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Follicular lymphoma patients with a high FLIPI score and a high tumor burden: A risk stratification model

Bolesnici sa folikularnim limfomom, visokim FLIPI skorom i velikom tumorskom masom: model za određivanje rizika

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Abstract

Background/Aim. The widely accepted Follicular Lymphoma International Prognostic Index (FLIPI) divides patients into three risk groups based on the score of adverse prognostic factors. The estimated 5-year survival in patients with a high FLIPI score is around 50%. The aim of this study was to analyse the prognostic value of clinical and laboratory parameters that are not included in the FLIPI and the New Prognostic Index for Follicular Lymphoma developed by the International Follicular Lymphoma Prognostic Factor Project (FLIPI2) indices, in follicular lymphoma (FL) patients with a high FLIPI score and high tumor burden. **Methods.** The retrospective analysis included 57 newly diagnosed patients with FL, a high FLIPI score and a high tumor burden. All the patients were diagnosed and treated between April 2000 and June 2007 at the Clinic for Hematology, Clinical Center of Serbia, Belgrade. **Results.** The patients with a histological grade > 1, erythrocyte sedimentation rate (ESR) ≥ 45 mm/h and hypoalbuminemia had a significantly worse overall survival ($p = 0.015$; $p = 0.001$; $p = 0.008$, respectively), while there was a tendency toward worse overall survival in the patients with an Eastern Cooperative Oncology Group (ECOG) > 1 ($p = 0.075$). Multivariate Cox regression analysis identified a histological grade > 1, ESR ≥ 45 mm/h and hypoalbuminemia as independent risk factors for a poor outcome. Based on a cumulative score of unfavourable prognostic factors, patients who had 0 or 1 unfavourable factors had a significantly better 5-year overall survival compared to patients with 2 or 3 risk factors (75% *vs* 24.1%, $p = 0.000$). **Conclusion.** The obtained results suggest that from the examined prognostic parameters histological grade > 1, ESR ≥ 45 mm/h and hypoalbuminemia can contribute in defining patients who need more aggressive initial treatment approach, if two or three of these parameters are present on presentation.

Key words:
lymphoma; follicular; antineoplastic combined chemotherapy protocols; prognosis.

Apstrakt

Uvod/Cilj. Široko prihvaćeni internacionalni prognozni indeks za folikularni limfom (FLIPI) svrstava bolesnike u tri grupe rizika na osnovu skora nepovoljnih prognoznih faktora. Procenjeno 5-ogodišnje preživljavanje bolesnika sa visokim FLIPI skorom je oko 50%. Cilj ove studije bio je analiza prognostičke vrednosti kliničkih i laboratorijskih parametara koji nisu uključeni u FLIPI i FLIPI2 indekse, kod bolesnika sa visokim FLIPI skorom i velikom tumorskom masom. **Metode.** Ova retrospektivna analiza obuhvatila je 57 novodijagnostikovanih bolesnika. Svi bolesnici dijagnostikovani su i lečeni u periodu između aprila 2000. i juna 2007. godine na Klinici za hematologiju Kliničkog centra Srbije, Beograd. **Rezultati.** Značajno lošije preživljavanje imali su bolesnici sa histološkim gradusom > 1 ($p = 0{,}015$), sedimentacijom eritrocita (SE) ≥ 45 mm/h ($p = 0{,}001$) i hipoalbuminemijom ($p = 0{,}008$), dok je tendencija lošijeg preživljavanja postojala kod bolesnika sa *Eastern Cooperative Oncology Group* (ECOG) > 1 ($p = 0{,}075$). Multivarijantnom Cox regresionom analizom identifikovani su histološki gradus > 1, SE ≥ 45 mm/h i hipoalbuminemija kao nezavisni prognostički faktori za nepovoljan ishod. Na osnovu kumulativnog skora nepovoljnih prognostičkih faktora, bolesnici koji su imali 0 ili 1 nepovoljan prognostički faktor imali su značajno bolje petogodišnje ukupno preživljavanje u poređenju sa bolesnicima sa 2 ili 3 faktora rizika (75% *vs* 24,1%, $p = 0{,}000$). **Zaključak.** Rezultati našeg ispitivanja pokazuju da od testiranih prognostičkih parametara histološki gradus > 1, SE ≥ 45 mm/h i hipoalbuminemija mogu doprineti izboru bolesnika koji zahtevaju inicijalno agresivniji modalitet lečenja, ukoliko su na prezentaciji prisutna dva ili tri od ovih parametara.

Ključne reči:
limfom, folikularni; lečenje kombinovanjem antineoplastika; prognoza.

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Introduction

Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma with the median survival of 8–10 years [1, 2]. The disease has a variable course, some patients have a slowly progressive disease, while the others have a rapidly progressive disease with the survival of around one year. Up to 15 years ago, the efforts to find an appropriate therapeutic strategy resulted in a prolonged event-free survival (EFS) and higher treatment response rate for these patients, but all of them were unsuccessful at prolonging the overall survival (OS) of these patients [3–7].

The first step towards the for many years elusive aim of prolonging OS in FL was recorded when interferon was included in the treatment of patients with FL [8]. The use of interferon in FL ceased due to its impact on the deterioration of quality of life, the necessity of its application in high doses and along with chemotherapy, as well retrieving the new drug, antiCD20 antibody [9]. The introduction of rituximab as the standard treatment for FL patients in combination with chemotherapy brought much better therapeutic results, including prolonging of OS [10–13]. The optimal first line immunochemotherapy is not yet defined, but is one of the purposes of on-going Primary Rituximab and Maintenance (PRIMA) studies [14].

In spite of the progress in treatment of FL, a significant portion of patients with FL still have poor outcome. During the past decades, a number of potential prognostic factors and risk models in patients with FL were studied with the aim of identifying patients at risk for poor outcome, but only the Follicular Lymphoma International Prognostic Index (FLIPI), which was established in 2004, was widely used as predictor of survival [15–19]. The FLIPI, consisting of age, stage, number of nodal sites, hemoglobin level and lactate dehydrogenase (LDH), identifies patients with a low risk (0–1 risk factors), intermediate risk (2 risk factors) and high risk (3–5 risk factors) with the expected 5-year overall survival of around 90%, 80% and 50%, respectively [19]. After the introduction of immunochemotherapy as the standard first line treatment of FL and after encouraging results in terms of survival, the need for new investigations with the aim of defining the risk profile of FL patients treated with immunochemotherapy became apparent. Thus, the recent study performed by Federico et al. [18] defined the new prognostic index FLIPI2 (consisting of age, β-2 microglobulin, longest diameter of the largest node involved, bone marrow involvement and hemoglobin level), as the appropriate prognostic index for FL patients treated with immunochemotherapy [20]. Nowadays, FLIPI is commonly used as enrolment criteria or stratification factor in clinical trials. Still, there is no evidence of risk adapted treatment strategy based on FLIPI indexes.

In this study on the group of high FLIPI risk patients with a high tumor burden who are theoretically at highest risk for poor outcome, we tried to identify a subgroup that probably require the more effective treatment approach. For the purpose of this analysis, we investigated routinely performed pathohistological, clinical and biochemical parameters that are not included in the FLIPI indexes. Also, we compared the outcome of patients treated with chemotherapy and immunochemotherapy.

Methods

Case Selection

This retrospective analysis was performed on 57 newly diagnosed FL patients at high risk according to FLIPI and with a high tumor burden. High tumor burden is defined as the presence of at least one of the following criteria: systemic symptoms (> 10% weight loss, temperature > 38°C for more than 5 days, abundant night sweats); performance status (PS) greater than 1 according to the Eastern Cooperative Oncology Group (ECOG) scale; elevated LDH level; β2-microglobulin level greater than 3 mg/L; single lymph node larger than 7 cm; spleen enlargement with a craniocaudal diameter greater than 200 mm; organ failure; pleural effusion or ascites; symptomatic compressive syndrome; the existence of 3 lymph nodes in 3 distinct nodal areas with a diameter greater than or equal to 3 cm [13]. All the patients were diagnosed and treated in our institution between April 2000 and December 2006. In all the cases, the diagnosis of FL was confirmed by immunophenotyping and classified according to the World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues in specialized Laboratory of Hematopathology [21]. The patients with histological grade 1, 2 and 3A according to Mann and Berard [22] criteria were eligible for this study.

Patients who were previously treated for another malignancy were not included in this study, nor those with high FLIPI risk without high tumor burden, since according to the institutional treatment guidelines in that period, they underwent “watch and wait”.

Medical records were reviewed to determine the FLIPI, bulky disease (the diameter of tumor > 7 cm), erithrocyte sedimentation rate (ESR), serum albumin level, ECOG performance status (ECOG PS) and the treatment outcome.

Treatment recommendations

All the patients were treated according to the institutional standard of care at the time of diagnosis. In the first line treatment, 32 patients received cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or cyclophosphamide, vincristine, prednisone (CVP) chemotherapy and 25 patients received R(rituximab)-CHOP or R(rituximab)-CVP immunochemotherapy. The patients who responded after four cycles of chemotherapy/immunochemotherapy proceeded with the treatment to complete 6 to 8 cycles, depending on the treatment response (complete or partial remission) and treatment tolerance. Patients with refractory disease or relapse after the initial chemotherapy received fludarabine-based second line therapy in combination with cyclophosphamide (FC) or mitoxantrone and dexamethasone (FMD), of whom 11 received additional rituximab. Six patients who transformed to diffuse large B-cell lymphoma received etoposide, cisplatinum, ara-c, methylprednisolone (ESHAP) regimen.

Statistical methods

The patients who achieved complete or partial remission were considered to have responded to the therapy. The early relapsed were those who initially responded to the therapy and relapsed inside 12 months after achieving remission. The association between the treatment modality and the response/early relapse rate was determined using the χ^2-test.

The overall survival was measured from the date of diagnosis until the date of death from any cause, or until the last follow up visit. The event-free survival was measured from the date of diagnosis to that of disease progression, relapse, death from any cause or the last follow-up visit.

The receiver operating curve (ROC) was used to determine the optimal cut-off value for laboratory parameters in the prediction of the overall survival for our group of patients. If the optimal cut-off value was not found, the analysis was performed using literature cut-off values.

Survival functions were estimated using the Kaplan-Meier method and compared using the log-rank test. A multivariate analysis was performed to evaluate the potential predictive value of the examined characteristics as a risk factor.

Table 1

Baseline characteristics of the patients

Characteristics	Patients, n (%)
Age (years), mean (range)	54 (range 35–74)
≤ 60	35 (61.4%)
> 60	22 (38.6%)
Stage of tumor	
II	1 (1.8%)
III	10 (17.5%)
IV	46 (80.7%)
Histology grade	
1	29 (50.9%)
2	19 (33.3%)
3a	9 (15.8%)
Bulky disease	
no	22 (38.6%)
yes	35 (61.4%)
ECOG PS	
≤ 1	39 (68.4%)
> 1	18 (31.6%)
ESR	
< 45 mm/h	25 (43.9%)
≥ 45 mm/h	32 (56.1%)
Albumin level	
low	28 (49.1%)
normal	29 (50.9%)

ECOG PS – Eastren Cooperative Oncology Group Performance Status; ESR – erythrocyte sedimentation rate.

Results

Baseline characteristics

The median follow-up was 58 months, from 6 to 122 months. The median age of the patients was 54 years (range 35–74 years). Twenty-two (38.6%) patients were older than 60 years.

Histological grade 1, 2 or 3a was present in 29 (50.9%), 19 (33.3%) and 9 (15.8%) patients, respectively. Bulky disease was present in 22 (38.6%) patients. ECOG PS > 1 on presentation had 18 (31.6%) patients.

The cut-off point for ESR identified by ROC analysis was 45 mm/h. Twenty-five (43.9%) patients had an ESR higher than the cut-off value. The ROC analysis could not identify the optimal cut-off value for albumin level. For the purpose of further analysis, 35 g/L was taken as the cut-off value [19]. Hypoalbuminemia was present in 28 (49.1%) of the patients.

The baseline characteristics of the patients are summarized in Table 1.

The outcome of the patients

A total of 51(89%) patients responded to the therapy. Early relapse occurred in 16 (31%) patients. Twenty-eight (49.1%) patients lived for 5 years or longer.

A higher response rate (RR) was observed in the group of patients treated with immunochemotherapy, but the difference was not statistically significant (92% *vs* 87.5%, χ^2, $p > 0.05$). In those who responded to the initial treatment with chemotherapy, a statistically higher percentage of early relapse occurred (42.9% *vs* 17.4%, χ^2, $p < 0.05$).

In survival analysis, the patients initially treated with immunochemotherapy had significantly longer EFS (5-year EFS, 40% *vs* 12.5%; $p = 0.016$) (Figure 1A), and OS (5-year OS, 68% *vs* 34.3%; $p = 0.022$), (Figure 1B) compared to the patients treated with chemotherapy.

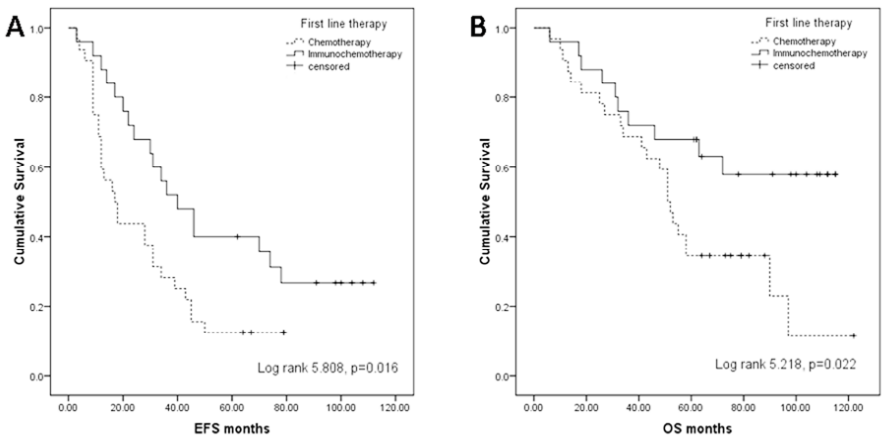

Fig. 1 – Comparison of the survival based on the first line treatment, chemotherapy *vs* immunochemotherapy: A) Event-free survival (EFS); B) Overall survival (OS)

Analysis of risk factors for poor outcome

Univariate analysis

Univariate analysis indicated that the patients with a histological grade > 1, ESR ≥ 45 mm/h and hypoalbuminemia had significantly shorter overall survival ($p = 0.009$; $p = 0.001$; $p = 0.008$, respectively) (Figure 2). There was a tendency to worse overall survival in the patients with an ECOG > 1 ($p = 0.075$). There was no difference in the outcome based on the presence of bulky disease on presentation ($p = 0.672$).

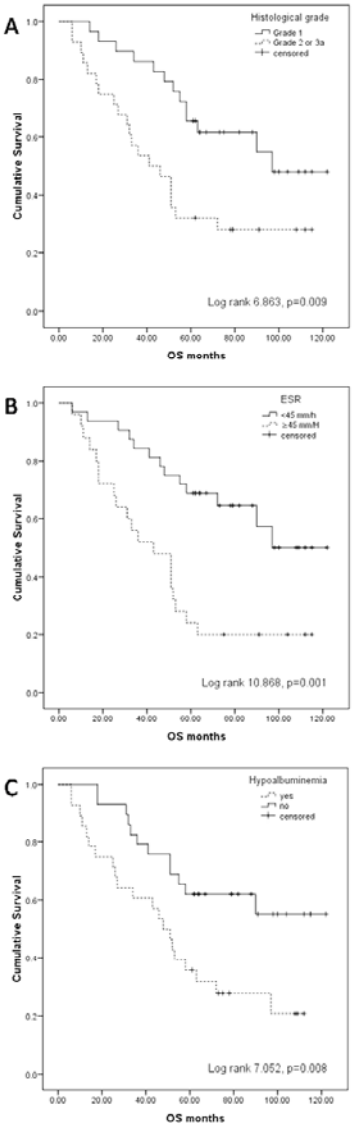

Fig. 2 – Overall survival (OS) depending on the disease characteristics:
A) Histological grade; B) Erythrocyte sedimentation rate (ESR); C) Albumin level.

Risk stratification model

Based on the cumulative score of the identified unfavourable prognostic factors, a risk stratification model was developed. Twenty-eight (49.1%) patients who had 0 or 1 unfavourable factor had significantly longer overall survival compared to 29 (50.9%) patients with 2 or 3 risk factors (5-year OS 75% *vs* 24.1%; $p = 0.000$) (Figure 3A), regardless frontline treatment with chemotherapy (5-year OS 62.5% *vs* 6.3%; $p = 0.000$) (Figure 3B) or immunochemotherapy (5-year OS 91.7% *vs* 46.2%; $p = 0.004$) (Figure 3C).

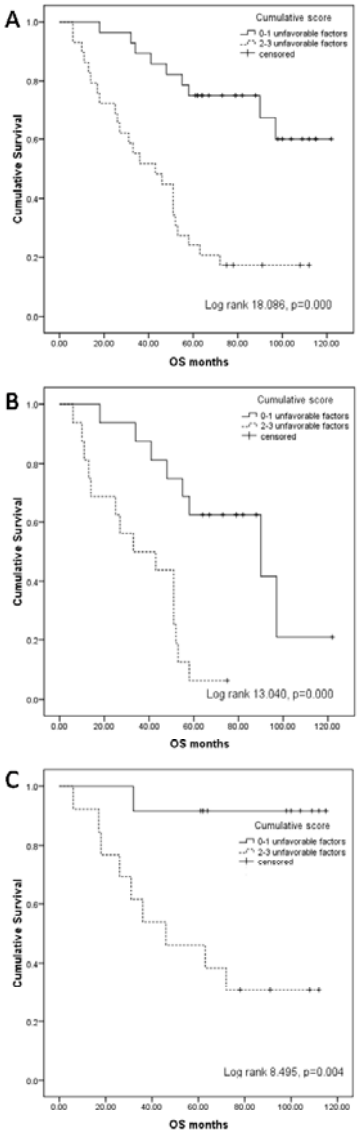

Fig. 3 – Overall survival (OS) based on the cumulative score of unfavourable prognostic factors, 0–1 *vs* 2–3:
A) The whole group of patients; B) The patients treated with chemotherapy; C) The patients treated with immunochemotherapy.

Multivariate Analysis

Multivariate analysis revealed that a histological grade > 1, ESR ≥ 45 mm/h and hypoalbuminemia were independent prognostic factors for shorter OS.

Discussion

Numerous clinical studies have now identified many clinical, biochemical and molecular findings as prognostic factors for a poor outcome in patients with FL [17–20, 23–25]. The

multicenter study that compared the influence of different clinical and biochemical findings on the outcome, established the FLIPI index for the risk stratification of newly diagnosed FL patients [18, 19]. Federico et al. [20] identified risk factors in FL patients treated with immunochemotherapy and designed the New Prognostic Index for Follicular Lymphoma developed by the International Follicular Lymphoma Prognotic Factor Project (FLIPI2). However, the primary endpoint in this study was EFS, while in the Solal-Celigny et al. [19] study, the primary endpoint was OS. Recent gene profiling analysis has suggested that the survival of patients with newly diagnosed follicular lymphoma can be affected by the host molecular signature, termed an immune response-1 (IR-1), which originates from non-malignant cells present in tumor tissue [26, 27]. The first studies that investigated the presence of CD68 positive lymphoma associated macrophages as the surrogate of IR-1 identified it as biological predictor of a poor outcome, but latter studies revealed that adding rituximab to standard chemotherapy overcame its negative impact on survival [28, 29]. Thus, prognostic value of biomarkers in follicular lymphoma has to be assessed in future studies with uniform methodology.

The results of our study on high FLIPI risk patients with high tumor burden confirmed the benefit in terms of early relapse rate and 5-year EFS of adding rituximab to chemotherapy in previously untreated FL patients. Also, addition of rituximab to chemotherapy brought a significant improvement in 5-year OS. These results are in accordance with results from randomized trials that reported an improvement in progression-free survival (PFS) or time to progression (TTP) and OS, associated with the addition of rituximab to standard chemotherapy in the first line treatment of FL [10–13]. Still in both groups of patients in our study as well as in the previous reports, a significant percent of patients remain with poor outcome. Therefore nowadays the main purpose of investigators is to identify patients with poor prognosis who maybe require the more aggressive therapeutic approach from the beginning.

In our study, by analysing the values of routinely performed pathohistological, clinical and biochemical parameters not included in the FLIPI indices, histological grade > 1, ESR ≥ 45 mm/h and hypoalbuminemia were identified as independent risk factors for a poor outcome in high FLIPI risk patients. According to the literature, in researches on unselected groups of patients, the prognostic role of these factors is the subject of controversy. Martin et al. [30] identified histological grade 3 as the independent risk factor for failure free and overall survival. However, a later research by Ott et al. [31] found that patients with grade 3a, as well as those with grade 1 or 2, are experiencing an indolent course of the disease, while patients with grade 3b are experiencing an aggressive course of the disease, similar to diffuse large B-cell lymphoma. Hans et al. [32] concluded that patients with grade 3a and more than 50% of centroblasts are experiencing an aggressive course similar to patients with grade 3b. Elevated ESR was identified as the risk factor in patients with FL in the prerituximab era [18, 19]. On the contrary, this was not the case in the study by Federico et al. [20]. Hypoalbuminemia was identified as risk factor in the Italian intergroup trial, but this was not the case in later studies, which defined FLIPI indices [18–20].

Treatment personalization is needed to achieve a successful balance of treatment effectiveness and toxicity. Based on the cumulative score of the identified negative prognostic parameters on presentation in our group of patients, the risk stratification model that we developed effectively identifies patients who clearly needed more effective treatment. However, the model is not eligible for the use in all newly diagnosed FL patients since the cut-off values are derived from parameters of high FLIPI risk patients with high tumor burden and it can not be tested even in other FLIPI risk groups with high tumor burden.

By now, in the younger population, several studies have been conducted using the aggressive approach in the first line and in relapse in high risk FL patients [23, 33–38]. The autologous stem cell transplantation (ASCT) in first remission brought improvement in disease-free survival (DFS) or PFS, but there is still no clear evidence of prolonging OS. However, only one study with ASCT in first remission was initiated in the rituximab era [38]. The allogeneic transplantation was examined in relapsed FL and it proved potentially curative, but the first reports on allogeneic transplantation with myeloablative regimens did not resolve whether there is a benefit in OS, mainly due to the high treatment related mortality (21–40%) [39–42]. Thus, the main focus at the present moment is to explore the efficacy of rituximab maintenance therapy in first remission with or without ASCT, as well the efficacy of radioimmunochemotherapy and allogeneic stem cell transplantation with the reduced-intensity conditioning (RIC) protocols, based on rituximab and fludarabine [43–46].

Conclusion

The results obtained in this study suggest that from examined prognostic parameters histological grade > 1, ESR ≥ 45 mm/h and hypoalbuminemia could contribute in defining a group of patients who need the more aggressive initial treatment approach, if two or three of these parameters exist on presentation. To our opinion, new prospective studies with more precise pretreatment risk stratification seem to be needed in order to define the best treatment strategy for high-risk follicular lymphoma patients.

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