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Reevaluating Prognostic Tools in Follicular Lymphoma: Should the PRIMA Prognostic Index Supersede FLIPI2?

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Abstract

Recent evidence suggests that the PRIMA prognostic index (PRIMA-PI) may serve as a straightforward tool for risk stratification in patients with follicular lymphoma (FL). This study aimed to provide further insight into the prognosis of FL and retrospectively evaluated the prognostic utility of PRIMA-PI in comparison with the follicular lymphoma international prognostic index 2 (FLIPI2). A total of 45 newly diagnosed FL patients who received chemotherapy were included in this analysis. All patients underwent bone marrow biopsy to assess marrow involvement, and histological grading was performed according to WHO criteria. Overall survival (OS) was assessed using the Kaplan-Meier method and Cox proportional hazards modeling to assess the prognostic significance of FLIPI2, PRIMA-PI, and histologic grade. Based on FLIPI2, 9-year OS rates were 100% in the low-risk group, 52.9% in the intermediate-risk group, and 49.5% in the high-risk group. In comparison, PRIMA-PI classified the 9-year OS rates as 83.9% (low-risk), 68.2% (intermediate-risk), and 43.3% (high-risk). Based on histologic grade, 9-year OS rates were 83.3% for grade 1, 73% for grade 2, 59.3% for grade 3a, and 25% for grade 3b. Both univariate and multivariate analyses identified FLIPI2 and histologic grade as independent prognostic factors for OS, with statistical significance (P = 0.03 and P = 0.012, respectively). In contrast, PRIMA-PI did not reach statistical significance in predicting OS (P = 0.056). These findings suggest that caution is warranted when considering the widespread adoption of PRIMA-PI as a substitute for FLIPI2 in the prognostic evaluation of follicular lymphoma.

Keywords: Histologic grading, PRIMA-PI, FLIPI2, Follicular lymphoma, Prognosis

Introduction

Follicular lymphoma (FL) is a malignancy originating from germinal center B cells and has traditionally been regarded as an indolent, slowly progressing tumor. Despite significant therapeutic advances in recent decades, FL remains an incurable disease [1, 2]. These developments necessitate the continuous refinement of prognostic models.

The original follicular lymphoma international prognostic index (FLIPI)—based on factors such as age over 60 years, hemoglobin level below 120 g/L, elevated lactate dehydrogenase (LDH), involvement of more than four lymph node regions, and advanced disease stage—was established using data from patients treated before the introduction of rituximab [3–5]. With rituximab significantly transforming FL treatment outcomes, an updated version, FLIPI2, was introduced. This model incorporates age over 60 years, hemoglobin level under 120 g/L, elevated beta-2 microglobulin, the presence of a lymph node larger than 6 cm, and bone marrow involvement, making it more suitable for the rituximab

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era [3–5]. Nonetheless, the original FLIPI has retained clinical utility even in the post-rituximab setting [3].

Further efforts to improve prognostic accuracy led to the development of m7-FLIPI, which combines the FLIPI score with mutational data from seven genes [6]. However, its predictive value may vary depending on the chemotherapy regimen used [7, 8].

In addition to composite indices, various single prognostic markers have also attracted interest. These include sex, lymphocyte-to-monocyte ratio (LMR), maximum standardized uptake value (SUVmax) on PET/CT imaging, and the number of prior treatment lines in relapsed or refractory FL cases [8–12]. Notably, the progression of the disease within 24 months of initial therapy (POD-24) has emerged as a strong predictor of poor prognosis in FL [13, 14].

Nevertheless, the need for simplified yet reliable prognostic tools has led to the proposal of the PRIMA Prognostic Index (PRIMA-PI), which is based solely on elevated beta-2 microglobulin and bone marrow involvement. Its simplicity and independence from age have made it appealing, particularly for patients over 60 years [15–17]. While initial studies suggest that PRIMA-PI may offer acceptable specificity and reliability, its performance compared to established tools like FLIPI2 remains insufficiently validated.

With the goal of contributing additional clinical insight, we conducted a retrospective study to evaluate the prognostic value of PRIMA-PI in comparison with FLIPI2 in patients with follicular lymphoma.

Materials and Methods

Study population

This retrospective study was carried out at the National Institute of Hematology and Blood Transfusion in Hanoi, Vietnam. It included 45 patients who were newly diagnosed with follicular lymphoma and underwent chemotherapy between January 2014 and December 2022.

Baseline assessment

Before the initiation of therapy, all patients underwent bone marrow biopsies to determine marrow infiltration.

Treatment regimen

Chemotherapy was administered using either the R-CHOP protocol (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) or the BR protocol (bendamustine and rituximab). Patients received 4 to 6 cycles of induction therapy, followed by rituximab maintenance therapy for two years.

Diagnostic and prognostic evaluation

Diagnoses were confirmed using the 2008 WHO classification for hematologic malignancies [18]. Histological grades were assigned based on WHO criteria [3], and disease staging followed the Ann Arbor system [3]. Risk stratification was conducted using two prognostic models: FLIPI2 and PRIMA-PI [3]. Treatment outcomes were evaluated according to RECIL 2017 guidelines for lymphoma response [19].

Data analysis

Overall survival (OS) was defined as the duration from diagnosis to either death or the last follow-up. Survival outcomes were analyzed using Kaplan-Meier survival curves, and prognostic factors were assessed through Cox proportional hazards regression models. Statistical significance was set at $P < 0.05$.

Results and Discussion

Patient overview

Among the 45 patients enrolled in this study, 21 were male, representing 46.7% of the total cohort. The participants ranged in age from 27 to 79 years, with a median age of 56 years. An overview of laboratory findings is presented in **Table 1**, while detailed clinical features are listed in **Table 2**.

Nearly half of the patients (46.7%, n = 21) had bone marrow involvement (BMI) at diagnosis. The most frequently observed bone marrow pattern was paratrabecular, though nodular, diffuse, and mixed infiltration types were also noted.

Table 1. Laboratory test summary in patients with follicular lymphoma

Parameter	No. of cases	Range (Min-Max)	Average value	Standard deviation
Hemoglobin (g/L)	45	92–162	125.4	15.7
Platelet count ($\times 10^9$/L)	45	24–932	251.3	142.7
White blood cell ($\times 10^9$/L)	45	0.46–89.21	9.3	13.3

Neutrophil count (×10⁹/L)	45	0.11–9.87	4.1	2.1
Beta-2 microglobulin (mg/L)	45	1.16–7.42	2.75	1.32
LDH (U/L)	45	230–1013	447.2	207.9

Bone marrow involvement and diagnostic considerations

Bone marrow infiltration is a known negative prognostic indicator in follicular lymphoma and is observed in approximately 40–70% of patients, which aligns with the rate seen in our cohort [20, 21]. Diagnosis of BMI was based on morphological examination of bone marrow biopsy specimens. Emerging data suggest that diagnostic sensitivity may vary between techniques. While PET/CT imaging has demonstrated higher accuracy in detecting marrow involvement, flow cytometry may fail to identify subtle infiltrates and is considered less reliable in some comparative studies [20, 22-25].

Table 2. Clinical and pathological characteristics of the patients (n = 45)

Feature	Category	Valid (%)	Frequency	Percent	Cumulative (%)
Lymph node enlargement	Yes	93.3	42	93.3	100.0
	No	6.7	3	6.7	6.7
Liver enlargement (hepatomegaly)	Yes	8.9	4	8.9	100.0
	No	91.1	41	91.1	91.1
Spleen enlargement (splenomegaly)	Yes	8.9	4	8.9	100.0
	No	91.1	41	91.1	91.1
Bone marrow involvement (BMI)	Yes	46.7	21	46.7	100.0
	No	53.3	24	53.3	53.3
BMI histology (n = 21)	Paratrabecular	42.9	9	20.0	66.7
	Nodular	23.8	5	11.1	23.8
	Mixed	19.0	4	8.9	100.0
	Diffuse	14.3	3	6.7	81.0
Ann arbor staging	IIIA	26.7	12	26.7	42.2
	IVA	22.2	10	22.2	82.2
	IIIB	17.8	8	17.8	60.0
	IVB	17.8	8	17.8	100.0
	IIA	11.1	5	11.1	11.1
	IIB	4.4	2	4.4	15.6
Tumor grade	Grade 2	53.3	24	53.3	71.1
	Grade 3a	20.0	9	20.0	91.1
	Grade 1	17.8	8	17.8	17.8
	Grade 3b	8.9	4	8.9	100.0
FLIPI2 risk group	Intermediate risk	40.0	18	40.0	73.3
	Low risk	33.3	15	33.3	33.3
	High risk	26.7	12	26.7	100.0
PRIMA-PI risk group	Low risk	46.7	21	46.7	46.7
	High risk	28.9	13	28.9	100.0
	Intermediate risk	24.4	11	24.4	71.1

Histological grading and risk stratification

Based on the WHO classification, the most common histological grade of follicular lymphoma observed in this cohort was grade 2, accounting for 53.3% of patients. Risk stratification was performed using both the FLIPI2 and PRIMA-PI prognostic indices. A discrepancy was noted between the two systems: FLIPI2 most frequently categorized patients into the intermediate-risk group, whereas PRIMA-PI identified the majority as belonging

to the low-risk category. Despite these differences in distribution, the comparison between the two indices did not reach statistical significance (P = 0.287).

Treatment outcomes

As illustrated in **Table 3**, the majority of patients (86.7%) responded to chemotherapy with a complete response (CR) before initiating rituximab maintenance therapy. In terms of overall survival (OS), the mean survival time was 77.43 months **(Table 4)**. Among the patients with bone marrow involvement (BMI), those with nodular BMI had the shortest OS. However, the differences in survival across different BMI types were not statistically significant.

Table 3. Chemotherapy response before rituximab maintenance (n = 45)

Response type	Frequency	Percentage (%)	Cumulative (%)
Complete response (CR)	39	86.7	100.0
Partial response (PR)	6	13.3	13.3
Total	45	100.0	—

Note: CR = complete response; PR = partial response

Table 4. Overall survival based on bone marrow involvement histology

Bone marrow involvement type	Mean OS (months)	Std. error	95% confidence interval	P-value
No BMI	85.67	8.21	69.58 – 101.77	0.684
Paratrabecular	75.56	15.98	44.23 – 106.88	—
Diffuse	62.50	10.25	42.40 – 82.60	—
Mixed	48.50	21.95	5.48 – 91.52	—
Nodular	31.40	5.01	21.58 – 41.22	—
Overall	77.43	7.27	63.18 – 91.68	—

Note: BMI = bone marrow involvement

While there has been limited research examining the impact of the BMI type on survival outcomes in follicular lymphoma, Canioni *et al.* [21] suggested that the lymphomatous foci (LFo) area relative to the bone marrow biopsy (BMB) size may be an important prognostic factor for survival.

In our analysis, both univariate and multivariate evaluations identified FLIPI2 and grade as significant independent factors for overall survival (OS) **(Table 5; Figures 1 and 2)**. However, PRIMA-PI did not demonstrate a meaningful impact on OS prognosis in this study **(Table 5)**.

Prognostic systems in survival analysis

Table 5. Analysis of prognostic factors for overall survival in univariate and multivariate models

Factor	Univariate OS	P-value (Log-rank)	Multivariate OS	P-value (Cox)
FLIPI2				
Low risk	100%	0.041	0.03	
Intermediate risk	52.9%			
High risk	49.5%			
Grade				
Grade 1	83.3%	0.041	0.012	
Grade 2	73.0%			
Grade 3a	59.3%			
Grade 3b	25.0%			
PRIMA-PI				
Low risk	83.9%	0.056		

Intermediate risk	68.2%
High risk	43.3%

Note: OS = overall survival

Our study confirmed that grade remains a crucial element in determining the prognosis of follicular lymphoma (FL). While earlier research typically focused on the differentiation between grade 3b and other grades, since grade 3b is often linked with diffuse large B cell lymphoma (DLBCL), we found a statistically significant variation in 9-year OS rates across all four grades.

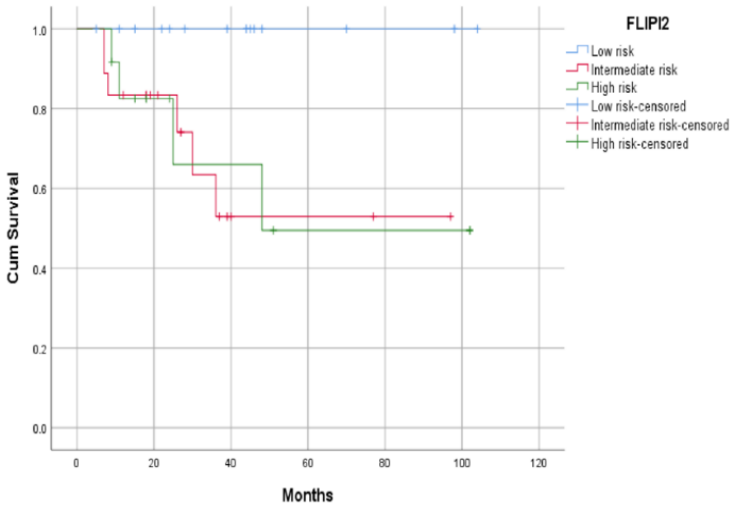

Figure 1. OS (overall survival) according to FLIPI2

PRIMA-PI is often regarded as a straightforward prognostic tool. Bachy *et al.* [16] demonstrated that PRIMA-PI is an effective, simplified scoring system for predicting progression-free survival (PFS) and showed a strong correlation with POD-24 (progression of disease within 24 months). Alig *et al.* [17] found that PRIMA-PI exhibited superior specificity in identifying high-risk patients compared to both FLIPI and FLIPI2. Additionally, Kimby *et al.* [15] revealed that PRIMA-PI may offer more predictive value than FLIPI, particularly in patients aged over 60 years [15].

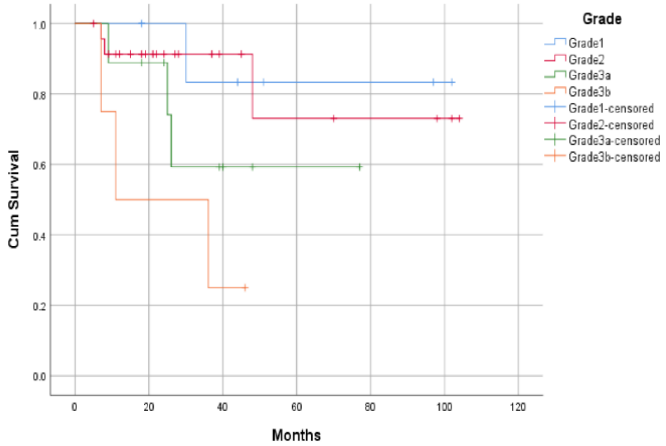

Figure 2. OS (overall survival) according to grade (histological grading of follicular lymphoma)

Mozas *et al.* [26] highlighted that PRIMA-PI is independent of age and can help identify high-risk patients, particularly those over 60 years old. However, they also noted that FLIPI remains a dominant prognostic index for follicular lymphoma (FL) [26]. Wu *et al.* [27] found that FLIPI exhibited the highest positive predictive value, while PRIMA-PI was more precise in predicting POD-24 (Progression of Disease within 24 months). Duras *et al.* [28] observed that the survival curves for the low- and intermediate-risk groups, based on PRIMA-PI, overlapped, indicating some limitations in distinguishing between these groups. Based on these findings, PRIMA-PI may have a specific value in assessing high-risk patients aged 60 years and above. However, it's important to note that most studies (except for Alig's) did not directly compare PRIMA-PI with FLIPI2. In our research, we found that PRIMA-PI did not significantly influence overall survival (OS), whereas FLIPI2 and grade emerged as independent prognostic factors (P = 0.03 and 0.012, respectively) in both univariate and multivariate analyses.

In summary, the current body of evidence does not support PRIMA-PI as a replacement for FLIPI2 in predicting outcomes for follicular lymphoma. Moreover, relying only on two factors—beta-2 microglobulin and bone marrow involvement—may not provide a comprehensive prognosis for such a complex condition. Additional research is necessary to assess the broader applicability of PRIMA-PI. Whether dealing with slow-growing lymphomas like FL or aggressive types like DLBCL (diffuse large B-cell lymphoma), further studies are required to unravel the complexity of prognostic factors [29].

Conclusion

It is advisable to proceed cautiously before considering PRIMA-PI as a widespread alternative to FLIPI2 for follicular lymphoma prognosis.

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