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ORIGINAL ARTICLE

Evaluation of patients diagnosed with follicular lymphoma: A multicenter study

Foliküler Lenfoma Tanılı Hastaların Değerlendirilmesi: Çok Merkezli Çalışma

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Highlights

- This multicenter real-world study included 89 patients with follicular lymphoma, of whom 62.9% had advanced-stage disease at diagnosis.
- R-CHOP was the predominant frontline regimen, and 67.8% of R-CHOP-treated patients received rituximab maintenance.
- At a median follow-up of 45.3 months, the five-year progression-free and overall survival rates were 70% and 85%, respectively.
- Relapse occurred in 5.6% of patients, all of whom subsequently underwent autologous stem cell transplantation.
- FLIPI and FLIPI-2 did not significantly discriminate progression-free or overall survival in this cohort.

ABSTRACT

Aim: Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma, characterized by variable clinical behavior and treatment responses. While rituximab-based immunochemotherapy is standard in frontline treatment, real-world data reflecting its effectiveness, particularly with maintenance strategies in multi-institutional settings, remain limited.We aimed to evaluate clinical features, therapeutic approaches, and survival outcomes of FL patients treated across multiple centers, emphasizing the impact of rituximab maintenance.
Materials and Methods: We included 89 patients diagnosed with FL between 2018-2022 from participating tertiary centers. Baseline demographic and prognostic data (including FLIPI and FLIPI-2), treatments received, and follow-up details were collected. Primary outcomes were progression-free survival (PFS) and overall survival (OS). Survival analyses used Kaplan–Meier curves and log-rank tests. Ethical approval was obtained (Necmettin Erbakan University Ethics Committee, decision no. 2023/4225).
Results: Median age was 51.9 years; 62.9% presented with advanced-stage disease. R-CHOP was the predominant frontline regimen; 67.8% of these patients received rituximab maintenance. At median follow-up of 45.3 months, median PFS was 140.7 months, and median OS was 243 months. Five-year PFS and OS rates were 70% and 85%, respectively. Relapse occurred in 5.6% of patients; all underwent autologous stem cell transplantation. No significant differences in survival outcomes were observed across FLIPI/FLIPI-2 risk groups.
Conclusion: In this multicenter real-world cohort, rituximab-based immunochemotherapy followed by maintenance therapy yielded durable disease control in FL. Standard prognostic indices may require recalibration in the current therapeutic landscape. National collaborative registries are essential to further validate these findings and integrate novel therapies into practice.

Keywords: Follicular lymphoma, immunochemotherapy, overall survival, progression-free survival

ÖZ

Amaç: Foliküler lenfoma (FL), değişken klinik seyir ve tedavi yanıtlarıyla karakterize, en sık görülen indolen non-Hodgkin lenfoma türüdür. Rituksimab temelli immünokemoterapi birinci basamak tedavinin standardı olmakla birlikte, özellikle idame tedavilerinin etkinliğini çok merkezli koşullarda değerlendiren gerçek yaşam verileri sınırlıdır. Bu çalışmada, birden fazla merkezde tedavi edilen FL hastalarının klinik özelliklerinin, tedavi yaklaşımlarının ve sağkalım sonuçlarının değerlendirilmesi ve rituksimab idame tedavisinin etkisinin incelenmesi amaçlandı.
Gereç ve Yöntem: Çalışmaya, katılımcı üçüncü basamak merkezlerde 2018–2022 yılları arasında FL tanısı konulan 89 hasta dahil edildi. Başlangıç demografik ve prognostik verileri, Follicular Lymphoma International Prognostic Index (FLIPI) ve FLIPI-2 skorları, uygulanan tedaviler ve takip bilgileri kaydedildi. Birincil sonlanım noktaları progresyonsuz sağkalım (PFS) ve genel sağkalım (OS) olarak belirlendi. Sağkalım analizlerinde Kaplan–Meier yöntemi ve log-rank testi kullanıldı. Çalışma için Necmettin Erbakan Üniversitesi Etik Kurulundan onay alındı (karar no: 2023/4225).
Bulgular: Hastaların ortalama yaşı 51,9 yıl olup %62,9'u ileri evre hastalıkla başvurdu. En sık kullanılan birinci basamak tedavi rejimi R-CHOP idi ve bu tedaviyi alan hastaların %67,8'ine rituksimab idame tedavisi uygulandı. Medyan 45,3 aylık takip süresinde medyan PFS 140,7 ay, medyan OS ise 243 ay olarak bulundu. Beş yıllık PFS ve OS oranları sırasıyla %70 ve %85 idi. Hastaların %5,6'sında relaps gelişti ve bu hastaların tamamına otolog kök hücre nakli uygulandı. FLIPI ve FLIPI-2 risk grupları arasında sağkalım sonuçları açısından anlamlı farklılık saptanmadı.
Sonuç: Bu çok merkezli gerçek yaşam kohortunda, rituksimab temelli immünokemoterapi ve sonrasında uygulanan idame tedavisi FL'de uzun süreli hastalık kontrolü sağlamıştır. Güncel tedavi koşullarında standart prognostik indekslerin yeniden değerlendirilmesi gerekebilir. Bulguların doğrulanması ve yeni tedavilerin klinik uygulamaya entegrasyonu için ulusal iş birliğine dayalı kayıt sistemlerine ihtiyaç vardır.

Anahtar Kelimeler: Foliküler lenfoma, genel sağkalım, immünokemoterapi, progresyonsuz sağkalım

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Introduction

Follicular lymphoma (FL) is the most common subtype of indolent B-cell non-Hodgkin lymphoma, accounting for approximately 20–30% of all lymphomas worldwide and representing a significant proportion of cases in Türkiye as well [1]. The disease is characterized by a slow clinical course; however, most patients present with advanced-stage disease, and bone marrow involvement is frequently observed at diagnosis [2]. Histopathologically, FL is defined by the hallmark t(14;18) translocation leading to BCL2 overexpression and demonstrates a typical immunophenotype with CD20, CD10, BCL2, and BCL6 positivity [3, 4].

Risk stratification remains critical in guiding therapeutic decision-making. The Follicular Lymphoma International Prognostic Index (FLIPI) and FLIPI-2 are widely adopted prognostic models integrating clinical and laboratory parameters to classify patients into low-, intermediate-, and high-risk groups [5, 6]. Recent refinements, such as the m7-FLIPI and PRIMA-PI, incorporate molecular alterations and biomarkers to enhance prognostic accuracy, particularly in patients treated with rituximab-based immunochemotherapy (IC) [7, 8].

The advent of anti-CD20 monoclonal antibodies, particularly rituximab, has transformed the treatment paradigm of FL, markedly improving long-term outcomes [9]. Combination regimens such as R-CHOP, R-CVP, and bendamustine-rituximab are currently standard frontline therapies, frequently followed by rituximab maintenance, which has been shown to provide significant progression-free survival (PFS) benefits [10–12]. Despite these advances, relapses are inevitable, and approximately 20% of patients experience early disease progression within 24 months (POD24), a subgroup associated with inferior overall survival [13].

Emerging targeted therapies, including lenalidomide, EZH2 inhibitors, PI3K inhibitors, and novel ICs such as CAR-T cells and bispecific antibodies, are reshaping the therapeutic landscape [14–16]. Nevertheless, access to these agents remains variable, and rituximab-based IC continues to be the backbone of treatment in many settings, particularly in resource-limited regions.

A recent comprehensive review highlighted these evolving strategies and underscored the importance of real-world data in refining prognostic models and optimizing treatment approaches in different populations (17). In line with this, the present study evaluates the clinical features, treatment patterns, and survival outcomes of FL patients managed at our center, with a focus on rituximab-based IC and maintenance strategies, and contextualizes these findings within contemporary literature.

Materials and Methods

Study Design and Patient Population

This was a multicenter, retrospective cohort study including patients diagnosed with follicular lymphoma (FL) between 2018 and 2022 at participating tertiary hematology centers. Clinical, epidemiological, and treatment-related data were retrieved from institutional electronic health records and patient charts. Inclusion criteria were: (i) a confirmed diagnosis of FL according to the World Health Organization (WHO) 2016 classification; (ii) availability of baseline clinical, laboratory, and staging information; and (iii) follow-up data sufficient to evaluate treatment outcomes. Patients with incomplete baseline data or loss to follow-up within three months of diagnosis were excluded.

Participating Centers and Treatment Variation

The study included patients from six tertiary hematology centers in Türkiye. While minor treatment variations existed between institutions, all centers followed national lymphoma management guidelines. Chemotherapy protocols were largely uniform, particularly for frontline IC approaches.

Clinical and Treatment Variables

Collected variables included age, sex, stage at diagnosis (Ann Arbor classification), performance status (ECOG), lactate dehydrogenase (LDH) levels, bone marrow involvement, and prognostic indices (FLIPI and FLIPI-2). Treatment characteristics were recorded, including type of first-line regimen, response rates, use of rituximab maintenance therapy, and the requirement for subsequent therapy or autologous stem cell transplantation (ASCT).

Follow-up and Outcome Measures

The primary endpoints were progression-free survival (PFS), defined as the time from diagnosis to disease progression or relapse, and overall survival (OS), defined as the time from diagnosis to death from any cause or last follow-up. Secondary endpoints included response rates to first-line therapy and the impact of rituximab maintenance on survival outcomes. Survival analyses were stratified by clinical and treatment-related factors. In a subset of patients, PFS and OS could not be calculated due to insufficient follow-up duration. These cases were retained in descriptive analyses but excluded from subgroup survival statistics.

Statistical Analysis

Descriptive statistics were presented as means ± standard deviation (SD) for normally distributed variables, and medians with ranges for skewed data. Categorical variables were expressed as counts and percentages. Comparisons between groups were performed using the chi-square test or Fisher's exact test for categorical variables, and Student's t-test or Mann–Whitney U test for continuous variables, as appropriate. Survival analyses were conducted using the Kaplan–Meier method, with differences between subgroups assessed by the log-rank test. A p-value of <0.05 was considered statistically significant. All analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

Ethical Considerations

The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the Non-Interventional

Clinical Research Ethics Committee of Necmettin Erbakan University, with decision number 2023/4225. As this was a retrospective study, the requirement for informed consent was waived by the ethics committee.

Results

Patient Characteristics

A total of 89 patients were included in the study. The mean age was 51.9±11.6 years, with 46 (51.7%) female and 43 (48.3%) male patients. There was no significant difference in mean age between genders (female: 51.7±11.4; male: 52.1±12.0; p=0.873). The majority of patients (62.9%) were diagnosed at an advanced stage. Epidemiological and clinical characteristics are summarized in Table 1.

Table 1. Epidemiological and Clinical Characteristics of the Patients

Parameter	n (%)
Sex	
Female	46 (51.7)
Male	43 (48.3)
Stage	
I	20 (22.5)
II	13 (14.6)
III	22 (24.7)
IV	34 (38.2)
Stage Grouping	
Stage I-II (Early)	33 (37.1)
Stage III-IV (Advanced)	56 (62.9)
Histologic Grade	
I	26 (29.2)
II	41 (46.1)
IIIa	15 (16.9)
IIIb	7 (7.9)
III	22 (24.8)
FLIPI-1 Risk	
Low	20 (22.5)
Intermediate	26 (29.2)
High	43 (48.3)
FLIPI-2 Risk	
Low	39 (43.8)
Intermediate	32 (36)
High	18 (20.2)
Bone Marrow Involvement	
Present	28 (31.5)
Absent	61 (68.5)

Treatment Evaluation

At diagnosis, 70 patients (78.7%) required treatment. All early-stage patients received therapy, while 37 of 56 advanced stage (Stage III–IV) patients (66%) required immediate treatment. Among the 19 patients who did not need treatment at diagnosis, 12 (63%) eventually required therapy after a median duration of 13.4 months (range: 4.5–48.2). All of these patients were started on R-CHOP, while 7 patients (27%) were managed with a watch-and-wait approach.

Among treated patients, 70 (85.4%) received IC and 12 (14.6%) received radiotherapy (RT) as first-line treatment. The most frequently used regimen was R-CHOP, administered to 56 patients (80%), followed by R-bendamustine and other regimens (R-CVP, R-HyperCVAD, and R-Chlorambucil). Of the patients receiving R-CHOP, 38 (67.8%) received rituximab maintenance therapy. During follow-up, 5 patients (5.6%) who experienced relapse underwent ASCT. Treatment characteristics are summarized in Table 2.

Table 2. Treatment Evaluation

	Total (n, %)	Early Stage	Advanced Stage
Treatment Indication at Diagnosis			
Present	70 (78.7)	33 (100)	37 (66)
Absent	19 (21.3)	-	19 (34)
Initial Treatment Approach*			
IC	70 (85.4)	22 (66.7)	48 (98)
RT	12 (14.6)	11 (33.3)	1 (2)
Administered IC Regimen (n=70)			
R-CHOP	56 (80)	18 (81.8)	38 (79.2)
R-Bendamustin	9 (12.9)	2 (9.1)	7 (14.6)
Other	5 (7.1)	2 (9.1)	3 (6.2)

*Excluding 7 patients who were managed without treatment

Follow-up and Survival Outcomes

The median follow-up duration was 45.3 months (range: 3.6–250). Estimated median PFS and OS were 140.7 months (range: 34.9–246.5) and 243 months, respectively. The five-year PFS and OS rates were 70% and 85%, respectively. Survival analyses stratified by clinical characteristics are provided in Table 3.

Table 3. OS and PFS According to Clinical Characteristics

	OS, months (95% CI)	p	PFS, months (95% CI)	p
Sex		0.943		0.229
Female	104.7 (34.4-247.1)		105.6 (36.2-174.9)	
Male	NR		NR	
Stage (Early/Advanced)				
I-II	NR	0.823	105.6 (87.2-124)	0.449
III-IV	140.7 (34.5-246.9)		243 (NR-NR)	
Grade				
I	NR	0.767	NR	0.980
II	140.7 (34.1-247.4)		105.6 (21.7-189.5)	
III	NR		96.3 (NR-NR)	
FLIPI-1				
Low	NR	0.442	NR	0.737
Intermediate	NR		96.3 (44.2-148.4)	
High	140.7 (33.0-248.4)		243.8 (NR-NR)	
FLIPI-1				
Low-Intermediate	NR	0.565	105.5 (65.9-145.2)	0.981
High	140.7 (33.0-248.4)		243.8 (NR-NR)	
FLIPI-2				
Low	NR	0.691	NR	0.645
Intermediate	140.7 (32.0-249.5)		96.3 (39.3-153.0)	
High	NR		NR	
FLIPI-2				0.282
Low-Intermediate	NR	0.425	128.6 (93.8-163.3)	
High	140.7 (33.0-248.4)		66.6 (26.9-106.2)	
Bone Marrow Involvement				0.444
Present	140.7 (NR-NR)	0.339	NR	
Absent	NR		243.8 (NR-NR)	

NR: Median not reached or insufficient events

Among the 70 patients who received rituximab-based IC, 38 (54.3%) received maintenance therapy, while 32 (45.7%) did not. In the non-maintenance group, PFS and OS could not be calculated, whereas in the maintenance group, median PFS and OS were 140.7 months (range: 34.4–247.1) and 243.8 months, respectively.

POD24 assessment was not performed because timepoint-specific progression data were not systematically available across all centers. Its evaluation is planned for forthcoming larger national studies.

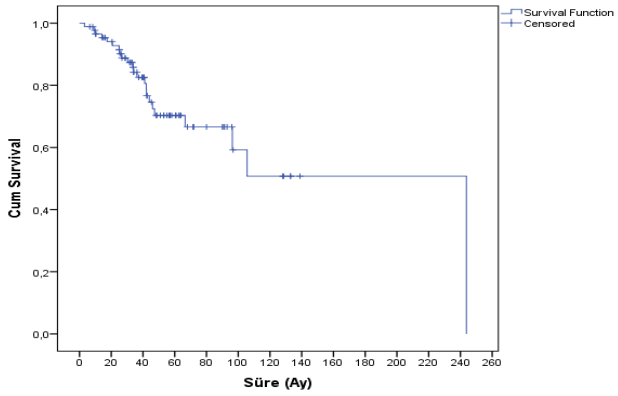

Figure 1. Progression Free Survival

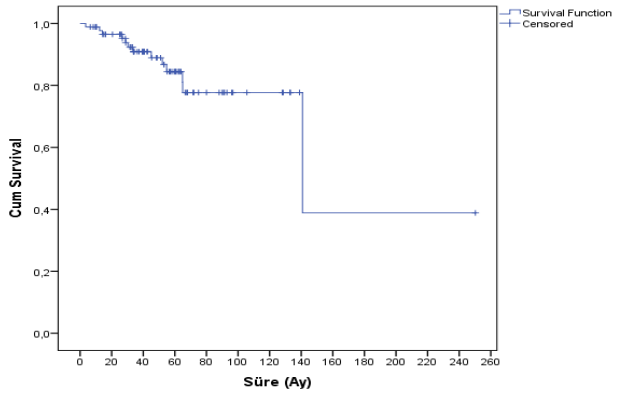

Figure 2. Overall Survival

Discussion

This multicenter real-world study provides valuable insights into the clinical characteristics, treatment strategies, and survival outcomes of patients with FL. Our findings are largely consistent with those of international cohorts, while also highlighting region-specific aspects such as a younger median age at diagnosis, treatment preferences, and access-related considerations.

The median age of our cohort was 51.9 years, notably lower than the 59–63 years typically reported in Western series [1, 2]. This discrepancy may reflect demographic differences in the Turkish population as well as referral and diagnostic patterns. The predominance of advanced-stage disease at presentation (62.9%) is in line with the indolent yet disseminated nature of FL [3, 4]. Late diagnosis may also be influenced by limited availability of screening and the asymptomatic course of many patients.

Risk stratification with FLIPI and FLIPI-2 placed the majority of patients in the intermediate- or high-risk categories, similar to other real-world reports [5, 6]. However, in our cohort, neither PFS nor OS differed significantly across FLIPI subgroups, a finding that echoes observations from PRIMA-PI and m7-FLIPI validation studies [7, 8]. This suggests that the prognostic power of traditional indices may be attenuated in the rituximab era, further underscoring the need for recalibration and integration of molecular markers in risk prediction. The prognostic performance of FLIPI and FLIPI-2 appeared modest in our cohort. This may be attributed to the relatively small number of high-risk patients (particularly within FLIPI-2), as well as the impact of rituximab-based IC, which may mitigate risk differences and attenuate survival stratification.

In first-line therapy, R-CHOP was the most frequently used regimen. While bendamustine–rituximab has gained popularity internationally for its favorable toxicity profile, limited access in our region continues to support the use of R-CHOP as the dominant approach. Rituximab maintenance therapy was administered to 54.3% of our patients, resulting in significantly prolonged PFS. These findings are consistent with the PRIMA trial, where 2 years of rituximab maintenance conferred a sustained PFS advantage over observation [9-12]. Nevertheless, the retrospective nature of our study carries the inherent risk of immortal time bias, and future landmark analyses would be required to confirm the observed benefit. Although multivariate Cox regression was not performed in the current analysis, we aim to incorporate it in extended national datasets to better clarify the independent prognostic impact of maintenance therapy.

The relapse rate in our series was 5.6%, and all relapsed patients underwent ASCT. The relapse rate was notably lower than expected compared with real-world cohorts (~10-20%). Although the number of patients was small, our results confirm the feasibility and potential efficacy of ASCT in carefully selected and chemosensitive relapsed FL patients, in agreement with previous observational studies [13]. This may reflect limited follow-up time in some centers, heterogeneous surveillance intervals, or potential underreporting due to retrospective data collection. A centralized national registry may help overcome these limitations.

Analysis of POD24 could not be performed because progression timepoints were not uniformly recorded across centers. As POD24 is now considered one of the strongest predictors of adverse outcomes in FL, its evaluation is planned in larger multicenter studies with standardized data entry [13]. This situation may partially account for the low relapse rate observed in our study. A planned national FL registry is expected to enable POD24 analysis and molecular correlation in a prospective manner.

Novel therapies such as lenalidomide in combination with rituximab (R^2), EZH2 inhibitors, CAR-T cell therapies, and bispecific antibodies have demonstrated encouraging outcomes in relapsed/refractory FL [14–16]. However, access to these therapies remains limited in our setting, underscoring the clinical relevance of long-term outcomes with rituximab-based regimens. The recent comprehensive review by

Merryman et al. also emphasized the importance of regional real-world data in shaping the applicability of global treatment algorithms [17].

Strengths of our study include the multicenter design, detailed clinicopathological characterization, and relatively long follow-up. Despite being retrospective, this study reflects real-world practice across six tertiary hematology centers. The multicenter structure enhances the generalizability of our findings and helps capture treatment variability within standard national guidelines. However, limitations should be acknowledged: its retrospective nature, modest sample size, absence of molecular profiling, and lack of POD24 evaluation. In addition, physician-driven decisions regarding rituximab maintenance may have introduced treatment heterogeneity.

In summary, our findings confirm that rituximab-based IC, combined with maintenance strategies, provides durable disease control in FL within real-world practice. Expanding multicenter registries at the national level will be critical to validate prognostic indices, assess the role of POD24, and facilitate the integration of novel agents into regional treatment algorithms.

Conclusion

This multicenter real-world study reinforces the role of rituximab-based IC as the cornerstone of first-line treatment in follicular lymphoma. Our findings demonstrate that R-CHOP, followed by rituximab maintenance in selected patients, achieves durable disease control and progression-free survival outcomes comparable to those reported in international cohorts. The relatively low relapse rate observed may reflect both the efficacy of maintenance strategies and regional treatment patterns.

Although autologous stem cell transplantation remains a feasible option for selected relapsed patients, the limited number of cases underscores the need for larger collaborative studies. The absence of significant prognostic discrimination by FLIPI and FLIPI-2 in our cohort highlights the necessity of incorporating novel prognostic tools, including POD24 and molecular-based indices, into routine practice.

In the current era of rapidly evolving therapeutic options -including bispecific antibodies, CAR-T cell therapy, and targeted agents- regional real-world data remain crucial to inform treatment algorithms and optimize patient outcomes. Future national and multicenter registries should aim to validate prognostic models, capture long-term survival outcomes, and facilitate access to innovative therapies in resource-variable settings.

Declarations

Conflict of Interest

The authors declare that they have no conflicts of interest, financial or otherwise, that could be perceived to influence the outcomes or interpretation of this study. No commercial or institutional affiliations exist that might constitute a potential conflict. All authors confirm that they have no relationships with any entities that might have an interest in the submitted work.

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