



# Follicular Lymphoma in China: Systematic Evaluation of Follicular Lymphoma Prognostic Models

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**Objects:** To systematically evaluate the baseline characteristics, tumour microenvironment indicators such as the lymphocyte/monocyte ratio (LMR) and treatment response (POD24) as prognostic predictors of follicular lymphoma (FL) among Chinese patients.

**Methods:** We retrospectively analysed 112 FL patients from 2000 to 2017, whose pathology grading included 1–3a. Absolute lymphocyte and monocyte counts were determined by cell blood counting. The Kaplan–Meier method was used to analyse the influence of prognostic predictors on progression-free survival (PFS) and overall survival (OS). Multivariate analysis was conducted using the Cox proportional risk model.

**Results:** The long-term survival of Chinese FL patients (median PFS, 74.8 months) was slightly better than that of patients in foreign countries. Among several prognostic models, the Follicular Lymphoma International Prognostic Index (FLIPI) score had a significant effect on both PFS and OS, while there were no independent prognostic predictors. Patients with  $LMR \leq 3.6$ ,  $ALC \leq 0.6 \times 10^9/L$  and  $AMC > 0.6 \times 10^9/L$  had worse OS, among which LMR was an independent indicator of OS. The POD24 subgroup had a higher frequency of high-risk patients according to FLIPI and FLIPI2 scores (63.0% vs 35.1%,  $P = 0.013$  and 18.5% vs 3.9%,  $P = 0.003$ ) and had a markedly shorter OS ( $P < 0.0001$ ).

**Conclusion:** This study is a systematic prognostic evaluation based on Chinese clinical data. We found a new factor, the LMR, that could independently predict prognosis compared with FLIPI or FLIPI2.

**Keywords:** follicular lymphoma, prognosis, clinical characteristics, lymphocyte/monocyte ratio, immunology

## Introduction

Follicular lymphoma (FL) is a low-grade non-Hodgkin lymphoma (NHL) with follicular-like growth derived from B cells.<sup>1</sup> The course of the disease is variable, usually starting from the upper mediastinum or abdominal lymph nodes and gradually involving extranodal tissues or organs such as bone marrow.<sup>2</sup> Studies have found that many factors may affect the prognosis of the disease. The commonly accepted baseline prognostic models mainly include the Follicular Lymphoma International Prognostic Index (FLIPI) and Follicular Lymphoma International Prognostic Index 2 (FLIPI2) models proposed in the “post-rituximab era”<sup>3</sup> and the extremely simplified PRIMA Prognostic Index (PRIMA-PI) score.<sup>4</sup> The BioFLIPI score developed from the tumour immune microenvironment and biological characteristics are gradually being used for clinical evaluation.<sup>5</sup> Recent studies on the tumour microenvironment of diffuse large B-cell lymphoma (DLBCL) have revealed the complex regulation of tumour growth and invasion, which involves lymphocytes and monocytes, and facilitate the identification of a more convenient biological prognostic marker.<sup>6,7</sup> However, most of the abovementioned studies on various indicators are based on clinical data from Western countries, and a systematic and comprehensive evaluation of prognostic factors among the characteristics of Chinese patients has not been performed. In this study, we performed a single-centre retrospective analysis to systematically and comprehensively assess the baseline characteristics, immune microenvironment, and treatment response of Chinese FL patients to evaluate prognostic factors.

## Materials and Methods

### Patients

We retrospectively analysed data for a total of 112 FL patients in the Department of Haematology of Peking Union Medical College Hospital from January 2000 to August 2017. The inclusion criteria were as follows: clinical diagnosis of FL, hospitalization in our hospital, follicular grade 1 to grade 3A, and intact and traceable baseline data and imaging information. Data verification and regular follow-up visits were used to prevent missing data. All patients were followed up by telephone until August 12, 2020. The follow-up rate was 90.2%. Eleven patients were lost to follow-up. The median follow-up time was 64.5 months (3.2–146.3 months).

### Data Collection

FL diagnosis is based on clinical manifestations; imaging examinations such as lymph node colour Doppler ultrasound, CT and PET-CT; and histopathology including immunohistochemistry. Antibodies included CD20, CD5, CD21, CD23, BCL2, BCL6, CD10, cyclin D1, MUM-1, and the Ki67 index (Ki67%) was assessed as a cell proliferation marker.

The absolute lymphocyte count (ALC) and absolute monocyte count (AMC) were determined through whole blood cell analysis, and the lymphocyte/monocyte ratio (LMR) was calculated at the same time. Other possible prognostic predictors included baseline/mid/end PET-CT performance, lactate dehydrogenase (LDH),  $\beta$ 2 microglobulin ( $\beta$ 2-MG) and other indicators. The samples were classified according to the WHO lymphoma classification and diagnostic criteria and staged according to the Ann Arbor staging scheme. The patients' short-term efficacy evaluations included complete remission (CR), partial response (PR), stable disease (SD) and disease progression (PD). POD24 is defined as progression or relapse within 2 years from the start of chemotherapy. Survival outcomes including overall survival (OS), which is the time from the diagnosis of FL to death from any cause or the end of follow-up, and progression-free survival (PFS), which is the time from the beginning of FL treatment to the end of disease progression or follow-up, were evaluated.

### Statistical Analysis

X-tile was used to select the discriminative cut-off values for the LMR, ALC and AMC, and IBM SPSS Statistics 20 was used to combine all quantitative data. For example, LMR, ALC, AMC, sex, age, clinical stage, FLIPI score, FLIPI2 score,  $\beta$ 2-MG, LDH, complications, and extranodal involvement were all treated as binary/three-category variables, shown in the form of absolute values and percentages. The  $\chi^2$  test was used to analyse the correlations between the LMR, ALC, AMC and other prognostic evaluation indicators and to evaluate the impact of the LMR, ALC, and AMC on short-term efficacy. The Spearman correlation analysis was used for the two-variable nonparametric tests, and the Pearson correlation test was used to assess continuous parameters. The Kaplan–Meier method was used to analyse the survival of patients over 10 years, and the Log rank test was used to calculate the effects of all prognostic predictors on PFS and OS. Multivariate analysis relied on the Cox proportional hazards model.  $P < 0.05$  was considered to indicate a statistically significant difference.

## Results

### Clinical Statistics of All Patients

Of the 112 initially treated FL patients assessed in this study, 21.4% had an age of onset  $>60$  years old; 54 patients were males, and 58 were females. 86.6% was diagnosed as Stage III-IV. The rest of the basic clinical information is shown in [Table 1](#) and [Supplemental Tables 1-2](#).

### Extranodal Involvement and Complications

Of the 112 patients, 29.5% (33/112) exhibited extranodal involvement based on imaging findings, pathology, and bone marrow examination. The bone marrow was the most common site for extranodal involvement, accounting for 19.6% (22/112) of cases. Other involved organs and common complications probably affecting the prognosis are listed in [Supplemental Tables 1-2](#).

**Table 1** Basic Clinical Characteristics of the 112 FL Patients

Factor	n	%
Age	112	
≤60	88	78.6
>60	24	21.4
Sex	112	
Male	54	48.6
Female	58	51.4
Ann Arbor stage	112	
I-II	15	13.4
III-IV	97	86.6
Number of nodal site areas	112	
0-4	28	25.0
>4	84	75.0
Extranodal sites	112	
0	70	62.5
1 or more	42	37.5
Bone marrow involvement	112	
Absence	90	80.4
Presence	22	19.6
Hb level	111	
Greater than 120 g/L	90	81.1
Less than 120 g/L	21	18.9
Serum LDH level	109	
Less than or equal to the ULN	83	76.1
More than the ULN	26	23.9
Serum β2-MG level	51	
Less than or equal to the ULN	4	7.8
More than the ULN	47	92.2
LMR	112	
≤3.6	51	45.5
>3.6	61	54.5
AMC	112	
≤0.6*10 <sup>9</sup> /L	99	88.4
>0.6*10 <sup>9</sup> /L	13	11.6
ALC	112	
≤0.6*10 <sup>9</sup> /L	15	13.4
>0.6*10 <sup>9</sup> /L	97	86.6
Grade	101	
1-2	64	63.4
3a	37	36.6
Ki67%		
≤50	75	75.8
>50	24	24.2

(Continued)

**Table 1** (Continued).

Factor	n	%
FLIPI	111	
0–1	25	22.5
2	37	33.3
3–5	49	43.8
FLIPI2	51	
0–1	30	58.8
2	13	25.5
3–5	8	15.7
Treatment	112	
CHOP±R	101	90.1
FC/FMD±R	3	2.7
R2	3	2.7
Others	5	4.5
Response to first-line therapy	85	
CR	29	34.1
PR	47	55.3
SD	3	3.5
PD	6	7.1

**Abbreviations:** CHOP±R, cyclophosphamide, epirubicin, vincristine, prednisone ±rituximab monoclonal antibody; FC/FMD±R, fludarabine, cyclophosphamide/fludarabine, mitoxantrone, dexamethasone ± rituximab; R2, rituximab + lenalidomide.

## Prognostic Factor Analysis

### Statistics of Patients' Clinical Baseline Characteristics

The most significant cut-off value of the LMR was determined to be 3.6, and the critical cut-off value of the ALC and AMC was determined to be  $0.6 \times 10^9/L$ . [Supplemental Table 3](#) shows the correlations between the LMR, ALC, AMC and other baseline clinical characteristics and prognostic factors. There was no significant difference in the clinical baseline data of patients with different LMR levels, suggesting that LMR acted as the immune status of patients could predict independent of other clinical factors.

## The Impact of Baseline Characteristics on Survival

Kaplan–Meier survival analysis was performed for indicators that might influence survival ([Table 2](#)). The FLIPI score had a significant effect on both PFS and OS ( $P < 0.05$ ), the FLIPI2 score only had a significant effect on PFS ( $P < 0.05$ ), and the PRIMA-PI did not significantly affect survival. In addition, pathological grade 3a and Ki67% > 50 could also indicate poor prognosis.

Multivariate analysis of the above survival factors using the Cox proportional hazards model showed that none of the three indicators could be used as an independent prognostic factor.

## Prognostic Evaluation of the LMR, ALC, and AMC

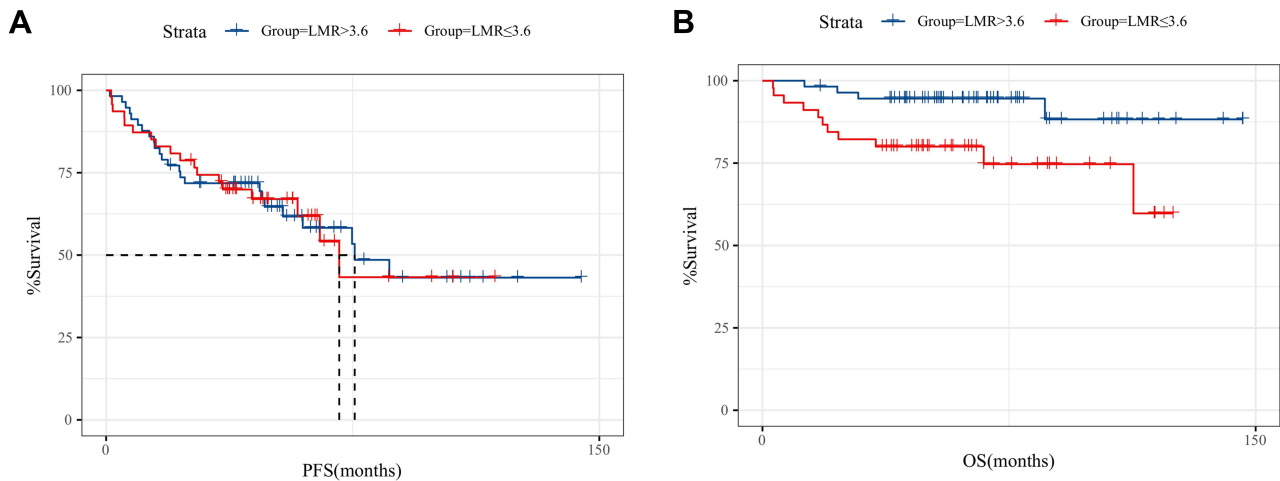
The Kaplan–Meier method was used to analyse the survival of all patients over a 10-year period. [Table 2](#) and [Figures 1–3](#) (detailed in [Supplemental Table 4](#)) show that patients with  $LMR \leq 3.6$ ,  $ALC \leq 0.6 \times 10^9/L$  and  $AMC > 0.6 \times 10^9/L$  had significantly worse OS than other patients and that the PFS of patients with a high AMC ( $AMC > 0.6 \times 10^9/L$ ) was also significantly shortened. A subsequent multivariate analysis with the Cox risk model ([Table 2](#)) showed that LMR could be used as an independent prognostic predictor for OS.

**Table 2** General Survival Analysis of Risk Factors for Prognostic Assessment

	n	PFS					OS				
		Kaplan–Meier (Univariate Analysis)		Multivariate Analysis			Kaplan–Meier (Univariate Analysis)		Multivariate Analysis		
		5-y PFS	P	P	95% CI	HR	5-y OS	P	P	95% CI	HR
FLIPI			0.013	0.765	0.106–5.197	0.743		0.029	0.100	0.734–34.777	5.051
0–1	24	0.770					1.000				
2	34	0.599					0.912				
3–5	42	0.515					0.784				
FLIPI2			0.019	0.240	0.653–5.504	1.895		0.080			
0–1	29	0.637					0.966				
2	13	0.692					0.846				
3–5	8	0.313					0.714				
PRIMA-PI			0.737					0.354			
0	30	0.527					0.933				
1	3	1.000					1.000				
2	16	0.642					0.813				
Grade			0.895						0.036	1.130–37.467	6.507
1–2	63	0.597					0.950	0.013			
3	34	0.592					0.762				
Ki67%			0.035	0.263	0.545–9.254	2.246		0.013	0.773	0.300–5.067	1.232
≤50	72	0.665					0.931				
>50	22	0.500					0.706				
Extranodal involvement			0.673					0.155			
Absence	63	0.562					0.917				
Presence	41	0.658					0.825				
Complication			0.153					0.367			
Absence	71	0.636					0.871				
Presence	33	0.506					0.903				
LMR			0.977					0.014	0.043	0.058–0.952	0.236
≤3.6	45	0.618					0.800				
>3.6	56	0.583					0.946				
AMC			0.396					0.012			
≤0.6*10 <sup>9</sup> /L	91	0.596					0.901				
>0.6*10 <sup>9</sup> /L	10	0.571					0.700				
ALC			0.047	0.609	0.049–5.873	0.535		0.023			
≤0.6*10 <sup>9</sup> /L	13	0.462					0.692				
>0.6*10 <sup>9</sup> /L	88	0.616					0.909				

## Impact of POD24 on Survival

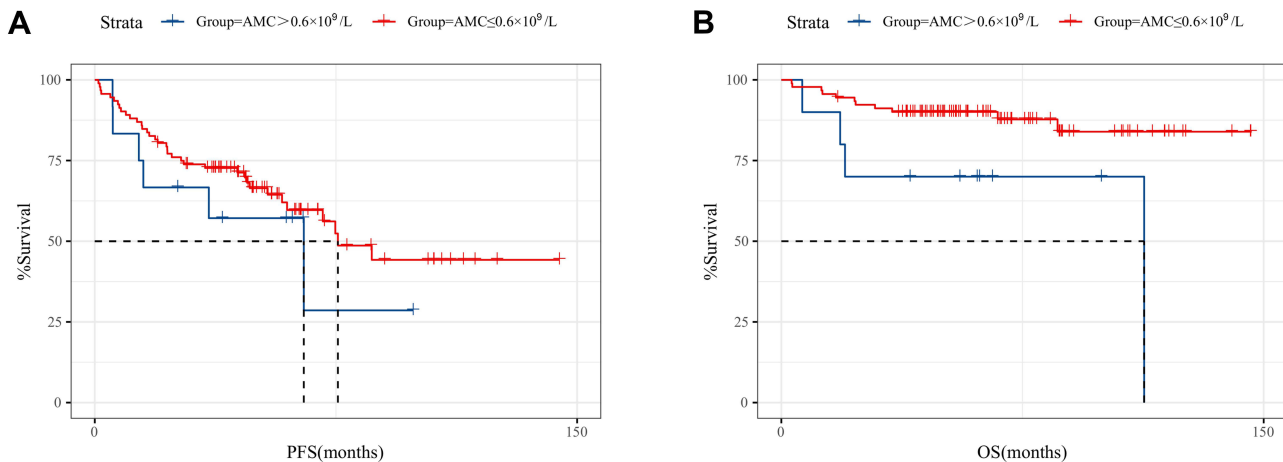
In terms of POD24 evaluation, 26% (27/104) of patients exhibited POD24 after treatment, and there was a higher frequency of patients with high risk according to the FLIPI and FLIPI2 scores in the POD24 subgroup than in the non-POD24 subgroup (63.0% vs 35.1%, P value=0.013 and 18.5% vs 3.9%, P value=0.003) ([Supplemental Table 5](#)). The median survival of the POD24 group was 34.5 months, which was significantly different from that of the non-POD24 group (P<0.0001) ([Figure 4](#)), suggesting that POD24 has good predictive value for the long-term survival of patients.



**Figure 1** Kaplan–Meier curve demonstrating differences in PFS and OS based on the cut-off value of the LMR.

**Notes:** (A) Kaplan–Meier curve demonstrating differences in PFS based on the cut-off value of the LMR. Event/total number of PFS: Group “LMR $\leq$ 3.6” is 18/47, Group “LMR $>$ 3.6” is 24/57; (B) Kaplan–Meier curve demonstrating differences in OS based on the cut-off value of the LMR. Event/total number of OS: Group “LMR $\leq$ 3.6” is 11/45; Group “LMR $>$ 3.6” is 4/56.

**Abbreviations:** PFS, progression-free survival; OS, overall survival; LMR, lymphocyte/monocyte ratio.



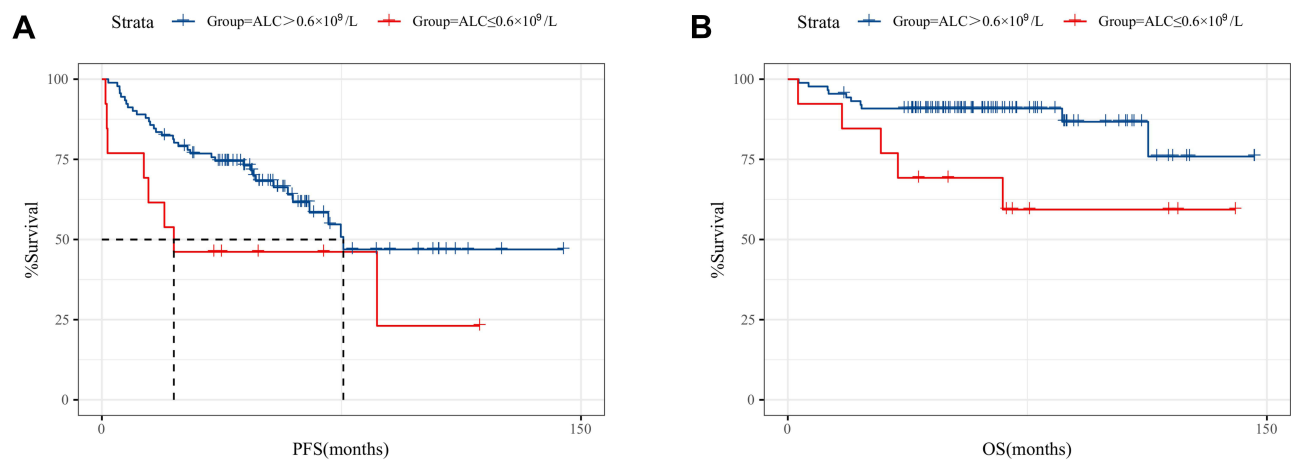
**Figure 2** Kaplan–Meier curve demonstrating differences in PFS and OS based on the cut-off value of AMC.

**Notes:** (A) Kaplan–Meier curve demonstrating differences in PFS based on the cut-off value of AMC. Event/total number of PFS: Group “AMC $\leq$ 0.6 $\times$ 10<sup>9</sup>/L” is 36/92, Group “AMC $>$ 0.6 $\times$ 10<sup>9</sup>/L” is 6/12; (B) Kaplan–Meier curve demonstrating differences in OS based on the cut-off value of AMC. Event/total number of OS: Group “AMC $\leq$ 0.6 $\times$ 10<sup>9</sup>/L” is 11/91, Group “AMC $>$ 0.6 $\times$ 10<sup>9</sup>/L” is 4/10.

**Abbreviations:** PFS, progression-free survival; OS, overall survival; AMC, absolute monocyte count.

## Discussion

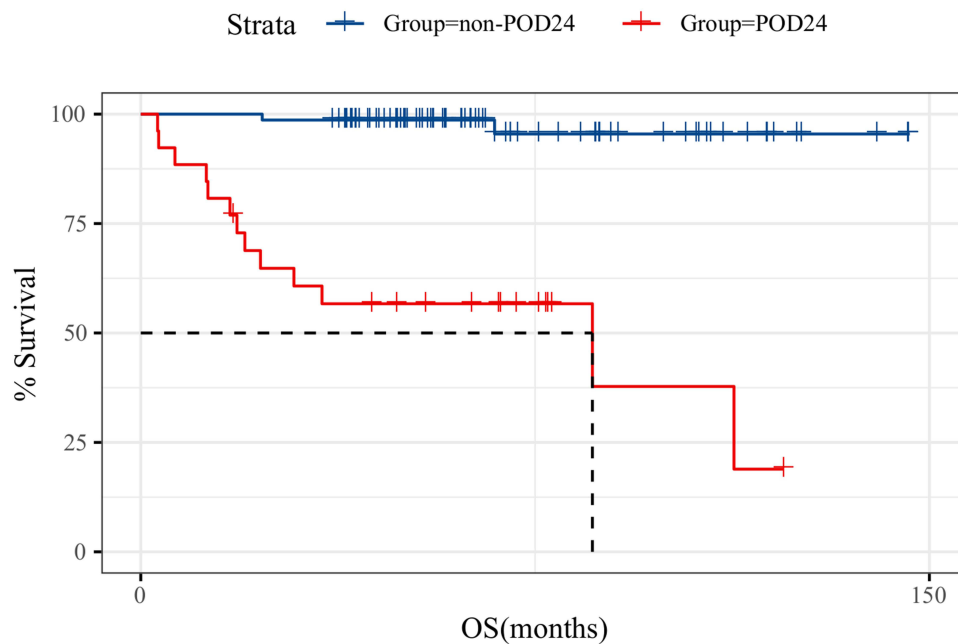
Analysis of the clinical data of this study showed that the median age of onset for FL in China was 52 years old, which was lower than that in foreign countries. Stage III–IV was the most common stage, accounting for 86.8% of cases in China. The incidence of stage III–IV disease was much lower compared with cohort study in Sweden (60%). The immunity levels before treatment were weaker in China than in Western countries (median AMC of 0.35 $\times$ 10<sup>9</sup>/L vs median ALC of 1.24 $\times$ 10<sup>9</sup>/L).<sup>8,9</sup> It has been suggested that the diagnosis of FL in China is relatively late, which may be associated with poor public physical examination awareness. However, with the application of immune-targeted therapeutics such as rituximab, prognosis has improved significantly. During our research, more than 80% of the patients received treatment regimens including rituximab, and their long-term survival was excellent; the median PFS was 74.8 months and the 10-year PFS rate was 43.1%, and these values were slightly better than those in foreign countries in the



**Figure 3** Kaplan–Meier curve demonstrating differences in PFS and OS based on the cut-off value of ALC.

**Notes:** (A) Kaplan–Meier curve demonstrating differences in PFS based on the cut-off value of ALC. Event/total number of PFS: Group “ALC≤0.6×10<sup>9</sup>/L” is 8/13, Group “ALC>0.6×10<sup>9</sup>/L” is 34/91; (B) Kaplan–Meier curve demonstrating differences in OS based on the cut-off value of ALC. Event/total number of OS: Group “ALC≤0.6×10<sup>9</sup>/L” is 5/13, Group “ALC>0.6×10<sup>9</sup>/L” is 10/88.

**Abbreviations:** PFS, progression-free survival; OS, overall survival; ALC, absolute lymphocyte count.



**Figure 4** Prediction of OS according to POD24 status.

**Note:** Event/total number of OS: Group “non-POD24” is 2/75, Group “POD24” is 13/26.

**Abbreviation:** POD24, progression or relapse within 2 years from chemotherapy.

same period.<sup>10</sup> The 5-year OS rate was 88.1%, and the 10-year OS rate was 75%, and these values were similar to those of studies abroad with the same treatment conditions.<sup>9</sup>

Regarding the prognostic impact of baseline characteristics, due to the long time span of more than 10 years,  $\beta$ 2-MG was not commonly used, and the clinical value of FLIPI2 may have been undervalued;<sup>11</sup> however, the predictive value of FLIPI2 in the post-rituximab era should be brought to the attention of clinicians. Therefore, we suggest following a standardized diagnosis process by obtaining the baseline data, such as  $\beta$ 2-MG, bone marrow examination and even gene rearrangement, before initial assessment to provide the conditions for individual prognosis evaluation. In terms of tumour microenvironment indicators, peripheral blood LMR evaluation is a simple process.

Previous studies have found that in patients with DLBCL and FL, OS after chemotherapy was significantly shortened in those with a low LMR ( $LMR \leq 2.6$ ).<sup>12-14</sup> Our study showed that the LMR is the only independent predictor of the long-term OS of FL patients in the Chinese population. ALC or AMC may also have some implications for OS. These results suggest that the immune microenvironment, especially cellular immunity, plays an important role in the progression of FL. Especially in recent years, drugs targeting the tumour microenvironment, such as lenalidomide and chidamide, have emerged. The LMR may serve as an important reference for clinical treatment decision making and may become a more popular indicator. In terms of the mechanism, previous literature has reported that peripheral blood lymphocytes can activate a variety of antigen-presenting cells, thus facilitating the recognition, uptake, presentation and immune system activation of tumour surface antigens. However, M2-type macrophages (tumour-associated macrophages [TAMs]) in peripheral blood are enriched around tumours under the guidance of regulatory T cells (Tregs), which directly promote tumour progression by endowing tumour tissues with functional polarity.<sup>15,16</sup> In terms of treatment response prediction, POD24 status demonstrated strong predictive power for long-term survival and strong associations with baseline risk stratification status. Overall, considering the accuracy of prognosis prediction with the M7-FLIPI and health economics concerns, POD24 may be an important inclusion criterion for further gene expression profiling of patients.

This study is a systematic and comprehensive prognostic evaluation based on clinical data of Chinese patients. Prognostic predictors cover three categories: clinical baseline characteristics, tumour microenvironment characteristics and treatment response. All patients were followed up for more than 3 years, and the longest follow-up time was 146.3 months. We found a new factor, the LMR, that could predict prognosis independent of FLIPI or FLIPI2 status. The first drawback of this study is that the PRIMA-PI is affected by  $\beta 2$ -MG and the small number of cases with bone marrow involvement, so the stratification results are not accurate. Second, due to the lack of gene expression profiling data for all of our patients, the prognostic assessment of tumour biological characteristics was incomplete. This study can be supplemented and corrected through prospective experiments in future clinical practice. Finally, because the sample size was insufficient, it was difficult to establish a prognostic evaluation model. Perhaps in the future, a more optimized FL prognostic model can be established with a larger cohort of patients from multiple centres with available data on the LMR and other independent prognostic predictors; this optimized model could be a simple, economical, and easy-to-apply evaluation system for guiding individualized treatment.

## Abbreviations

LMR, lymphocyte/monocyte ratio; FL, follicular lymphoma; NHL, non-Hodgkin lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; FLIPI2, Follicular Lymphoma International Prognostic Index 2; PRIMA-PI, PRIMA Prognostic Index; DLBCL, diffuse large B-cell lymphoma; ALC, absolute lymphocyte count; AMC, absolute monocyte count; LDH, lactate dehydrogenase;  $\beta 2$ -MG,  $\beta 2$  microglobulin; CR, complete remission; PR, partial response; SD, stable disease; PD, disease progression; OS, overall survival; PFS, progression-free survival; TAMs, tumour-associated macrophages.

## Data Sharing Statement

No additional data available.

## Ethics Approval and Informed Consent

Our study was approved by the PUMCH Institutional Review Board (protocol number: S-k1861). Because our study is a retrospective research, a waiver of patients consent was obtained from the PUMCH Institutional Review Board. We guaranteed the anonymity and privacy of patient information and the accessed data conformed to the data and privacy regulations of Declaration of Helsinki.

## Funding

This study was supported by no agents.

## Disclosure

The authors report no potential conflicts of interest in this work.

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