Original Article

Integration of PET/CT parameters and a clinical variable to predict the risk of progression of disease within 24 months (POD24) in follicular lymphoma

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Background: Patients with follicular lymphoma (FL) who experience progression of disease within 24 months (POD24) of receiving first-line therapy had a significantly poorer prognosis than that without early progression. Due to the established prognostic relevance of positron emission tomography/computed tomography (PET/CT) parameters in FL and their clinical accessibility, we aimed to investigate the predictive role of PET/CT metabolism and dissemination parameters in POD24 for FL.

Methods: The POD24 status of 155 patients who underwent PET/CT examinations at initial diagnosis was evaluated. Various baseline characteristics were collected, along with PET/CT-derived parameters, including the maximum tumor dissemination (Dmax), maximum standardized uptake (SUVmax) value, total metabolic tumor volume (TMTV), and total lesion glycolysis (TLG). A Cox proportional regression analysis was used to identify potential risk predictors of POD24. Receiver operating characteristic (ROC) curves were used to define the optimal cut-off values.

Results: In our cohort, POD24 was observed in 21 (13.5%) FL patients. The univariate and multivariate Cox regression analyses revealed that elevated lactate dehydrogenase (LDH) was a significant predictor of POD24. Additionally, survival analyses based on the cut-off values showed that the risk of POD24 was significantly increased in patients with a Dmax >64.24 cm, SUVmax >11.23, TMTV >144.16 cm^2, and TLG >586.79 g. Further, a Dmax >64.24 cm, a TMTV >144.16 cm^2, and elevated LDH were selected for inclusion in a risk model [concordance index (C-index) =0.82], and the patients were divided into three risk groups, in which the rates of POD24 were 1.69%, 10.42%, and 35.29%, respectively (P<0.001). Our model exhibited

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excellent performance in terms of both the C-index and ROC curve analysis, surpassing the performance of models commonly used in the field.

Conclusions: PET/CT parameters have prognostic value for POD24 in FL. The risk model, which combined PET/CT parameters with clinical indicators, could improve risk stratification and help guide therapeutic decisions.

Keywords: Follicular lymphoma (FL); positron emission tomography/computed tomography (PET/CT); progression of disease within 24 months (POD24)

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Introduction

Follicular lymphoma (FL) is the most common subtype of indolent non-Hodgkin's lymphoma, originating from follicular germinal center B cells (1). Many FL patients respond to a variety of therapies and achieve long-term survival; however, 13–30% of FL patients experience progression of disease within 24 months (POD24) of receiving first-line therapy (2-4). These patients typically have inferior clinical prognosis, and a 5-year overall survival (OS) rate of 34–50%, which can be compared to that of 90% for those without early progression (5). However, currently, no ideal model exists to predict POD24 accurately. The POD24-prognostic index (POD24-PI), a clinical risk model specifically designed to predict POD24 in FL patients, has the highest sensitivity in predicting POD24, but at the cost of reduced specificity (6). Additionally, its reliance on gene testing limits its broader application. Thus, a simple, practical model urgently needs to be established to predict POD24 and guide treatment decisions in FL.

In recent years, with the development and application of machine-learning methods and texture analysis (7), positron emission tomography/computed tomography (PET/CT) has become a standard, non-invasive tool for lymphoma diagnosis, staging, and follow-up (8-10). Numerous studies have shown that PET/CT-derived quantitative and qualitative parameters provide valuable prognostic information in FL (11,12). For example, the maximum standardized uptake (SUVmax) value is widely used to assess tumor malignancy, and is associated with inferior prognosis (13). Both the total metabolic tumor volume (TMTV) and total lesion glycolysis (TLG) reflect the systemic tumor load and have strong independent predictive value for FL, improving risk stratification (14-16). Additionally, the tumor dissemination, as measured by the maximum tumor dissemination (Dmax) (17), has been associated with a poor prognosis in other lymphoma subtypes, but research on its role in FL is limited (14,18,19).

To date, despite the potential of PET/CT parameters, their combined predictive power for early progression in FL has not been fully explored, particularly in terms of the role of the Dmax. Existing FL prognostic models, such as the Follicular Lymphoma International Prognostic Index (FLIPI) (20), FLIPI-2 (21), POD24-PI (6), and m7-FLIPI (22), primarily rely on clinical characteristics, with or without the inclusion of genetic mutations as predictive variables. However, genetic mutation testing is not universally available in clinical settings. Thus, we hypothesized that combining PET/CT metabolic parameters (e.g., the SUVmax, TMTV, and TLG) and the Dmax with baseline clinical characteristics would improve the prediction of POD24, ultimately enabling easily obtainable and more precise risk stratification and guiding treatment strategies for FL patients. We present this article in accordance with the TRIPOD reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-1504/rc).

Methods

Patients

Newly diagnosed FL patients, who underwent PET/CT baseline examinations at the First Affiliated Hospital of Xiamen University and the West China Hospital of Sichuan University between January 2017 and January 2024, were retrospectively included in the study. Patients were excluded from the study if they met any of the following exclusion criteria: (I) showed histological transformation at diagnosis; (II) were aged under 18 years; and/or (III) had a follow-up

of less than 24 months. Initially, 273 patients with newly diagnosed FL were identified After applying the exclusion criteria, a total of 155 patients were included in the study.

The clinical and laboratory baseline data of the included patients were meticulously collected from the medical records, and established prognostic scores, including the FLIPI (20), FLIPI-2 (21), and PRIMA-PI (23) scores, were assessed.

The study was performed in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Institutional Review Boards of the First Affiliated Hospital of Xiamen University (approval No. 2022-070) and the West China Hospital of Sichuan University (approval No. 2024-1010). The requirement of written informed consent was waived by the Institutional Review Boards due to the retrospective nature of the study.

PET/CT scanning

PET/CT scans were conducted using a Discovery Molecular Imaging (MI)system (GE Healthcare, Milwaukee/Waukesha, WI, USA), Gemini GXL, UM780 PET/CT, and GE discovery PET/CT clarity 710. Following a 6-hour fast, blood glucose levels were assessed, and no patient had a level exceeding 140 mg/dL. The patients received an intravenous injection of fluorine-18-fluorodeoxygluse (5.18 MBq/kg), and after 30 minutes, they then underwent a comprehensive whole-body PET/CT scan, encompassing regions from the top of the head to the upper thighs. Attenuation correction was applied using data obtained from the CT scan, and the corrected PET images were reconstructed employing an ordered subset expectation maximization iterative algorithm. The resultant CT and PET images were subsequently merged for the integrated analysis.

Semi-automatic delineation was performed using LIFEx-7.3.0 software (https://www.lifexsoft.org/) (24). The evaluation of all PET images was performed by two board-certified nuclear medicine physicians, and any discrepancies in interpretation were resolved by discussion to reach a consensus. The maximum uptake value of the lesions on the fluorine-18-fluorodeoxygluse PET scans was identified as the patient's SUVmax. The metabolic tumor volume (MTV) was delineated using the 41% SUVmax threshold method, as recommended by the European Society of Nuclear Medicine (25). The TMTV was calculated as the aggregate of the MTVs from all identified lesions. The TLG was calculated by summing the products of the MTVs and the mean SUV values for each lesion. The Dmax between the most distant lesions was also calculated. In cases in which a patient presented with a solitary lesion, the Dmax was recorded as 0 cm.

Statistical analysis

POD24 was the main focus of this study, and was defined as disease progression within 24 months of frontline treatment. Differences between groups were compared using the *t*-test or rank-sum test for the continuous variables, and the Chi-squared test for the categorical variables. The prognostic significance of the PET parameters and clinical variables was assessed by univariate and multivariate Cox regression analyses. Variables with a P value <0.01 in the univariate analysis were included in the multivariate Cox regression model to assess their independent prognostic value. To determine the optimal cut-off value for the continuous variables, we conducted a receiver operating characteristic (ROC) curve analysis, selecting the threshold point that maximized the sum of [sensitivity + (specificity) – 1]. Survival curves were constructed using the Kaplan-Meier method, and the log-rank test was used to compare survival times between groups. The discriminatory power of the prognostic model was assessed using Harrell's concordance index (C-index), ROC curves, areas under the curve (AUCs), a decision curve analysis, and calibration curve plots. All the statistical analyses were performed using SPSS version 22.0, R version 4.3.0., and GraphPad Prism version 8.0. A two-sided P value ≤0.05 was considered statistically significant.

Results

Comparison of characteristics between POD24 patients and non-POD24 patients

In our cohort, 155 patients with FL were followed-up for more than 24 months after first-line treatment, 21 of whom experienced POD24. The OS was significantly worse in the POD24 group than the non-POD24 group (62.5% *vs.* 11.43%, P<0.001; Figure S1). As *Table 1* shows, compared to the non-POD24 patients, those with POD24 had significantly higher FLIPI scores (P=0.005), higher pathological 3a gradings (71.43% *vs.* 34.59%, P=0.001), and elevated lactate dehydrogenase (LDH) levels (47.37% *vs.* 14.63%, P=0.002), and a higher proportion had at least four area lymph nodes involved (85.71% *vs.* 54.62%, P=0.007).

Table 1 Clinical characteristics and parameters of FL patients with or without POD24

Variables	Total (n=155)	Non-POD24 (n=134)	POD24 (n=21)	P
Age >60 years				>0.99
No	121 (78.06)	105 (78.36)	16 (76.19)	
Yes	34 (21.94)	29 (21.64)	5 (23.81)	
Sex				0.647
Female	81 (52.26)	71 (52.99)	10 (47.62)	
Male	74 (47.74)	63 (47.01)	11 (52.38)	
FLIPI score	n=152	n=131		0.005
0–1	49 (32.24)	47 (35.88)	2 (9.52)	
2	59 (38.82)	52 (39.69)	7 (33.33)	
3–5	44 (28.95)	32 (24.43)	12 (57.14)	
PRIMA-PI risk	n=96	n=82	n=14	0.097
Low	40 (41.67)	37 (45.12)	3 (21.43)	
Median-high	56 (58.33)	45 (54.88)	11 (78.57)	
Histologic grade	n=154	n=133		0.001
1–2	93 (60.39)	87 (65.41)	6 (28.57)	
3a	61 (39.61)	46 (34.59)	15 (71.43)	
B symptoms	n=118	n=100	n=18	0.816
No	91 (77.12)	78 (78.00)	13 (72.22)	
Yes	27 (22.88)	22 (22.00)	5 (27.78)	
HGB <120 g/L	n=150	n=129		0.345
No	128 (85.33)	112 (86.82)	16 (76.19)	
Yes	22 (14.67)	17 (13.18)	5 (23.81)	
Ann Arbor stage				0.139
I–II	43 (27.74)	40 (29.85)	3 (14.29)	
III–IV	112 (72.26)	94 (70.15)	18 (85.71)	
LDH	n=142	n=123	n=19	0.002
Normal	115 (80.99)	105 (85.37)	10 (52.63)	
Elevated	27 (19.01)	18 (14.63)	9 (47.37)	
Area of enlarged lymph nodes	n=151	n=130		0.007
<4	62 (41.06)	59 (45.38)	3 (14.29)	
≥4	89 (58.94)	71 (54.62)	18 (85.71)	
Bone marrow involvement	n=153	n=132		0.233
No	91 (59.48)	81 (61.36)	10 (47.62)	
Yes	62 (40.52)	51 (38.64)	11 (52.38)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Total (n=155)	Non-POD24 (n=134)	POD24 (n=21)	P
β2-MG	n=103	n=89	n=14	0.658
Normal	95 (92.23)	83 (93.26)	12 (85.71)	
Elevated	8 (7.77)	6 (6.74)	2 (14.29)	
Longest diameter of the largest node	n=152	n=132	n=20	0.219
≤6	137 (90.13)	121 (91.67)	16 (80.00)	
>6	15 (9.87)	11 (8.33)	4 (20.00)	
Extra-nodal involvement	n=151	n=131	n=20	0.075
No	88 (58.28)	80 (61.07)	8 (40.00)	
Yes	63 (41.72)	51 (38.93)	12 (60.00)	
Ki-67	n=145	n=124		0.034
<40%	92 (63.45)	83 (66.94)	9 (42.86)	
≥40%	53 (36.55)	41 (33.06)	12 (57.14)	
Treatment				
R-based regimen	113 (72.90)	96 (71.64)	17 (80.95)	0.372
G-based regimen	13 (8.39)	11 (8.21)	2 (9.52)	0.999
CHOP-like regimen	84 (54.19)	71 (52.99)	13 (61.90)	0.446
B-based regimen	31 (20.00)	25 (18.66)	6 (28.57)	0.446
Others	33 (21.29)	30 (22.39)	3 (14.29)	0.578
Dmax (cm)	46.17 (7.10, 61.29)	43.07 (6.54, 59.20)	59.85 (35.80, 68.89)	0.014
SUVmax	8.63 (5.95, 12.94)	8.49 (5.64, 11.82)	12.55 (8.86, 16.14)	0.004
TMTV (cm^2)	152.32 (32.43, 511.49)	96.70 (22.49, 472.90)	493.25 (253.67, 1,140.44)	<0.001
TLG (g)	606.21 (66.45, 2,269.58)	355.03 (56.07, 1,868.28)	2,053.76 (1,559.44, 4,422.20)	<0.001

Data are presented as n (%) or M (Q_1, Q_3). FL, follicular lymphoma; POD24, progression of disease within 24 months; FLIPI, Follicular Lymphoma International Prognostic Index; PRIMA-PI, PRIMA-prognostic index; HGB, hemoglobin; LDH, lactate dehydrogenase, β2-MG, beta-2-microglobulin; R, rituximab; G, obinutuzumab; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; B, bendamustine; Dmax, maximum tumor dissemination; SUVmax, maximum standardized uptake value; TMTV, total metabolic tumor volume; TLG, total lesion glycolysis; M, median, Q_1, 1st quartile, Q_3, 3rd quartile.

In terms of immunohistochemistry, the POD24 patients had a higher frequency of having a Ki-67 index of 40% or greater. In terms of the PET parameters, the baseline Dmax, SUVmax, TMTV, and TLG were significantly higher in the POD24 patients than the non-POD24 patients (P<0.05).

Clinical risk factors for POD24

To further examine the risk factors associated with early progression in FL patients, we conducted univariate Cox regression analyses to identify the baseline characteristic variables that differed significantly between the groups (*Table 2*). Our analysis revealed that a high FLIPI sore risk stratification, a histological 3a grading, elevated LDH, and the involvement of more than four lymph nodes were significantly associated with POD24. In the multivariate Cox model, which included clinical prognostic factors (i.e., the FLIPI sore risk stratification, histological grade, elevated LDH, the involvement of more than four lymph

Table 2 Univariate and multivariate Cox proportional hazard regression of clinical parameters for POD24

Variables	Univariate Cox regression					Multivariate Cox regression				
	β	SE	Z	P	HR (95% CI)	β	SE	Z	P	HR (95% CI)
FLIPI risk (high *vs.* low)	1.99	0.76	2.61	0.009	7.33 (1.64–32.76)					
Histologic grade (IIIa *vs.* I–II)	1.42	0.48	2.93	0.003	4.12 (1.60–10.62)					
LDH elevated	1.48	0.46	3.21	0.001	4.38 (1.78–10.78)	1.42	0.48	2.99	0.003	4.14 (1.63–10.52)
≥4 enlarged lymph nodes	1.50	0.62	2.41	0.016	4.49 (1.32–15.23)					
Extra-nodal involvement	0.78	0.46	1.72	0.086	2.19 (0.90–5.36)					
Ki-67 ≥40%	0.90	0.44	2.03	0.042	2.45 (1.03–5.82)					

POD24, progression of disease within 24 months; SE, standard error; HR, hazard ratio; CI, confidence interval; FLIPI, Follicular Lymphoma International Prognostic Index; LDH, lactate dehydrogenase.

Table 3 Univariate Cox proportional hazard regression analysis of PET/CT parameters to predict the risk of POD24

Variables	β	SE	Z	P	HR (95% CI)
Dmax (cm)	0.02	0.01	2.14	0.032	1.02 (1.01–1.04)
SUVmax	0.03	0.01	2.62	0.009	1.03 (1.01–1.06)
TMTV (cm^3)	0.01	0.00	2.00	0.045	1.01 (1.01–1.01)
TLG (g)	0.01	0.00	2.15	0.031	1.01 (1.01–1.01)
Dmax >64.24 cm	1.31	0.47	2.75	0.006	3.69 (1.46–9.35)
SUVmax >11.23	1.39	0.48	2.87	0.004	4.01 (1.56–10.36)
TMTV >144.16 cm^2	2.84	1.03	2.76	0.006	17.19 (2.29–129.15)
TLG >586.79 g	2.88	1.03	2.79	0.005	17.74 (2.36–133.32)

PET, positron emission tomography; CT, computed tomography; POD24, progression of disease within 24 months; SE, standard error; HR, hazard ratio; CI, confidence interval; Dmax, maximum tumor dissemination; SUVmax, maximum standardized uptake value; TMTV, total metabolic tumor volume; TLG, total lesion glycolysis.

nodes, extra-nodal involvement, and Ki-67 ≥40%), only elevated LDH retained its statistical significance {hazard ratio (HR) [95% confidence interval (CI)]: 4.14 (1.63–10.52); P=0.003}.

PET/CT parameters and POD24

In addition to the clinical factors, we also assessed PET/CT parameters as prognostic factors for POD24. The Dmax, SUVmax, TMTV, and TLG were incorporated into a univariate Cox regression model, and the results showed that each parameter was significantly associated with POD24 (*Table 3*). We further evaluated the diagnostic efficacy of these parameters using ROC curves, and found that the Dmax, SUVmax, TMTV, and TLG had AUCs of 0.680, 0.710, 0.749, and 0.763, respectively. We then determined the optimal cut-off values for each parameter by maximizing the difference between sensitivity and (1 – specificity) to identify the cut-off values that optimally discriminated between the patients with and without POD24. The resulting cut-off values for the Dmax, SUVmax, TMTV, and TLG were 64.24 cm, 11.23, 144.16 cm^2, 586.79 g, respectively, and had good discriminatory power. The univariate analysis results indicated that a Dmax >64.24 cm [HR (95% CI): 3.69 (1.46–9.35), P=0.006], SUVmax >11.23 [HR (95% CI): 4.01 (1.56–10.36), P=0.004], TMTV >144.16 cm^2 [HR (95% CI): 17.19 (2.29–129.15), P=0.006], and TLG >586.79 g [HR (95% CI): 17.74 (2.36–133.32), P=0.005] were significant risk factors for POD24. *Figure 1* shows the results of the Kaplan-Meier analysis of POD24 according to the Dmax, SUVmax, TMTV, and TLG stratification using the optimal

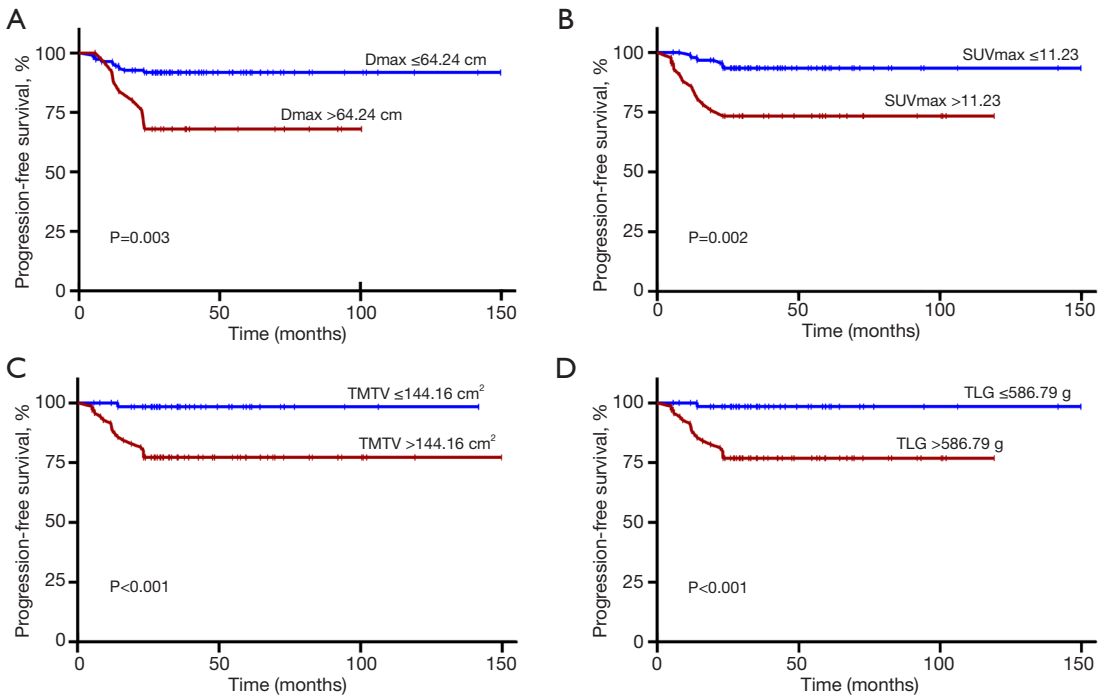

Figure 1 Kaplan-Meier survival analysis of 2-year PFS according to the (A) Dmax, (B) SUVmax value, (C) TMTV, and (D) TLG. Dmax, maximum tumor dissemination; SUVmax, maximum standardized uptake; TMTV, total metabolic tumor volume; TLG, total lesion glycolysis; PFS, progression-free survival.

cut-off values. Notably, the high-level of Dmax, SUVmax, TMTV, and TLG group had substantially worse 2-year progression-free survival (PFS) compared to those without elevated levels.

Prognostic stratification for POD24

Building on these findings, we integrated the clinically relevant baseline variables and PET/CT parameters into a prognostic model to predict POD24. We selected elevated LDH, a Dmax >64.24 cm, and a TMTV >144.16 cm^2 as the key factors for inclusion in the model. Each of these factors was assigned one point, and patients were categorized into the following three risk groups based on their total score: low risk (0 adverse factors, n=59); intermediate risk (1 adverse factor, n = 48); and high risk (2–3 adverse factors, n=34). The POD24 rates of each risk group were 1.69%, 10.42%, and 35.29%, respectively (P<0.001). As *Figure 2* shows, the subgroups with higher scores had significantly worse survival outcomes than that of lower scores (P<0.001).

The maximum intensity projection (MIP) images from PET/CT illustrate the regions with the highest radiotracer uptake, highlighting areas of significant tumor burden and metabolic activity. To visualize the predictive power of the constructed model, representative MIP images of FL patients classified into different risk categories based on three key predictors (i.e., Dmax, TMTV, and LDH levels) were generated (*Figure 3*).

To further evaluate the performance of our prognostic model, we developed a nomogram (*Figure 4A*) to predict the individual probabilities of POD24. The sensitivity (true-positive rate) and specificity (true-negative rate) for identifying POD24 for patients with scores of 2–3 in our model were 66.7% and 82.1%, respectively. As Table S1 shows, the C-index of our established new scoring system was 0.82 (0.73–0.91), which was higher than that of the FLIPI (0.75, 0.66–0.85), FLIPI-2 (0.69, 0.55–0.83), and PRIMA-PI (0.57, 0.43–0.71). Additionally, the ROC curve analysis of the model showed that the AUC of our scoring system was higher than that of the FLIPI, FLIPI-2, and PRIMA-PI (*Figure 4B*). The decision curve analysis showed that our scoring system had superior clinical utility (Figure S2), thus highlighting its potential for widespread clinical application.

Finally, the calibration curves (Figure S3) showed good agreement between the predicted probabilities and actual POD24 rates, supporting the robustness of the model. The area under the time-dependent ROC curve showed the robustness of our model in predicting POD24 (Figure S4). We then conducted internal validation by splitting our data using a 7:3 ratio, and evaluated the performance of the developed predictive model. As *Figure 4C,4D* show, the results consistently showed the superiority of our model over the FLIPI, FLIPI-2, and PRIMA-PI models in both the training and validation sets. These findings highlight the robustness and effectiveness of our model in accurately predicting the early progression of FL in clinical practice.

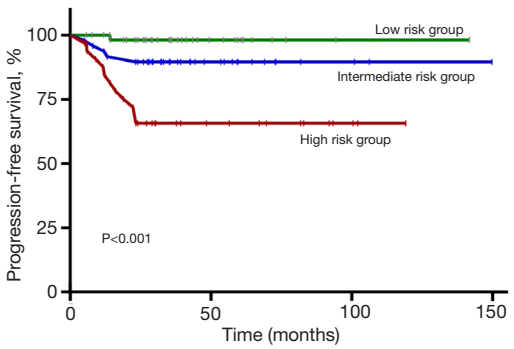

Figure 2 Kaplan-Meier analysis of 2-year PFS in patients with FL according to the present grading system. PFS, progression-free survival; FL, follicular lymphoma.

Discussion

In the present study, we found that baseline PET/CT parameters were predictive of POD24 in patients with FL. By integrating a clinical variable (i.e., elevated LDH) identified through multifactorial regression analyses with the new PET/CT parameter, Dmax, which reflects lesion dissemination, and the metabolic parameter, TMTV, we developed a practical predictive scoring system that could enhance the prediction of early FL progression.

The predictive role of elevated LDH as a component variable of the FLIPI scoring system for FL prognosis has been widely recognized (26,27). In our study, patients with elevated LDH were significantly more likely to develop POD24 than those with normal LDH. The results of the univariate and multifactorial analyses indicated that elevated LDH was a strong predictor of POD24. The risk of POD24 increased 3.14-fold in patients with elevated LDH. Our findings highlight the value of LDH value in predicting early FL progression.

The association between PET metabolic parameters and the prognosis of FL have been extensively studied (28,29). Recently, a pooled analysis of 185 FL patients with a high tumor burden showed that the baseline TMTV was an independent predictor of PFS, capable of

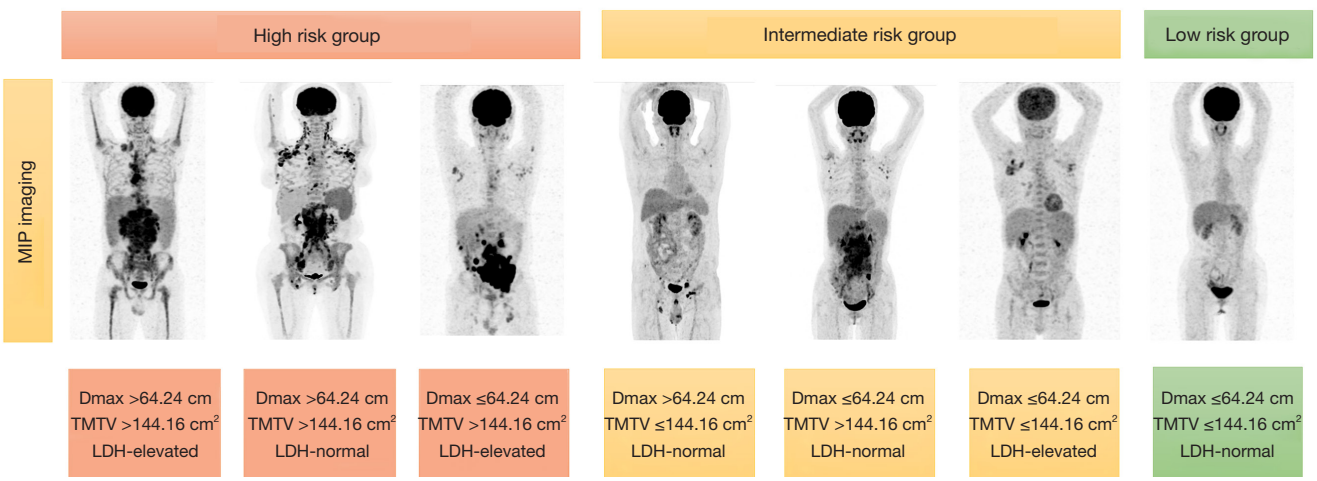

Figure 3 Demonstration of the present risk model using maximum intensity projection of fluorine-18-fluorodeoxygluse PET/CT images. MIP, maximum intensity projection; Dmax, maximum tumor dissemination; TMTV, total metabolic tumor volume; LDH, lactate dehydrogenase; PET, positron emission tomography; CT, computed tomography.

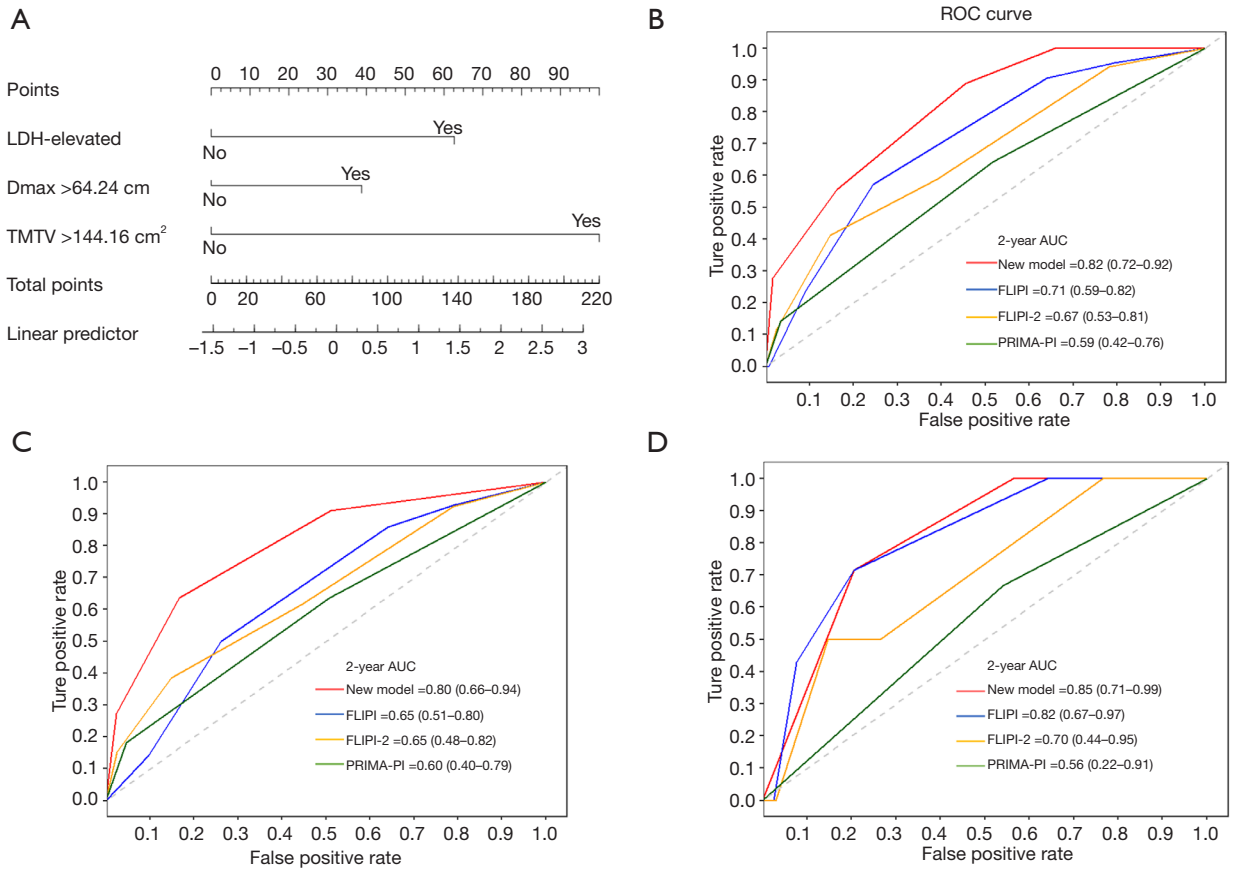

Figure 4 Analysis of the prognostic scoring system. (A) Nomogram for the new prognostic scoring system model. (B) AUC values of overall subjects for the new model, FLIPI, FLIPI-2, and PRIMA-PI scoring systems at the 2-year point. (C) AUC values of the training set, and (D) AUC values of the validation set. Data in brackets represent 95% CI. LDH, lactate dehydrogenase; Dmax, maximum tumor dissemination; TMTV, total metabolic tumor volume; AUC, area under the curve; FLIPI, Follicular Lymphoma International Prognostic Index; PRIMA-PI, PRIMA-prognostic index; CI, confidence interval.

identifying patients at high risk of early progression (30). Liang *et al.* also reported that in addition to the baseline TMTV, the TLG was an independent risk factor for FL patients (31). Consistent with these findings, we observed the predictive effects of the TMTV and TLG on the prognosis of FL (POD24 and PFS). As an emerging PET indicator in recent years, the Dmax can reflect the state of lesion dissemination. Li *et al.* demonstrated that a high Dmax (HR =2.877, P=0.046) is an independent predictor of PFS in FL (15), but they did not assess the potential effects of the Dmax on POD24. In our study, the correlation between the Dmax and POD24 was examined for the first time. We also constructed ROC curves to estimate the ideal Dmax cut-off value for predicting POD24, which showed that FL patients with a Dmax >64.24 cm had a higher risk of developing POD24.

Over the years, prognostic scoring systems for FL, from the FLIPI (20) and FLIPI-2 (21) to the PRIMA-PI (23) and m7-FLIPI (22), have emerged, which assess the PFS and OS of FL patients by integrating clinical risk factors and even gene expression profiles. However, the ability of these existing predictive models to predict POD24 is limited. A real-world study (32) evaluated the predictive performance of these risk-scoring system models for POD24. Among them, the FLIPI had the highest c-index for predicting POD24, but had a specificity of only 34%. Maurer *et al.* (33) proposed a new prognostic model, the FLIPI24, which includes five continuous variables (i.e., age, hemoglobin, leukocyte count, LDH, and β2-microglobulin), which outperformed the FLIPI and PRIMA-PI models, but its precision was not satisfactory. The Bio-FLIPI model (34) combined the expression of cluster of

differentiation (CD)4 in follicles with the FLIPI to assess the risk of FL patients. The sensitivity of the Bio-FLIPI with a score of 3–4 for predicting early progression was 72%, but its accuracy was low (44% of the patients who had event-free survival at 24 months were assigned to the high-risk Bio-FLIPI subgroup). Huet *et al.* (35) identified 23 genes related to the immune microenvironment and B-cell biology, and further adjusted clinical prognostic tools such as FLIPI and the use of rituximab maintenance, which had good specificity but low sensitivity for predicting POD24. Additionally, the POD24-PI model (6), which was specifically established to predict POD24, and includes three genes (EP300, FOX01, and EZH2), physical condition, and the FLIPI score, was shown to have high sensitivity in identifying POD24 patients but at the cost of reduced specificity. Moreover, due to the need for sequencing or digital gene expression profiling, the wide implementation of this model is challenging.

Currently, PET/CT is commonly used as a non-invasive tool for the diagnosis and efficacy assessment of FL. To date, few studies have incorporated PET/CT parameters into prediction models for POD24. However, Kuroki *et al.* (36) established a model that combined the baseline TLG and initial treatment response, which was shown to accurately identify patients at high risk for POD24 (sensitivity: 56%, specificity: 100%); however, due to the small sample size of the study (35 cases), the results require further validation.

Our model, which had a sensitivity of 66.7% and specificity of 82.1%, included clinical variables and PET/CT metabolic and distribution parameters, which are assessed on diagnosis and routinely obtainable in clinical practice. Our model could facilitate the prediction of POD24 and aid clinicians in adjusting treatment strategies. For patients identified as high risk based on the model, clinicians may consider intensifying therapy. These POD24 patients, who are at higher risk of early disease progression, could benefit from more aggressive treatment regimens, such as dose-adjusted immunochemotherapy, the addition of novel therapies like anti-CD20 monoclonal antibodies or immunotherapy agents, or stem cell transplantation. They may also require closer monitoring with more frequent imaging (e.g., repeat PET/CT scans) to assess early signs of progression.

Our study had certain limitations. First, it lacked mid-term-treatment and end-of-treatment PET/CT data, which would have provided a longitudinal perspective and a more comprehensive POD24 prediction. Notably, interim and post-treatment PET/CT parameters can also provide important imaging-based insights for the prognostic evaluation of FL (37-39). For example, Liang *et al.* highlighted that interim TMTV (ΔTMTV >66.3%) and TLG (ΔTLG >64.5%) reduction are valuable tools for early treatment response assessment in FL patients (31). Additionally, post-treatment PET/CT parameters, such as the SUVmax, have been identified as important predictors of long-term prognosis (37). Therefore, future research should seek to integrate imaging parameters from different stages of treatment with clinical variables to further optimize prognostic models for FL and enhance the accuracy of predictions. Second, the retrospective nature of this study could have led to confounding bias. Third, the sample size of our cohort was limited. Future research, including larger cohorts and prospective randomized clinical trials, is essential to further validate our model and help establish whether earlier interventions, closer follow-up, and timely treatment adjustments in high-risk patients with FL truly leads to improved outcomes in terms of POD24 and OS.

Conclusions

PET/CT parameters have value in predicting the early progression of FL. Newly diagnosed FL patients could be scored using PET parameter cut-off values combined with clinical variables to determine their risk of POD24. Clinicians need to be alert to the risk of POD24 in FL patients with a Dmax >64.24 cm, a TMTV >144.16 cm^2, and elevated LDH. Further studies with larger sample sizes should be conducted to better characterize the prognostic effects of these parameters and assess the generalizability of this scoring system.

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Footnote

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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). The study was approved by the Institutional Review Boards of the First Affiliated Hospital of Xiamen University (approval No. 2022-070) and the West China Hospital of Sichuan University (approval No. 2024-1010). The requirement of written informed consent was waived by the Institutional Review Boards due to the retrospective nature of the study.

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