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Follicular Lymphoma: Frequency and Timing of Treatment: Single Center Experience

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ABSTRACT

Introduction: This study aimed to investigate how often follicular lymphoma (FL) occurs in patients diagnosed with non-Hodgkin lymphoma (NHL). Additionally, we investigated whether patients with FL required treatment, and if so, whether the need for treatment arose at the initial diagnosis or during subsequent follow-up periods.

Methods: Six thousand five hundred sixty patients diagnosed with NHL or chronic lymphocytic leukemia were reached, and healthy data were obtained from 1,719 of them. Data from 176 patients diagnosed with FL were evaluated. Demographic information (age, gender) of the patients was collected. The classifications were grouped by taking into account World Health Organization data, the histological subtype of the tumor, gender and need for treatment were evaluated.

Results: Among the patients, 55.1% (n=97) were men and 44.9% (n=79) were women. The median age of those with FL was 50 years, with ages ranging from 18 to 87. When looking at histological subtypes, the FL accounts for 10.2% of cases (n=176). The proportion of patients requiring treatment was 70.9% (125), and the proportion of patients followed up without treatment was 27.8% (49). Of the patients who needed treatment, 57.1% (n=101) required it at the time of diagnosis and 13.6% (n=24) during follow-up.

Conclusion: FL, making up around 20% of all NHL, is the second most prevalent type of lymphoma in adults. The incidence, as well as the gender and age distribution, of FL can differ across populations. This may be related to ethnicity, geographical conditions, and socioeconomic status. In addition, the proportion of patients requiring treatment may also vary. When all these are taken into account, social differences are some of the main determinants in the approach to FL.

Keywords: Follicular lymphoma, frequency, treatment demand

Introduction

Non-Hodgkin's lymphoma (NHL) stands as the most common hematological malignancy worldwide, encompassing a diverse array of B-cell and T-cell proliferative disorders. Unlike Hodgkin's lymphoma, NHL is characterized by specific clinical features and the absence of Reed-Sternberg cells, as well as negative CD15 and CD30 staining in histological analyses. While there are over 40 major subtypes, the most prevalent forms include the indolent follicular lymphoma (FL) and the aggressive diffuse large B-cell lymphoma (DLBCL) (1). According to the latest World Health Organization (WHO) classification, DLBCL is the most frequent NHL in Western countries, accounting for about 31% of adult cases. Other common aggressive B-cell subtypes include mantle cell lymphoma (MCL) (6% of cases) and Burkitt lymphoma (BL) (2% of cases). Among indolent B-cell NHL, FL represents 22% of cases in Western nations, followed by marginal zone lymphoma (MZL) (8% of cases), chronic lymphocytic leukemia/small-cell lymphocytic lymphoma (CLL/SLL) (6% of cases), and lymphoplasmacytic lymphoma (LPL) (1% of cases). T-cell lymphomas, comprising only 10-15% of NHL diagnoses, primarily consist of peripheral T-cell lymphoma (6% of cases) and cutaneous T-cell lymphoma (4% of cases) (1).

Limited data exist for global comparisons, but a comprehensive international pathology study examining NHL subtype frequencies across 24 nations revealed that FL constituted a greater proportion in developed countries (25.5%) than in developing ones (15.3%) (2). While FL incidence rates plateaued in France during 2000-2009, they continued to rise in Australia from 1997-2008, Singapore from 1998-2012, and Japan from 1993-2008 (3-6).

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At initial diagnosis, FL is often found in an advanced stage, as demonstrated by bone marrow (BM) biopsy and positron emission tomography-based staging (7). However, approximately 10% to 15% of patients exhibit localized disease that may be treated with potentially curative radiotherapy. Another 20% to 25% of patients present with advanced stage, asymptomatic, and low-volume disease, which does not require immediate treatment; hence, observation is recommended for these cases until clear disease progression occurs. The remaining 60% to 70% of patients have advanced and/or high tumor burden disease that necessitates upfront systemic treatment (8).

Our research focused on determining how often this specific subtype occurred within the broader category of NHL. Additionally, we investigated whether patients with FL required treatment, and if so, whether the need for treatment arose at the initial diagnosis or during subsequent follow-up periods.

Methods

This study was designed retrospectively to evaluate the frequency of FL and the need for treatment. The study included data from patients with FL diagnosed at the University of Health Sciences Türkiye, İstanbul Training and Research Hospital, Clinic of Hematology between January 2008 and November 2024.

The study was conducted after obtaining approval from the Ethics Committee of the University of Health Sciences Türkiye, İstanbul Training and Research Hospital (approval number: 127, date: 29.11.2024).

In total, 6,560 patients diagnosed with NHL or CLL were reached, and health data were obtained from 1,719 of them. Data from 176 patients diagnosed with FL were evaluated within this patient group.

Inclusion Criteria

- Patients with a diagnosis of FL confirmed histopathologically and immunohistochemically.

- Patients who were followed for at least 12 months after diagnosis.

- Patients with complete clinical and laboratory information in their electronic health record.

Exclusion Criteria

- Diagnosed with other hematological malignancies.

- Patients with insufficient clinical data records.

Demographic information (age, gender) of the patients was collected. The classifications were grouped by taking into account WHO data; the histological subtype of the tumor, gender and need for treatment were evaluated.

Statistical Analysis

The descriptive statistics of the qualitative variables in the study are presented as numbers and percentages, and the descriptive statistics of the quantitative variables are presented as mean, standard deviation, median, minimum, and maximum. The conformity of the quantitative variables to the normal distribution was evaluated with the Kolmogorov-Smirnov test.

Results

Among the patients, 55.1% (n=97) were men and 44.9% (n=79) were women. The median age of those with FL was 50 years, with ages ranging from 18 to 87. When looking at histological subtypes, aggressive B-cell subtypes include DLBCL, 35.6% of cases (n=612), T-cell lymphomas, 6.3% of cases (n=108), MCL, 4.8% of cases (n=82), BL, 2.3% of cases (n=39), and aggressive B-cell lymphoma, 2.2% of cases (n=38). Within indolent B-cell NHL, CLL/SLL, accounts for 25.6% of cases (n=440), FL accounts for 10.2% of cases (n=176), MZL accounts for 6.5% of cases (n=112), low grade B-cell lymphoma accounts for 3.8% of cases (n=64), hairy cell leukemia accounts for 2.3% of patients (n=39), and LPL accounts for 0.5% of cases (n=9). Histological subtypes of the cases are shown in Table 1.

The proportion of patients requiring treatment was 70.9% (125), and the proportion of patients followed up without treatment was 27.8% (n=49). Of the patients who needed treatment, 57.1% (n=101) needed treatment at the time of diagnosis and 13.6% (n=24) needed treatment during follow-up. Of the 24 patients treated during follow-up, 58.3% (n=14) were men and 41.7% (n=10) were women. Distributions according to treatment need are shown in Tables 2, 3.

Discussion

NHL is the leading type of blood cancer worldwide (9). It is more frequently seen in developed countries and includes more than 40

Table 1. Subtypes of non-Hodgkin's lymphoma

Diagnosis	(n=1719)	(%)
DLBCL	612	35.6
CLL/SLL	440	25.6
FL	176	10.2
MZL	112	6.5
NKTL	108	6.3
MCL	82	4.8
Low grade B-cell lymphoma	64	3.8
HCL	39	2.7
BL	39	2.7
High grade B-cell lymphoma	38	2.2
LPL	9	0.5

DLBCL: Diffuse large B-cell lymphoma, CLL: Chronic lymphocytic leukemia, SLL: Small lymphocytic lymphoma, FL: Follicular lymphoma, MZL: Marginal zone lymphoma, NK/TL: Natural killer/T-cell lymphoma, MCL: Mantle cell lymphoma, HCL: Hairy cell leukemia, BL: Burkitt lymphoma, LPL: Lymphoplasmacytic lymphoma

Table 2. Age, gender and treatment distribution

Follicular lymphoma	(n=176)
Gender	
Female	79 (44.9%)
Male	97 (55.1%)
Treatment	
At diagnosis	101 (57.3%)
No treatment	49 (27.8%)
During follow-up	24 (13.6%)
Unknown	2 (1.1%)
Age	50.5 (18-87)

Table 3. Need for treatment according to gender

Treatment	At diagnosis	Untreatment	During follow-up	Unknown
Females (n=79)	45	10	24	
Males (n=97)	56	14	25	2

distinct subtypes, each characterized by unique genetic, morphological, and clinical traits. The distribution of NHL subtypes varies according to age, gender, ethnicity, and geographic location (10).

In developed countries, FL comprises approximately 15-20% of adult NHL cases and is known for its slow-progressing nature (11). Our research, which included 1,719 NHL patients, found FL frequency to be 10.2%. This discrepancy may be attributed to differences in geography, race, socioeconomic conditions, and environmental factors.

In high-income countries, the age-standardized incidence rate of FL is about 2 to 3 per 100,000 person-years, with the median age at diagnosis falling in the 60s (12). Our study revealed a mean age of 50.

Unlike most NHL subtypes that show a higher male prevalence, FL exhibits a smaller or even reversed gender ratio, suggesting potential links to hormonal and reproductive factors. One analysis found an inverse relationship between FL risk and number of pregnancies, and a positive association with hormonal contraceptive use (13). In women, Sjögren's syndrome and smoking history were connected to an elevated risk of FL, whereas factors like alcohol consumption, hay fever, and food allergies were linked to a reduced likelihood of developing the disease. These findings indicate that FL has multiple contributing factors, with smoking potentially being a more significant risk factor for females (14). In our study, males comprised 55.1% of cases, while females accounted for 44.9%.

Various outcome measures have been developed for FL patients, including the FLIPI and tumor grade (15). The FLIPI evaluates five prognostic factors: age, stage, number of affected nodal regions, serum lactate dehydrogenase, and hemoglobin (16). An updated version, FLIPI-2, assesses five parameters, some of which overlap with the original FLIPI: beta-2 microglobulin, BM involvement, age, hemoglobin, and the longest diameter of the largest lymph node (17). The superiority of FLIPI-2 over the original FLIPI remains uncertain, with the latter still serving as a valuable prognostic tool (18). The FLIPI-2 is a simple and reliable prognostic tool that utilizes basic clinical information to assess outcomes in patients with FL. It plays a key role in improving prognostic predictions, guiding personalized treatment decisions, and organizing patient groups for prospective clinical studies. We analyzed cases using the FLIPI-2 score to determine treatment necessity.

FL treatment selection heavily depends on patient and disease characteristics. Most FL patients are diagnosed at an advanced stage. While many respond to initial treatment, they typically relapse and require additional therapy (19). Currently, conventional chemotherapy cannot cure advanced-stage FL. Consequently, asymptomatic patients may be observed without treatment (known as watchful waiting) for several years (20). In our study, 70.9% of patients required treatment, while 27.8% were monitored without intervention. Among those needing treatment, 57.1% required it at diagnosis, and 13.6% during follow-up.

Study Limitations

There were important limitations in our study. The limited number of patients was the most important limitation. Therefore, it was not possible to detail the subgroup analyses.

Conclusion

The frequency, gender and age distribution of FL may vary among societies. This may be related to ethnicity, geographical conditions and socioeconomic status. In addition, the proportion of patients requiring treatment may also vary. When all these are taken into account, social differences are one of the main determinants in the approach to FL.

Ethics

Ethics Committee Approval: The study was conducted after obtaining approval from the Ethics Committee of the University of Health Sciences Türkiye, İstanbul Training and Research Hospital (approval number: 127, date: 29.11.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions: Surgical and Medical Practices - A.K., İ.S.; Concept - A.K., M.H.D., R.E.; Design - A.K., İ.S., C.A., R.E.; Data Collection or Processing - V.C.Ç., İ.S., M.H.D., R.E.; Analysis or Interpretation - A.K., İ.S., C.A.; Literature Search - A.K., V.C.Ç., M.H.D., C.A.; Writing - A.K., R.E.

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