Original Article

Predicting diffuse large B-cell lymphoma outcomes with lesion-to-liver maximum standardized uptake value for interim-treatment and end-of-treatment positron emission tomography-computed tomography

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Background: ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography-computed tomography (PET-CT) has been used in response evaluation systems for malignant lymphomas and is an important tool for determining efficacy and prognosis. The Deauville 5-point scale (D-5PS) is an ^{18}F-FDG PET-CT image-interpretation protocol for patients with lymphoma. Nevertheless, a number of limitations in visual image interpretation, such as interobserver disagreement and the increase of false-positive results, suggests that new parameters are needed. In this study, we aimed to evaluate the prognostic values of interim-treatment (I-) and end-of-treatment (EOT) PET-CT by comparing D-5PS to the semiquantitative lesion-to-liver maximum standardized uptake value ratio (RLL).

Methods: A total of 90 patients with diffuse large B-cell lymphoma (DLBCL) (45 I-PET and 45 EOT-PET) were analyzed, and the RLL was calculated. Patients were additionally evaluated using the D-5PS system. We determined the optimal cutoff value of RLL using receiver operating characteristic (ROC) analysis. Kaplan-Meier survival analysis was used to compare the outcome predictions, while multivariate Cox regression analysis was used to identify the predictive factors.

Results: Among the patients examined, 41 (20 I-PET and 21 EOT-PET) experienced progression, and 49 (25 I-PET, 24 EOT-PET) did not. The optimal cutoff values of the RLL for predicting disease progression were 1.37 for I-PET (sensitivity 75%, specificity 88%) and 2.03 for EOT-PET (sensitivity 45.5%, specificity 100%), while the cutoffs of the D-5PS were scores 4 for I-PET (sensitivity 80%, specificity 72%) and 5 for EOT-PET (sensitivity 40.9%, specificity 100%). The prognostic efficacy was higher for the RLL at interim than for the D-5PS [area under the curve (AUC) =0.848 *vs.* 0.741]. The EOT prognostic efficacy of both evaluation methods was essentially equivalent (AUC =0.785 *vs.* 0.725). Univariate and multivariate analyses showed that RLL and D-5PS were independent factors affecting DLBCL outcomes for both interim and EOT assessment.

Conclusions: RLL and D-5PS have independent predictive values for the interim and EOT evaluation of outcomes in patients with DLBCL. The RLL has better interim predictive ability than does D-5PS and can optimize D-5PS interpretation, thus improving interim outcome prediction.

Keywords: Lesion-to-liver maximum standardized uptake value ratio (RLL); Deauville 5-point scale (D-5PS); diffuse large B-cell lymphoma (DLBCL)

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma. Standard chemoimmunotherapy for this condition consists of 6 cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (1). The addition of rituximab to cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) therapy has resulted in a major improvement in survival outcomes in patients with DLBCL (2,3). Accurately assessing the disease status and response to antilymphoma therapy has important clinical implications for patient outcomes and can guide subsequent treatment.

^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography-computed tomography (PET-CT) has been used in response evaluation systems for malignant lymphomas and is an important tool for determining efficacy and prognosis (4-7). PET-CT can be used during the course of treatment [interim-treatment PET (I-PET)] and when treatment has been completed [end-of-treatment (EOT)-PET]. In the framework of I-PET, Yang *et al.* (8) found that a I-PET scan has significant predictive values for disease progression and survival and may be the most important determinant of outcomes among patients with the same international prognostic index (IPI) risk. However, Kim *et al.* found no difference in progression-free survival (PFS) between patients with positive and negative I-PET scans. Patients with positive I-PET are at risk of relapse; however, complete remission after treatment has also been observed in 68% of patients with positive I-PET scans (9). To the best of our knowledge, the prognostic value of EOT-PET has been less extensively studied than has that of I-PET in patients with DLBCL. As with I-PET, the negative predictive value of EOT-PET is reassuringly high, but the positive predictive value (PPV) is not (10,11). Thus, the currently used criteria for the interpretation of treatment response needs to be improved to ensure the accuracy of prognostic assessment based on I-PET and EOT-PET.

The Deauville 5-point scale (D-5PS) is an ^{18}F-FDG PET-CT image-interpretation protocol for patients with DLBCL after treatment. It uses a visual assessment method to classify the results into 5 grades depending on the ^{18}F-FDG uptake level in residual lesions (12). However, some studies have shown that although it has a good negative predictive value, it has a poor PPV, possibly because of false positives caused by inflammatory responses to immunotherapy (13,14). Fan *et al.* (15) evaluated a novel semiquantitative method for PET-CT that uses the ratio of the maximum standardized uptake value (SUV_{max}) of the lesion to the maximum cross-sectional SUV_{max} of the liver (SUV_{max}-liver) for I-PET scan evaluation of patients with DLBCL and found that survival significantly differed between patients with positive and negative residue with respect to the SUV_{max}-liver interpretation. The routine use of lesion-to-liver SUV_{max} ratio (RLL) could provide certain advantages, such as an independence from the administered activity and body weight and the transition from a visual qualitative scale (e.g., D-5PS) to a continuous semiquantitative one.

In this study, we aimed to evaluate the prognostic values of I-PET and EOT-PET by comparing D-5PS to the semiquantitative RLL.

Methods

Patients and study design

We retrospectively analyzed the data of patients with DLBCL between January 2013 and February 2020. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and performed with approval from the Investigational Review Board of Shengjing Hospital of China Medical University. Individual consent for this retrospective analysis was waived.

The inclusion criteria were as follows: (I) pathological diagnosis of DLBCL, complete medical history, and clinical data available; (II) administration ^{18}F-FDG PET-CT after 3 or 4 cycles of treatment (I-PET) or after 6 or even up to 8 cycles of treatment (EOT-PET), with 2 weeks elapsing from the end of the preceding treatment to the scan; and (III) a minimum follow-up of 6 months after the end of first-line treatment. The exclusion criteria included presence of a second primary malignancy at diagnosis; presence of a serious concomitant disease affecting survival, such as refractory cardiac insufficiency; and primary central nervous system lymphoma (*Figure 1*).

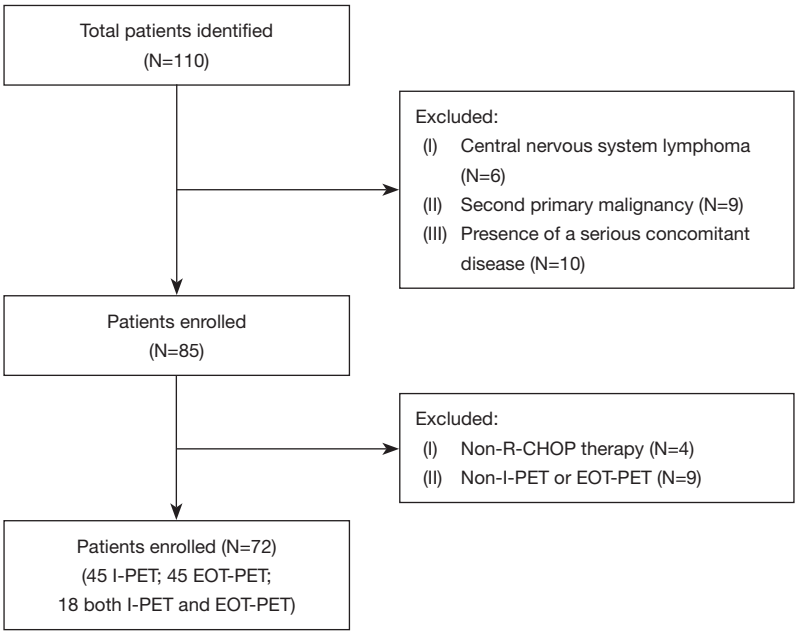

Figure 1 The flowchart of patient selection. R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; I-PET, interim-treatment PET-CT; PET-CT, positron emission tomography-computed tomography; EOT-PET, end-of-treatment PET-CT.

A total of 72 patients qualified for inclusion in the study: 45 patients had undergone I-PET, 45 patients had undergone EOT-PET, and 18 patients had undergone both I-PET and EOT-PET.

Treatment regimens

Most patients in this cohort were initially treated with rituximab-based therapy. A total of 67 patients (93%) received R-CHOP, 4 (6%) received rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (R-EPOCH), and 1 (1%) received rituximab, vincristine, etoposide, cyclophosphamide, and prednisolone (R-CEOP).

^{18}F-FDG PET-CT instrument, tracer, and parameters

A Discovery Elite PET-CT scanner (GE HealthCare, Chicago, IL, USA) was used for imaging. ^{18}F-FDG was produced with the MINItracer cyclotron (GE HealthCare) and was synthesized in an automated mode, with a radiochemical purity of >99%. Patients fasted for at least 6 h before examination to ensure blood glucose levels were <160 mg/dL. ^{18}F-FDG was administered intravenously at a dose of 3.7 MBq/kg, after which the patient rested quietly for approximately 60 min. The scan ranged from the base of the skull to the middle of the femur. The CT scan was performed first with a tube voltage of 120 kV, automatic tube current modulation (15–180 mA), a gantry rotation speed of 0.8 s/rotation, and a scan layer thickness of 3.8 mm. This was followed by the PET scan in the 3-dimensional scanning mode in 6 to 7 bed positions (depending on the patient's height), with an acquisition time of 2 min per bed position.

^{18}F-FDG PET-CT image analysis methods

Visualization and semiquantitative analysis methods were used. I-PET and EOT-PET were clinically reviewed by 2 nuclear medicine physicians. The physicians were blinded to the clinical data of the patients. Any differences between the physicians were resolved via discussion

D-5PS criteria

The D-5PS criteria were used to assess the degrees of response at I-PET scan and EOT-PET scan. The relative uptake of ^{18}F-FDG at the site of involvement (using the mediastinum and liver as the reference) was assessed using a 5-point scale based on the degree of lesion FDG metabolic activity and was defined as follows: 1, no uptake; 2, uptake

less than or the equal to that of the mediastinum; 3, uptake more than the mediastinum but less than the liver; 4, uptake moderately more than the liver; and 5, uptake markedly more than the liver or by new sites of disease (12,16).

RLL

PET images were interpreted based on the $SUV_{max\text{-}liver}$. For each PET image, the metabolic level of residual lymphoma with the most intense ^{18}F-FDG uptake was measured and calculated using the region-of-interest (ROI) technique and was recorded as the SUV_{max}. For measurement of the background liver SUV, we avoided the junction area of 2 bed positions and the region of large vessels while placing a 3-cm-diameter ROI in the right lobe of a normal liver (17). This was recorded as the SUV_{max} of the ROI. The ROI was placed at 3 randomly selected locations, and the mean of the SUV_{max} of the 3 ROIs was recorded as the $SUV_{max\text{-}liver}$ (15). The ratio of the SUV_{max} of the lesion to the $SUV_{max\text{-}liver}$ was calculated as the RLL.

Follow-up

The relationship between tumor stage and baseline patient characteristics, including sex, age, Ann Arbor stage, IPI score, and imaging (CT, ultrasound, and PET-CT), was assessed in the interim and at the end of treatment. Follow-up periods ranged from 6 to 72 months. The primary endpoint of the study was PFS, which was defined as the time from diagnosis to the first appearance of progression, recurrence, all-cause death, or last follow-up.

Statistical analyses

Measurement data conforming to a normal distribution are expressed as the mean ± standard deviation. Categorical variables were compared using the chi-squared (χ^2) test. We compared the prognostic value of the D-5PS scores of 3 (scores 3–5 considered positive), 4 (scores 4–5 considered positive), and 5 (a score of 5 considered positive) in terms of sensitivity, specificity, and area under the curve (AUC). The receiver operating characteristic (ROC) curve was used to determine an optimal cutoff value for the RLL to predict disease progression. The sensitivity, specificity, and AUC of prognosis for an optimal cutoff RLL were also compared between the interim and end of treatment. Spearman rank correlation coefficient (Spearman rho) between the D-5PS score and RLL was calculated. Kaplan-Meier analysis with the log-rank test was used for univariate survival analysis, while the Cox regression model was used for multivariate analysis. SPSS 22.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analyses.

Results

Clinical characteristics

The associations between the prognosis of DLBCL patients and gender, age, immunophenotypes of germinal center B cell (GCB), B symptoms, Ann Arbor stage, IPI score, and serum lactate dehydrogenase (LDH) level after interim or end of treatment are separately listed in *Table 1*.

For the response assessment based on the D-5PS, 22 patients were assigned a D-5PS score of 1–3, 11 patients a D-5PS score of 4, and 12 patients a D-5PS score of 5 at I-PET; in contrast, 26 patients were assigned a D-5PS score of 1–3, 10 patients a D-5PS score of 4, and 9 patients a D-5PS score of 5 at EOT-PET. Moreover, 41 patients (20 I-PET, 21 EOT-PET) experienced disease progression and 49 (25 I-PET, 24 EOT-PET) did not.

Comparative analysis

The prognostic value of an interim-of-treatment D-5PS score of 4 for disease progression status was higher than those of D-5PS scores 3 and 5, as assessed by ROC curve analysis (AUC_{score3} =0.589, AUC_{score4} =0.741, AUC_{score5} =0.725). In contrast, an EOT D-5PS score of 5 had a higher prognostic value than did D-5PS scores of 3 and 4 for disease progression (AUC_{score3} =0.665, AUC_{score4} =0.615, AUC_{score5} =0.725). Data on the sensitivity, specificity, PPV and AUC of D-5PS scores 3–5 are listed in *Table 2*. The patients had median, minimum, and maximum RLL values of 1.06, 0.35, and 10.60 at I-PET, respectively, and values of 0.86, 0.18, and 9.17 at EOT-PET, respectively. Moreover, the best cutoff for RLL as a prognostic parameter for disease progression after the interim of treatment was found to be 1.37, while for end of treatment it was 2.03. The optimal cutoff value for RLL as a prognostic parameter for disease progression was 1.37; that is, where an RLL of >1.37 was considered positive and an RLL of ≤1.37 was considered negative (AUC =0.848). The optimal cutoff value for the RLL as an EOT prognostic parameter was 2.03; that is, where an RLL of >2.03 was considered positive and an RLL of ≤2.03 was considered negative (AUC =0.785)

Table 1 Clinical characteristics of patients and relationship to disease progression

Clinical characteristics	Interim treatment			End of treatment		
	Progress rate	χ^2	P value	Progress rate	χ^2	P value
Sex (male *vs.* female)	42.9% (12/28) *vs.* 47.1% (8/17)	0.43	0.51	44.8% (13/29) *vs.* 50.0% (8/16)	0.11	0.74
Age (<60 *vs.* ≥60 years)	45.5% (10/22) *vs.* 43.5% (10/23)	0.02	0.89	59.1% (13/22) *vs.* 34.8% (8/23)	2.67	0.1
Immunophenotype (GCB *vs.* non-GCB)	50.0% (7/14) *vs.* 48.1% (13/27)	0.01	0.9	40% (6/15) *vs.* 52% (13/25)	0.54	0.46
Ann Arbor stage (I–II *vs.* III–IV)	27.3% (3/11) *vs.* 50% (17/34)	1.74	0.30	40.9% (9/22) *vs.* 52.2% (12/23)	0.57	0.45
IPI (0–2 *vs.* 3–5)	38.9% (7/18) *vs.* 48.1% (13/27)	0.08	0.78	46.4% (13/28) *vs.* 47.1% (8/17)	0.002	0.98
LDH (<248 *vs.* ≥248 U/L)	40.0% (12/30) *vs.* 53.3% (8/15)	0.72	0.4	50% (14/28) *vs.* 41.2% (7/17)	0.33	0.57

GCB, germinal center B cell; IPI, International Prognostic Index; LDH, lactate dehydrogenase.

Table 2 Sensitivity, specificity, PPV, and AUC of the interim-treatment and end-of-treatment D-5PS scores 3, 4, and 5 for predicting disease progression

D-5PS	Interim treatment			End of treatment		
	Score 3	Score 4	Score 5	Score 3	Score 4	Score 5
Sensitivity	95% (19/20)	80% (16/20)	52.6% (10/19)	81% (17/21)	54.5% (12/22)	40.9% (9/22)
Specificity	24% (6/25)	72% (18/25)	92.3% (24/26)	45.8% (11/24)	69.5% (16/23)	100% (23/23)
PPV	50% (19/38)	70% (16/23)	83.3% (10/12)	56.7% (17/30)	63.2% (12/19)	100% (9/9)
AUC (95% CI)	0.589 (42.3–75.6%)	0.741 (59.1–89.1%)	0.725 (56.5–88.4%)	0.665 (50.5–82.5%)	0.615 (44.7–78.3%)	0.725 (56.7–88.3%)

D-5PS (score 3): D-5PS scores 1–2 are considered negative; D-5PS (score 4): D-5PS scores 1–3 are considered negative; D-5PS (score 5): D-5PS scores 1–4 are considered negative. PPV, positive predictive value; AUC, area under the curve; D-5PS, Deauville 5-point scale; CI, confidence interval.

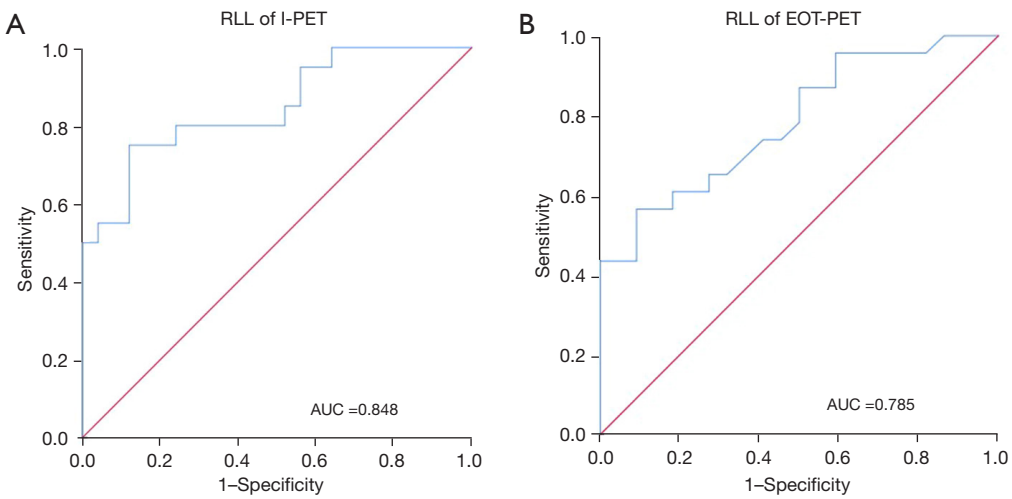

Figure 2 ROC analysis of the RLL on the I-PET (A) and EOT-PET (B). RLL, lesion-to-liver maximum standardized uptake value ratio; I-PET, interim-treatment PET-CT; PET-CT, positron emission tomography-computed tomography; ROC, receiver operating characteristic; EOT-PET, end-of-treatment PET-CT.

Table 3 Sensitivity, specificity, PPV, and AUC of the cutoff values for D-5PS (interim-treatment score 4, end-of-treatment score 5) and RLL for disease outcomes

Predictive performance	D-5PS				RLL			
	I-PET	EOT-PET	χ^2	P value	I-PET	EOT-PET	χ^2	P value
Sensitivity	80% (16/20)	40.9% (9/22)	6.65	0.01	75% (15/20)	45.5% (10/22)	3.78	0.049
Specificity	72% (18/25)	100% (23/23)	7.54	0.01	88% (22/25)	100% (23/23)	2.94	0.086
PPV	70% (16/23)	100% (9/9)	3.5	0.15	83% (15/18)	100% (10/10)	1.87	0.53
AUC (95% CI)	0.741 (0.591–0.891)	0.725 (0.567–0.883)			0.848 (0.735–0.963)	0.785 (0.652–0.918)		

AUC, area under the curve; PPV, positive predictive value; D-5PS, Deauville 5-point scale; RLL, lesion-to-liver maximum standardized uptake value ratio; CI, confidence interval; I-PET, interim-treatment PET-CT; PET-CT, positron emission tomography-computed tomography; EOT-PET, end of treatment PET-CT.

Table 4 Comparison of sensitivity, specificity, PPV, and AUC for disease prognosis between D-5PS (interim-treatment score 4, end-of-treatment score 5) and RLL at the interim-treatment and end-of-treatment time points.

Predictive performance	I-PET				EOT-PET			
	D-5PS	RLL	χ^2	P value	D-5PS	RLL	χ^2	P value
Sensitivity	80% (16/20)	75% (15/20)	0.14	0.700	40.9% (9/22)	45.5% (10/22)	0.09	0.760
Specificity	72% (18/25)	88% (22/25)	2.00	0.157	100% (23/23)	100% (23/23)	–	–
PPV	70% (16/23)	83% (15/18)	1.04	0.470	100% (9/9)	100% (10/10)	–	–
AUC (95% CI)	0.741 (0.591–0.891)	0.848 (0.735–0.963)			0.725 (0.567–0.883)	0.785 (0.652–0.918)		

PPV, positive predictive value; AUC, area under the curve; D-5PS, Deauville 5-point scale; RLL, lesion-to-liver maximum standardized uptake value ratio; I-PET, interim-treatment PET-CT; PET-CT, positron-emission tomography-computed tomography; EOT-PET, end-of-treatment PET-CT; CI, confidence interval.

(*Figure 2*). We detected a significant difference between the prognostic values (sensitivity, specificity) obtained between I-PET and EOT-PET when applying the D-5PS method (*Table 3*). However, there also was no significant difference observed between I-PET and EOT-PET when applying the RLL method.

At the interim time point, an RLL of 1.37 had a sensitivity of 75% and a specificity of 88% for predicting tumor progression, whereas a D-5PS score of 4 had a sensitivity of 80% and a specificity of 72% for predicting tumor progression or recurrence. Thus, interim prognostic evaluation using the RLL was more effective than was the D-5PS (AUC =0.848 *vs.* 0.741). At the end of treatment, with an RLL threshold of 2.03, the prediction of tumor progression or recurrence had a sensitivity of 45.5% and a specificity of 100%. When the D-5PS score was 5, the prediction of tumor progression or recurrence had a sensitivity of 40.9% and a specificity of 100%. The prognostic efficacy of the RLL and D-5PS methods at the end of chemotherapy was comparable (AUC =0.785 *vs.* 0.725) (*Table 4*).

Survival analysis of D-5PS and RLL

Patients were categorized according to the D-5PS scoring method (interim score =4; EOT score =5). The differences in PFS between 2 groups were found to be significant at the interim (χ^2=9.68; P=0.002; *Figure 3A*) and end of treatment (χ^2=19.53; P<0.001; *Figure 3B*).

When the specific cutoff for RLL was applied, we found a significant difference in PFS in both groups, with the group imaged at interim treatment having a PFS of 1.37 (χ^2=17.73; P<0.001; *Figure 3C*) and the group imaged after the end of treatment having a PFS of 2.03 (χ^2=21.95; P<0.001; *Figure 3D*).

Correlation of PET-CT imaging analysis methods

The semiquantitative RLL method was positively correlated with the D-5PS score method on I-PET and EOT-PET

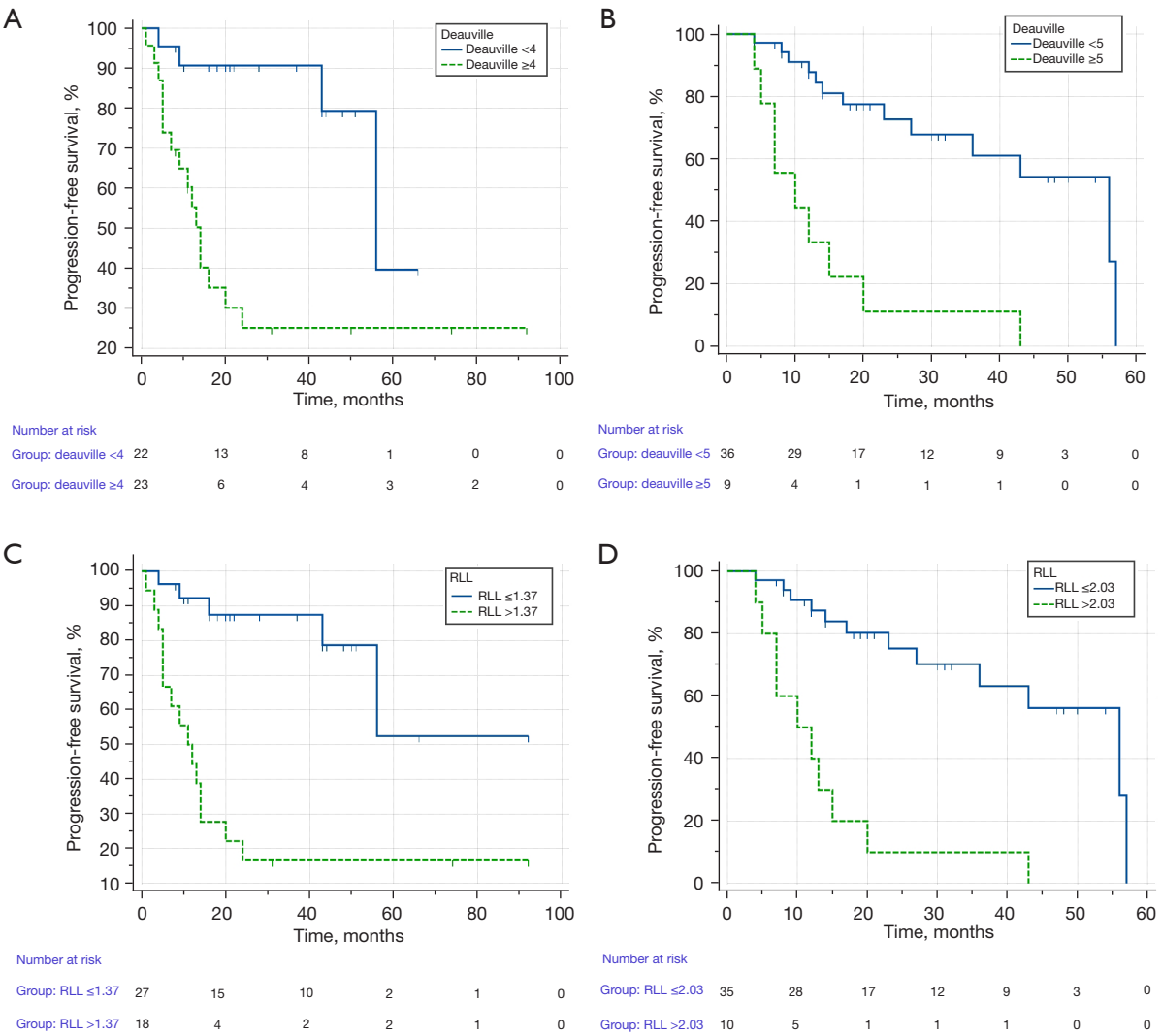

Figure 3 Kaplan-Meier of PFS according to the D-5PS and RLL in patient subgroups. (A) Patients categorized with D-5PS scores 1–3 and scores 4–5. (B) Patients categorized with D-5PS scores 1–4 and score 5. (C) Patients categorized as RLL ≤1.37 and RLL >1.37; (D) patients categorized as RLL ≤2.03 and RLL >2.03. (A) and (C) indicate interim patients; (B) and (D) indicate patients at the end of treatment. PFS, progression-free survival; D-5PS, Deauville 5-point scale; RLL, lesion-to-liver maximum standardized uptake value ratio.

(I-PET: r=0.883; EOT-PET: r=0.958; both P values <0.001).

Univariate analysis of factors affecting patient outcomes

In univariate analyses, no correlation between clinical factors and patient outcomes were found (*Table 1*). Both the RLL and D-5PS of I-PET and EOT-PET were associated with patient outcomes (*Figure 2*).

Multivariate analysis of factors associated with patient outcomes

Because the RLL and D-5PS methods were correlated, multivariate Cox regression analysis of the clinical factors was performed for each method. The results showed that the RLL and D-5PS of I-PET and EOT-PET were independent factors associated with patient outcomes (*Tables 5*,*6*).

Table 5 Cox multivariate regression analysis of interim-treatment and end-of-treatment factors influencing progression-free survival in patients with DLBCL (image analysis: RLL)

Risk factor	PFS (interim of treatment)			PFS (end of treatment)		
	HR	95% CI	P value	HR	95% CI	P value
Sex (male *vs.* female)	1.665	0.528–5.253	0.385	1.059	0.368–3.046	0.915
Age (<60 *vs.* ≥60 years)	0.842	0.265–2.674	0.770	0.525	0.104–2.647	0.525
Immunophenotype (GCB *vs.* non-GCB)	3.340	0.883–12.643	0.076	1.871	0.596–5.874	0.283
Ann Arbor stage (I–II *vs.* III–IV)	2.575	0.473–14.026	0.274	2.3	0.661–8.002	0.190
IPI (0–2 *vs.* 3–5)	0.740	0.180–3.052	0.678	1.780	0.308–10.283	0.520
LDH (<248 *vs.* ≥248 U/L)	0.312	0.094–1.032	0.056	0.556	0.148–2.086	0.385
RLL	2.145	1.565–2.939	0.000	1.255	1.062–1.482	0.008

DLBCL, diffuse large B-cell lymphoma; RLL, lesion-to-liver maximum standardized uptake value ratio; CI, confidence interval; GCB, germinal center B cell; HR, hazard ratio; IPI, International Prognostic Index; LDH, lactate dehydrogenase; PFS, progression-free survival.

Table 6 Cox multivariate regression analysis of interim-treatment and end-of-treatment factors influencing progression-free survival in patients with DLBCL (image analysis: D-5PS)

Risk factor	PFS (interim of treatment)			PFS (end of treatment)		
	HR	95% CI	P value	HR	95% CI	P value
Sex (male *vs.* female)	0.732	0.265–2.025	0.548	0.864	0.316–2.363	0.777
Age (<60 *vs.* ≥60 years)	0.447	0.114–1.757	0.249	0.397	0.073–2.172	0.287
Immunophenotype (GCB *vs.* non-GCB)	5.175	1.173–22.836	0.03	1.576	0.529–4.691	0.414
Ann Arbor stage (I–II *vs.* III–IV)	1.589	0.327–7.724	0.566	2.525	0.728–8.757	0.144
IPI (0–2 *vs.* 3–5)	0.784	1.94–3.168	0.732	1.309	0.234–7.307	0.759
LDH (<248 *vs.* ≥248 U/L)	0.309	0.095–1.004	0.051	0.673	0.166–2.723	0.578
D-5PS	7.83	2.311–26.523	0.001	1.568	1.017–2.418	0.042

DLBCL, diffuse large B-cell lymphoma; D-5PS, Deauville 5-point scale; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; GCB, germinal center B cell; IPI, International Prognostic Index; LDH, lactate dehydrogenase.

Discussion

With the availability of rituximab, approximately two-thirds of DLBCL cases are curable, and the 5-year survival rate of patients with DLBCL is now 30–50% (18,19). Thus, accurate response evaluation is essential for the optimal treatment of patients with DLBCL. In this study, we used 2 evaluation methods: the semiquantitative RLL (the ratio of the lesion SUV_{max} to the $SUV_{max\text{-}liver}$) and the D-5PS. The ROC curve was used to determine the optimal cutoff values of the interim-treatment and EOT RLL for PFS, which were found to be 1.37 and 2.03, respectively. A difference was observed in sensitivity (P=0.05), but not in specificity (P=0.09), when comparing the 2 time points, and the interim ^{18}F-FDG PET-CT examination demonstrated a slightly higher outcome prediction performance than did the EOT examination (AUC =0.848 *vs.* 0.785). The optimal cutoff values of the D-5PS were 4 (sensitivity 80%, specificity 72%) and 5 (sensitivity 40.9%, specificity 100%) for the interim and end of treatment, respectively. At interim treatment, RLL had better prognostic efficacy than did the D-5PS (AUC =0.848 *vs.* 0.741), and the EOT prognostic efficacy was similar for the 2 evaluation methods (AUC =0.785 *vs.* 0.725). Univariate and multivariate analyses showed that the RLL and D-5PS were independent predictors of DLBCL outcomes at both time points. Thus,

both RLL and D-5PS have independent predictive values for interim-treatment and EOT evaluation of outcomes in patients with DLBCL.

The advantage of interim-treatment and EOT PET-CT scans is the ability to differentiate between surviving tumors and necrosis or fibrosis in residual masses that often appear after treatment (20). This approach may be used to identify patients with good prognosis, thereby reducing the intensity of subsequent treatments and avoiding toxicity, as well as to screen for cases of poor prognosis, indicating the need to increase the intensity of subsequent treatments and to improve efficacy.

Zhang *et al.* (21) analyzed the interim-treatment (4 cycles of chemotherapy) and EOT PET-CT results of patients with DLBCL and found that the $SUV_{max\text{-}liver}$–based interpretation was superior to the ΔSUV_{max} and D-5PS interpretation. The optimal thresholds for RLL were 1.6 and 1.4, respectively. Itti *et al.* (17) analyzed PET-CT images of patients with DLBCL after 2 cycles of chemotherapy and reported that an RLL increase from 1.25 to 1.4 could improve the accuracy, specificity, and PPV value of prognosis. However, this did not reveal the best threshold for interpreting interim PET-CT imaging. Fan *et al.* (15) evaluated the interim PET-CT results of 119 patients with DLBCL, comparing the values of the ΔSUV_{max}, $SUV_{max\text{-}liver}$–based interpretation, and D-5PS in the prognostic evaluation of patients. They found that the $SUV_{max\text{-}liver}$–based interpretation had the best predictive efficacy, with an optimal cutoff value of 1.6. In this study, we compared the prognostic value of PET-CT between interim and end of treatment and found that the optimal cutoff values of the RLL for predicting disease progression were 1.37 (sensitivity 75%, specificity 88%) and 2.03 (sensitivity 45.5%, specificity 100%) for the 2 time points, respectively. The nonuniform timing of I-PET, as indicated in our study (3–4 chemotherapy cycles) and that of Fan *et al.* (15) (2 chemotherapy cycles), may limit the generalizability of our results, although intrastudy variability can be explained partly by differences in the total number of treatment cycles. An RLL cutoff value of 2.07 obtained in our study with EOT-PET was higher than the cutoff value of 1.4 reported by Zhang *et al.* (21). The differences in the number of study participants, high proportion of older adult patients, and high IPI score might explain this discrepancy. Further prospective studies with a larger sample are required to confirm our results. We reanalyzed our data using 1.6 as the cutoff at I-PET and 1.4 as the cutoff at EOT-PET, and the outcomes of the PET-positive and PET-negative groups differed significantly in the Kaplan-Meier survival analysis. However, the cutoff value of 1.6 at I-PET (sensitivity 65%, specificity 88%) did not increase the specificity of 1.37 but reduced the sensitivity of the latter. Moreover, the cutoff value of 1.4 at EOT-PET (sensitivity 45.5%, specificity 87%) did not increase the sensitivity of 2.03 but did reduce the specificity of the latter. In our study, despite the smaller sample size, the RLL -based criterion exhibited a PPV of 83% at I-PET and that of 100% at EOT-PET for predicting progression, exceeding that of D-5PS. Cox multivariate analysis results showed that the RLL is an independent factor affecting outcomes. Kaplan-Meier survival plots showed that the interim-treatment and EOT survival of patients in the positive and negative groups was significantly different when grouped using the optimal RLL cutoff values ($P<0.001$). Therefore, we posit that the optimal cutoff of RLL is a promising tool for PET evaluation and for better guidance of additional treatment after the first-line of immunochemotherapy.

The D-5PS quantifies and divides ^{18}F-FDG uptake into 5 grades via comparison of the degree of ^{18}F-FDG uptake in the lesion with that in the liver and mediastinal blood pool. The cutoff value for negative and positive scan results assessed using the D-5PS is controversial, with D-5PS scores of 1–3 usually being defined as negative and D-5PS scores of 4–5 being defined as positive (18,22). Li *et al.* (18) defined D-5PS scores 1–3 as negative and D-5PS scores 4–5 as positive to assess the interim prognosis of patients, which yielded a sensitivity of 90.63% and an accuracy of 87.23%. Yuan *et al.* (23) compared prognostic values after 1 or 2 cycles of R-CHOP and found that a D-5PS score of 5 had the highest prognostic value across chemotherapy cycles compared with D-5PS scores 3 and 4. We found that the best cutoff values for predicting disease progression were D-5PS scores 4 (I-PET) and 5 (EOT-PET), with sensitivities of 80% and 40.9% and specificities of 72% and 100%, respectively. According to the Deauville criteria, a D-5PS score of 4 or 5, as a positive ^{18}F-FDG PET-CT result, is defined as patients having residual activity in the liver that in sites of previous disease (7). In the present study, a D-5PS score of 5 showed the highest outcome prediction ability compared to either a score of 3 or 4 on EOT-PET. The reason for this result might be found in the limited number of participants in the study, the heterogeneity of tumors, and changes in the uptake of liver background after treatment (9,24). The use of semiquantitative analysis to assess early response in DLBCL may be preferred over the D-5PS, as the calculation of the

RLL appears to be more reproducible than is the D-5PS and possesses higher predictive power. Additionally, RLL presents metabolic information of the lesion as a continuous quantitative indicator that facilitates measurement and comparison.

Although some studies have shown that interim PET is suboptimal for guiding treatment decisions (9), results of other studies have found a 2- to 5-year PFS of approximately 45–97.0% in patients with a negative interim PET-CT result that drops to 19–57% in patients with a positive result (18,25). Our multivariate analysis showed that the interim RLL and D-5PS were independent predictors of PFS and that the interim stage may be crucial for the development of treatment plans by providing detailed prognostic information for patients with DLBCL. Additionally, RLL had higher predictive power for outcomes of patients with DLBCL at the interim than at the end of treatment. The D-5PS possessed the same predictive power at both interim-treatment and EOT stages. The different optimal cutoff values for the RLL and D-5PS for the 2 time points may be related to the different dynamic patterns/kinetics of tumor destruction and regeneration in different stages of chemotherapy (25), necessitating different optimal cutoff values for defining PET-CT positivity. PET-CT response prediction at the interim stage appears feasible, but should be confirmed in larger clinical trials.

This study has several limitations. First, we employed a single-center, retrospective study with a small sample size, and thus the results of the study need to be validated in a large sample. Further studies are warranted to confirm that the prognostic stratification can be performed with RLL in patients with DLBCL who have a D-5PS score of 4 or 5. Furthermore, the estimated 2-year PFS rate was 34.7%. The reasons for the low 2-year PFS rate might be related to the inclusion of a limited number of study participants, high proportion of older adults patients, and a high overall IPI score. Finally, no deaths occurred during the follow-up period; thus, the overall survival time could not be analyzed.

Conclusions

The results of this study confirmed that compared to EOT-PET, interim ^{18}F-FDG PET-CT has slightly higher outcome prediction performance for PFS and is an independent predictor of PFS in patients with DLBCL. Additionally, the novel semiquantitative index RLL is superior to the D-5PS in predicting the prognosis of patients with DLBCL at an interim time point. Thus, interim response prediction appears to be feasible although this should be confirmed in larger clinical trials.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-251/coif). JX reports that this work was supported by the 345 Talent Project from Shengjing Hospital of China Medical University (No. M0441). 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Investigational Review Board of Shengjing Hospital of China Medical University. Individual consent for this retrospective analysis was waived.

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