used for univariate and multivariate analyses for the risk factors associated with the prognosis.

Results: There was an increase of D-dimer levels in advanced DLBCL patients, who were combined with a significant reduction in TTP and WOT and a significant increase in PI and AUC. D-dimer levels and quantitative parameters of CEUS were strongly correlated with the Ann Arbor, B symptoms, International Prognostic Index (IPI), LDH and CRP levels. The results of the Cox regression model indicated that D-dimer levels, TTP and PI, the quantitative parameters of CEUS, were important prognostic factors for DLBCL.

Conclusion: CEUS results and D-dimer levels can be used as independent prognostic factors for DLBCL.

Keywords: diffuse large B-cell lymphoma, contrast-enhanced ultrasonography, D-dimer, prognosis

Introduction

Lymphoma is a hematologic cancer featured by high malignancy. Its incidence and mortality rank the eleventh and the tenth of all cancers, respectively.[1] In recent years, an increase in the incidence of lymphoma has been witnessed both at home and abroad. Non-Hodgkin's lymphoma (NHL) accounts for 80–90% of all lymphomas,[2] and diffuse large B-cell lymphoma (DLBCL) is the most common type of NHL, accounting for about 1/3.[3] DLBCL is a highly heterogeneous neoplasm, and the prognosis may vary dramatically across the patients. Over 60% of the DLBCL patients can be cured by rituximab, which has been clinically used in recent years. However, some patients are unresponsive to rituximab.[4] Therefore, accurate risk classification is conducive to improving the efficacy of DLBCL. International Prognostic Index (IPI) is a common prognostic indicator for survival, but it may perform poorly in lymphoma.[5] It is highly urgent to develop novel and useful early detection methods and laboratory indicators to improve the prognosis of DLBCL patients.

Contrast-enhanced ultrasonography (CEUS) is a classic non-invasive examination method that detects intra-tumor microvascular perfusion. CEUS is generally used in the diagnosis of many tumors (eg, breast cancer and liver cancer).[6] Ultrasonography is a preferred choice to detect superficial lymph node enlargement.[7] As compared with the conventional ultrasound method, CEUS is more capable of visualizing the capillaries within the lesions, which significantly enhances the diagnostic value of ultrasonography in lymph nodes.[8] Similar to solid tumors, a large number of new blood vessels are formed around DLBCL. CEUS can accurately show angiogenesis and features of the new blood vessels in DLBCL. However, CEUS has been rarely used in DLBCL, and the application value of CEUS in DLBCL deserves further investigation.

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D-dimer is the product of fibrin hydrolysis, and a high D-dimer level indicates a hypercoagulable state or secondary fibrinolytic hyperactivity. Tumor patients are usually combined with a hypercoagulable state,[9] which implies a risk of embolism. Therefore, D-dimer levels are closely related to prognosis of tumor patients. Many studies have shown that plasma D-dimer levels are higher in solid tumor patients with worse prognosis, such as breast cancer, lung cancer, gastric cancer, colon cancer, pancreatic cancer, and prostate cancer.[10] In addition to some shared features between lymphoma as hematologic cancer and solid tumors, lymphoma also has some distinctive features. It is still controversial whether D-dimer levels in lymphoma, especially DLBCL, have a diagnostic and prognostic value.

In this study, the predictive value of CEUS with plasma D-dimer levels in the survival and prognosis of DLBC patients was assessed.

Materials and Methods

Subjects and Clinical Data

From January 2013 to December 2015, there were 186 patients who received CEUS at our Hospital and were confirmed as DLBCL. All of them satisfied the following criteria: no recent history of infection; no personal history of underlying diseases, such as hypertension, diabetes, coronary heart disease, kidney diseases, and tumors of other positions. They were aged 20 to 70 years old (median age, 50 years old). The clinical data and laboratory indicators were collected from these patients using the case management system, including the followings: age, gender, Ann Arbor symptom, B symptom (fever above 38°C for unknown reasons, night sweat, and body weight reduction for over 10% within the last six months), IPI, serum lactate dehydrogenase (LDH) levels, C-reactive protein (CRP) levels, D-dimer levels, and the use of rituximab. All patients were followed up. Informed consent was obtained from all patients. The protocol was approved by the ethics committee of the first affiliated hospital of Zhengzhou University and the Declaration of Helsinki was followed.

CEUS Procedures

The IU22 ultrasound system (Royal Philips Electronics NV, Eindhoven, the Netherlands) was used for routine examination of the neck of patients with DLBCL, and suspicious lymph nodes were selected for CEUS (The CEUS of the patient's cervical lymph nodes is shown in Figure 1), following the standard operating procedures. The informed consent for CEUS was signed by all patients, and the procedure was performed by ultrasound physicians who had over five years of experience and were blinded to the pathological results of the patients. Philips L12-5 scanner was used for CEUS. Before the examination, all patients received an injection of 2.4 mL SonoVue (Bracco, Italy) via the superficial cubital vein, followed by washing with 5 mL of normal saline. CEUS lasted for 90s within 4 min after injection of the contrast medium, and the lesions were observed. Dynamic images were stored in the hard disk of the ultrasound machine. The microvascular images were analyzed by using the Qlab software. The following parameters of CEUS were recorded:

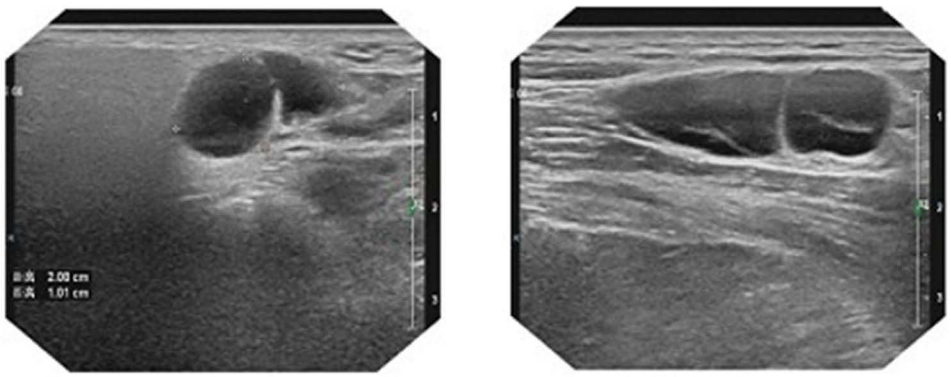

Figure 1 CEUS examination results of cervical lymph nodes in DLBCL patients. Several hypoechoic nodules can be seen on both sides of the neck, with clear boundaries, capsules, and abnormal ratio of cortex to medulla. The larger one on the left and the right is located in the V area, and the size is 21*19mm/19*9mm. CDFI Shows blood flow signals in the bilateral hypoechoic nodules of the neck. CEUS examination result suggests multiple lymph nodes on both sides of the neck.

peak intensity (PI), area under the curve (AUC), time to peak (TTP), and washout time (WOT). The intensity of enhancement was also determined as the qualitative parameter. The correlation analyses were conducted between these CEUS parameters and clinical features of the patients.

Statistical Analysis

All statistical analyses were performed using SPSS 22.0 software. The correlation between D-dimer levels and quantitative parameters of CEUS and the clinical stage of patients was analyzed by using *t*-test. The relationship of D-dimer levels and quantitative parameters of CEUS to clinicopathological features of the patients was analyzed by χ^2 test. The relationship between D-dimer levels and intensity of enhancement in CEUS was examined by the Spearman's rank correlation coefficient. The Cox regression model was used to assess the relative risk of poor prognosis for each clinicopathological parameter. P<0.05 indicated a significant difference.

Results

Comparison of D-Dimer Levels and Quantitative Parameters of CEUS Across DLBCL Patients in Different Clinical Stages

As compared with the early-stage patients (stage I–II), advanced (stage III–IV) patients showed significantly enhanced angiogenesis. The perfusion time-intensity curve was further analyzed, and it was found that TTP and WOT were significantly shortened in advanced DLBCL patients. At the same time, PI and AUC increased dramatically (Figure 2 and Table 1, P<0.05). Besides, D-dimer levels were compared among the DLBCL patients in different clinical stages. The results showed that plasma D-dimer levels in the advanced patients (stage III–IV) were considerably higher than those of the early-stage patients (stage I–II) (Table 1 and Figure 1, P<0.05).

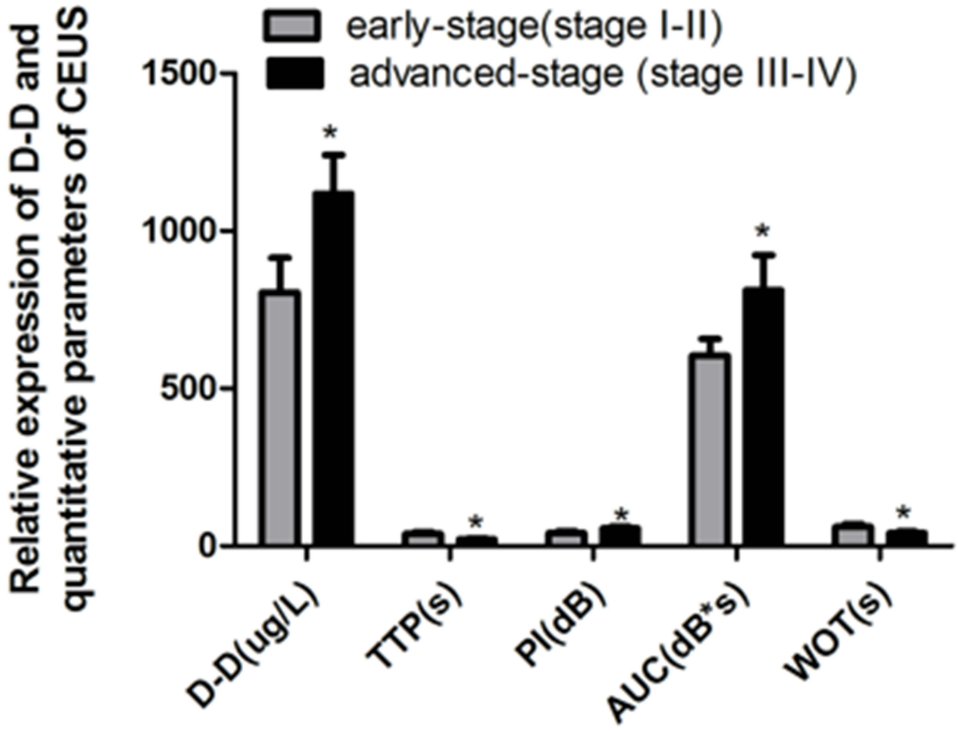

Figure 2 D-dimer levels and quantitative parameters of CEUS in 186 patients in different clinical stages. *P<0.05, as compared with the early stage.

Table 1 D-Dimer Levels and Quantitative Parameters of CEUS in 186 Patients with DLBCL

	D-D(ug/L)	TTP(s)	PI(dB)	AUC(dB*s)	WOT(s)
Early-stage(stage I–II)	804.52±110.33	37.51±6.72	40.48±5.77	603.92±52.67	60.63±8.34
Advanced-stage (stage III–IV)	1118.32±121.83*	20.34±4.21*	55.24±7.22*	812.43±110.21*	40.45±5.34*

Note: *P<0.05, as compared with the early stage.
Abbreviations: DLBCL, diffuse large B-cell lymphoma; CEUS, contrast-enhanced ultrasonography; D-D, D-dimer; TTP, time to peak; PI, peak intensity; AUC, area under the curve; WOT, washout time.

Relationship Between D-Dimer Levels and Clinicopathological Features of the DLBCL Patients

The 186 DLBLC patients were divided into normal D-dimer level group and high D-dimer level group based on D-dimer levels. There were 80 patients in the normal D-dimer level group and 106 patients in the high D-dimer level group. As compared with the normal D-dimer level group, there was a significant increase in the proportion of patients in stage III–IV in the high D-dimer level group, according to the Ann Arbor staging system. Moreover, patients in the high D-dimer level group were more likely to have B symptom and also had a significant increase in IPI (Table 2, P<0.01). Besides, the proportion of patients with high LDH and CRP levels in the high D-dimer level group was significantly increased than that in the normal D-dimer group (Table 3, P<0.01).

Table 2 Correlation Between D-Dimer Levels and Clinicopathological Features of 186 DLBCL Patients

Clinicopathological Features	Normal D-D Group n=80	High D-D Group n=106	P value
Gender			0.388
Male	46(57.5%)	56(52.8%)	
Female	34(42.6%)	50(47.2%)	
Age (years)			0.218
<60	42(52.5%)	54(50.9%)	
≥60	38(47,5%)	52(49.1%)	
Ann Arbor stage			<0.01
Stage I–II	31(38.8%)	26(24.5%)	
Stage III–IV	49(61.2%)	80(75.5%)	
B symptom			<0.01
Yes	45(54.9%)	73(68.9%)	
No	35(45.1%)	33(31.1%)	
IPI score			<0.01
0–2	57(71.2%)	46(43.3%)	
3–5	23(28.8%)	60(56.6%)	
LDH (U/L)			<0.01
≤250	53(66.2%)	37(34.9%)	
>250	27(33.8%)	69(65.1%)	
CRP (mg/L)			<0.01
≤8	57(71.3%)	34(32.1%)	
>8	23(28.7%)	72(67.9%)	
Chemotherapy regimens			0.137
R-CHOP	65(81.3%)	89(83.9%)	
CHOP	15(18.7%)	17(16.1%)	

Note: B symptom: fever above 38°C for unknown reasons, night sweat, and body weight reduction for over 10% within the last six months.
Abbreviations: DLBCL, diffuse large B-cell lymphoma; D-D, D-dimer; IPI, International Prognostic Index; LDH, lactate dehydrogenase; CRP, C-reactive protein; R-CHOP, rituximab plus chemotherapy-cyclophosphamide, doxorubicin, vincristine, and prednisone; CHOP, chemotherapy-cyclophosphamide, doxorubicin, vincristine, and prednisone.

Table 3 Relationship Between the Quantitative Parameters of CEUS and Clinicopathological Features of 186 DLBCL Patients

Clinicopathological Features	TTP(s)	PI(dB)	AUC(dB*s)	WOT(s)	P value
Gender					0.322
Male	22.34±2.01	45.21±5.29	701.12±52.22	56.24±7.32	
Female	21.22±1.91	42.76±4.33	692.83±48.51	55.03±7.81	
Age (years)					0.203
<60	21.55±1.93	43.76±4.21	680.32±48.56	53.72±8.90	
≥60	23.87±1.84	45.21±3.93	682.71±47.98	55.43±7.35	
Ann Arbor stage					<0.01
Stage I–II	37.51±6.72	40.48±5.77	603.92±52.67	60.63±8.34	
Stage III–IV	20.34±4.21	55.24±7.22	812.43±110.21	40.45±5.34	
B symptom					<0.01
Yes	21.91±1.95	48.45±4.13	685.34±40.81	47.84±4.99	
No	28.43±2.09	39.81±3.19	660.35±39.75	59.41±5.02	
IPI score					<0.01
0–2	27.94±1.65	42.93±5.27	690.36±47.83	56.88±4.95	
3–5	21.93±1.02	53.53±4.99	700.84±46,92	45.57±5.17	
LDH (U/L)					<0.01
≤250	28.88±2.36	44.82±6.03	684.34±44.37	60.01±6.93	
>250	21.84±1.97	55.39±5.86	698.57±45.71	50.82±5.57	
CRP (mg/L)					0.062
≤8	25.64±1.93	48.91±4.92	702.17±50.29	58.76±8.52	
>8	20.81±1.37	47.67±5.31	701.86±49.91	56.48±7.18	
Chemotherapy regimens					0.192
R-CHOP	23.57±1.68	47.63±6.99	695.22±62.65	57.42±5.78	
CHOP	24.82±2.35	46.76±5.83	698.79±68.15	56.93±6.88	

Note: B symptom: fever above 38°C for unknown reasons, night sweat, and body weight reduction for over 10% within the last six months.
Abbreviations: DLBCL, diffuse large B-cell lymphoma; CEUS, Contrast-enhanced ultrasonography; IPI, International Prognostic Index; LDH, lactate dehydrogenase; CRP, C-reactive protein; TTP, time to peak; PI, peak intensity; AUC, area under the curve; WOT, washout time; R-CHOP, rituximab plus chemotherapy-cyclophosph amide, doxorubicin,vincristine,andprednisone; CHOP, chemotherapy-cyclophosphamide, doxorubicin, vincristine, and prednisone.

Relationship Between Quantitative Parameters of CEUS and Clinicopathological Features of DLBCL Patients

The quantitative parameters of CEUS examined in this study included TTP, PI, AUC, and WOT. A correlation analysis showed that TTP, PI, AUC, and WOT were not correlated with the patients' age, gender, CRP levels, and the use of rituximab. Instead, they were closely related to the Ann Arbor stage, B symptom, IPI, and LDH levels (Table 3, P<0.01).

Correlation Analysis Between D-Dimer Levels and Qualitative Parameters of CEUS

CEUS was performed for 186 DLBCL patients using Sonovue. The patients were divided into hyper-enhancement and non-hyper-enhancement (iso-enhancement and hypo-enhancement) groups based on the intensity of enhancement, the qualitative parameter. Among 186 DLBCL patients, there were 99 patients in the hyper-enhancement group, and 87 patients in the non-hyper-enhancement group. The correlation analysis showed that the intensity of enhancement in CEUS was correlated significantly with D-dimer levels (Table 4, P<0.05). Those with hyper-enhancement in CEUS also had a higher D-dimer level.

Influence of D-Dimer Levels and Intensity of Enhancement in CEUS on the Prognosis of DLBCL Patients

All patients were followed up, and the influence of D-dimer levels and intensity of enhancement in CEUS on the prognosis of the patients was analyzed. The results showed that the progression-free survival (PFS) in the high D-dimer level group was significantly shortened as compared with the normal D-dimer level group (Figure 3, P=0.003). The intensity of enhancement

Table 4 Correlation Between D-Dimer Levels and Intensity of Enhancement in CEUS

Intensity of Enhancement of CEUS	D-D			P value
	Normal D-D Group	High D-D Group	Total	
Hyper-enhancement	34	65	99	0.04
Non-hyper-enhancement	46	41	87	
Total	80	106	186	

Abbreviations: CEUS, contrast-enhanced ultrasonography; D-D, D-dimer.

in CEUS had a similar influence on PFS. That is, PFS was significantly shortened in patients with hyper-enhancement in CEUS (Figure 3, P=0.02). Given the significant correlation between the D-dimer level and intensity of enhancement in CEUS, we further investigated the correlation between these two factors combined and PFS. It was found that the PFS in patients with high D-dimer level and hyper-enhancement in CEUS was dramatically shorter than that in those with normal D-dimer level and non-hyper-enhancement (Figure 3, P<0.001). The above results indicated that the D-dimer level and intensity of enhancement in CEUS could be used as important prognostic factors in DLBCL.

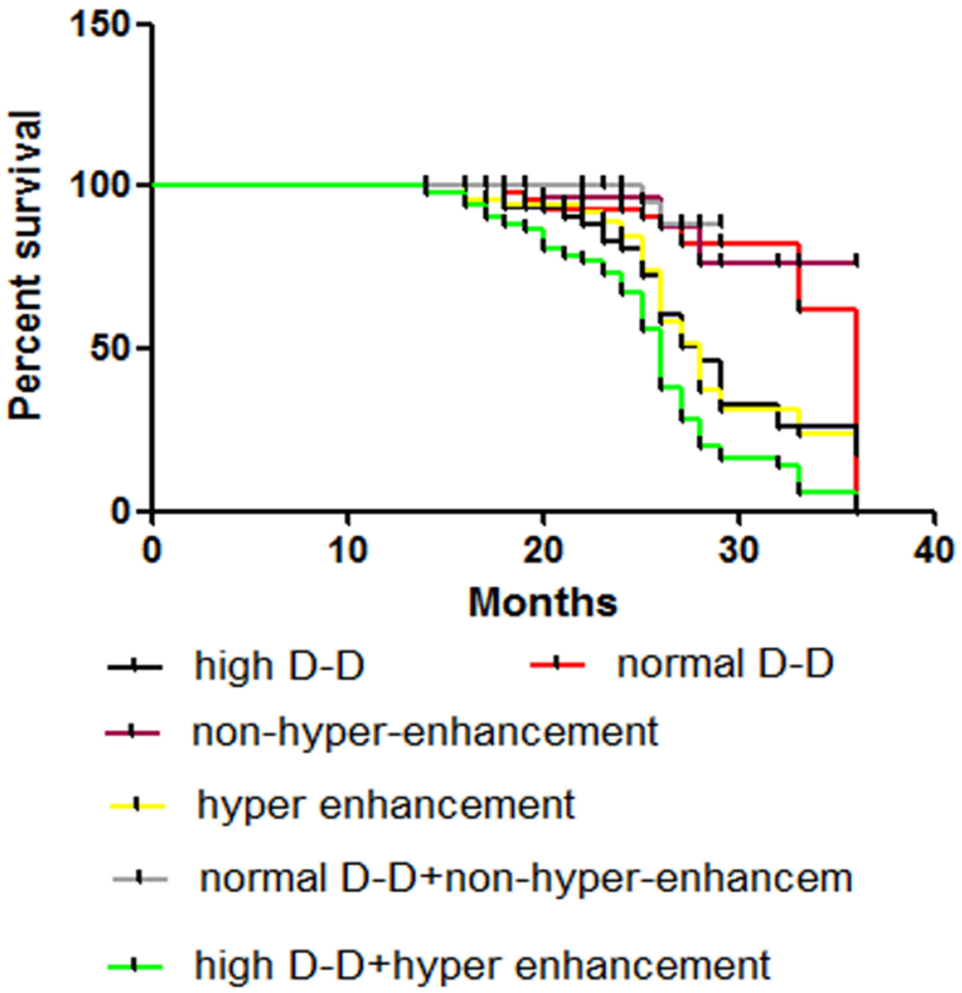

Figure 3 Influence of D-dimer levels and intensity of enhancement in CEUS on the prognosis of DLBCL patients.

Correlation of the Prognostic Factors in DLBCL Patients

Next, the potential correlations between clinicopathological features, laboratory indicators, and prognosis were further analyzed. Univariate analysis was performed respectively for age, gender, Ann Arbor stage, B symptom, IPI, LDH level, CRP levels, D-dimer levels, quantitative parameters of CEUS (TTP, PI, AUC, WOT) and the use of rituximab (Table 5). According to the univariate analysis, age, Ann Arbor stage, B symptom, IPI, LDH level, CRP levels, D-dimer levels, TTP, PI, AUC, WOT and use of rituximab were all correlated with prognosis of the patients (P<0.05). The potential influence factors were further included for multivariate analysis using the Cox regression model. The results showed that age, Ann Arbor stage, IPI, D-dimer levels, TTP, PI, and use of rituximab were independent prognostic factors in DLBCL patients (Table 6, P<0.05).

Discussion

DLBCL is a common malignancy originating from the hematopoietic and lymphatic system, and it is also the most common type of NHL. DLBCL is featured by high invasiveness and heterogeneity. One large-size study has shown that in China, DLBCL accounts for 45.8% of all NHL and 40.1% of all lymphomas.[11] DLBCL may affect any age group, and the elderly patients account for the largest proportion. The median age of onset is 70 years old. In China, the median age of onset is about 60 years old for DCBCL.[12,13] About 60% of the patients can be cured by rituximab and hematopoietic

Table 5 Univariate Analysis of Progression-Free Survival (PFS) in DLBCL Patients

Factors	HR	95% CI	P value
Gender	0.83	0.452–1.076	0.144
Age	2.376	1.793–2.989	<0.001
Ann Arbor stage	2.198	1.583–3.677	<0.001
B symptom	1.711	1.227–2.502	<0.001
IPI score	2.096	1.794–2.447	<0.001
LDH	2.671	1.898–3.963	<0.001
CRP	2.773	1.798–3.858	<0.001
D-D	3.132	2.376–4.893	<0.001
Rituximab	0.639	0.367–0.877	<0.001
TTP	2.016	1.476=2.543	<0.001
PI	1.586	1.243–2.556	<0.001
AUC	0.894	0.701–0.993	<0.001
WOT	0.837	0.692–1.031	<0.001

Note: B symptom: fever above 38°C for unknown reasons, night sweat, and body weight reduction for over 10% within the last six months.

Abbreviations: DLBCL, diffuse large B-cell lymphoma; IPI, International Prognostic Index; LDH, lactate dehydrogenase; CRP, C-reactive protein; D-D, D-dimer; TTP, time to peak; PI, peak intensity; AUC, area under the curve; WOT, washout time; HR, hazard ratio; CI, confidence interval.

Table 6 Multivariate Analysis of Prognosis in DLBCL Patients

Factors	HR	95% CI	P value
Age	1.897	1.492–2.633	<0.001
Ann Arbor stage	2.188	1.539–2.876	<0.001
IPI score	1.604	1.229–1.937	<0.001
LDH	2.011	1.506–2.774	0.022
D-D	1.893	1.247–2.899	0.015
Rituximab	0.476	0.212–0.757	0.036
TTP	2.115	1.487–2.793	0.027
PI	1.683	1.129–2.253	0.019

Abbreviations: DLBCL, diffuse large B-cell lymphoma; IPI, International Prognostic Index; LDH, lactate dehydrogenase, D-D, D-dimer; TTP, time to peak; PI, peak intensity; HR, hazard ratio; CI, confidence interval.

stem cell transplantation. However, there are still 1/3 of the DLBCL patients who are unresponsive to chemotherapy or relapse within a short time after remission. DLBCL is highly heterogeneous in clinical manifestations, clinical efficacy, and prognosis, which adds to the difficulty of making a right therapeutic choice and prognostic prediction.[14] Therefore, a fast and accurate prognostic evaluation of DLBCL patients is highly important for individualized therapy.

The use of SonoVue in CEUS can greatly increase the backscattering of the ultrasonic wave, thereby providing more accurate information on the microvasculature system.[15] CEUS is a non-invasive diagnostic technique that combines qualitative analysis (intensity of enhancement) and quantitative analysis (time-intensity curve). CEUS offers an early evaluation of microvascular perfusion within the tumor lesions[16] and therefore plays an important role in the early diagnosis and prognostic prediction for many solid tumors.[17–20] However, CEUS is rarely used in hematologic malignancies, especially DLBCL. By comparing the quantitative parameters of CEUS across DLBCL patients in different clinical stages, we found that both PPT and WOT were significantly shortened in advanced DLBCL, while PI and AUC increased dramatically. The quantitative parameters of CEUS are closely related to microvascular perfusion. As the disease progresses, the number of new blood vessels within the DLBCL lesions increases, which leads to a fast and massive flow of contrast agents into the blood vessels. Consequently, PPT is shortened while PI increases. The results above suggested that CEUS can provide an important basis for differentiating early-stage and advanced DLBCL. In addition, the relationship between the quantitative parameters of CEUS and clinicopathological features of DLBCL patients was further analyzed. The findings showed that the quantitative parameters of CEUS were closely correlated with the Ann Arbor stage, B symptom, IPI, and LDH level. Thus CEUS may be used as an early diagnostic method for DLBCL.

D-dimer is the product of fibrin hydrolysis, which reflects the fibrinolysis status in humans and has a high predictive value for thrombotic diseases. A high D-dimer level has a good predictive value for poor prognosis in many solid tumor patients.[10] It has been shown that the 3-year overall survival of liver cancer patients with a higher D-dimer level decreases dramatically.[21] But according to other studies, D-dimer levels are not an independent prognostic factor for PFS in non-small cell lung cancer patients.[22] The prognostic role of D-dimer levels in hematologic malignancies has received similar attention. Geng et al[23] showed that the plasma D-dimer level decreased dramatically after the first chemotherapy in DLBCL patients. However, the baseline D-dimer level was not an independent prognostic factor in DLBCL. The present study indicated that D-dimer levels increased considerably in advanced DLBCL patients. Hence early-stage and advanced DLBCL can be differentiated based on D-dimer levels. Besides, the correlation between D-dimer levels and clinicopathological features of DLBCL patients was analyzed. The results showed that the Ann Arbor stage, B symptom, IPI, LDH levels, and CRP levels were correlated with D-dimer levels. Therefore, D-dimer levels can be used as a useful laboratory indicator for the diagnosis of DLBCL.

The relationship between the intensity of enhancement in CEUS and the prognosis in DLBCL patients was discussed for the first time. The correlation between the intensity of enhancement in CEUS and D-dimer levels was also assessed. Then the predictive value of these two factors combined for the prognosis of DLBCL patients was determined. Our study showed that a higher D-dimer level and hyper-enhancement in CEUS could significantly influence PFS of the patients. Of note, the intensity of enhancement in CEUS was positively correlated with D-dimer levels and that the prognosis was worse for those with a higher D-dimer level and hyper-enhancement in CEUS. From the results above, it can be inferred that CEUS combined with laboratory test may guide the treatment and prognostic prediction of DLBCL. Multivariate analysis was performed to identify risk factors using the Cox regression model. The results showed that age, Ann Arbor stage, IPI, D-dimer levels, TTP, PI, and use of rituximab were independent prognostic factors in DLBCL patients. In a word, D-dimer levels and CEUS are not only useful early diagnostic tools for DLBCL, but also important prognostic factors for DLBCL.

CEUS features and D-dimer levels were closely related to the pathological indicators and prognosis of DLBCL patients. They can be combined to aid early diagnosis and prognostic prediction of DLBCL. In the future, more patients should be included in the study to verify our research results and to offer more convincing evidence for their value in prognostic prediction in DLBCL.

Ethics Approval and Informed Consent

This study was approved by the Ethics Committee of the first affiliated hospital of Zhengzhou University. Informed consent was obtained from each subject in accordance with the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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