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ORIGINAL REPORT

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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Follicular Lymphoma International Prognostic Index 2: A New Prognostic Index for Follicular Lymphoma Developed by the International Follicular Lymphoma Prognostic Factor Project

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ABSTRACT

Purpose
The aim of the F2 study was to verify whether a prospective collection of data would enable the development of a more accurate prognostic index for follicular lymphoma (FL) by using parameters which could not be retrospectively studied before, and by choosing progression-free survival (PFS) as principal end point.

Patients and Methods
Between January 2003 and May 2005, 1,093 patients with a newly diagnosed FL were registered and 942 individuals receiving antilymphoma therapy were selected as the study population. The variables we used for score definition were selected by means of bootstrap resampling procedures on 832 patients with complete data. Procedures to select the model that would minimize errors were also performed.

Results
After a median follow-up of 38 months, 261 events for PFS evaluation were recorded. β2-microglobulin higher than the upper limit of normal, longest diameter of the largest involved node longer than 6 cm, bone marrow involvement, hemoglobin level lower than 12 g/dL, and age older than 60 years were factors independently predictive for PFS. Using these variables, a prognostic model was devised to identify three groups at different levels of risk. The 3-year PFS rate was 91%, 69%, and 51% for patients at low, intermediate, and high risk, respectively (log-rank = 64.6; $P < .00001$). The 3-year survival rate was 99%, 96%, and 84% for patients at low, intermediate, and high risk, respectively ($P < .0001$).

Conclusion
Follicular Lymphoma International Prognostic Index 2 is a simple prognostic index based on easily available clinical data and may represent a promising new tool for the identification of patients with FL at different risk in the era of immunochemotherapy.

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INTRODUCTION

Although there have been significant improvements in the past decade, the prognosis of follicular lymphoma (FL) remains heterogenous as does its treatment options.[1-3] Thus, prognostic indices are still necessary to help the physician's choice and to design trials. Thus far, a variety of prognostic factors have been identified in patients with FL including age, stage, tumor burden (TB), bone marrow involvement (BMI), systemic symptoms, performance status, serum lactate dehydrogenase (LDH), hemoglobin (Hb), erythrocyte sedimentation rate (ESR), and β2-microglobulin (B2M).[4-9] A predictive model specifically devised for FL and based on age, sex, systemic symptoms, the number of extranodal sites of disease, ESR, and LDH was proposed in 2000 by the Intergruppo Italiano Linfomi.[7] In 2004, as a result of a large international cooperative effort, the Follicular Lymphoma International Prognostic Index (FLIPI) was developed.[8] The index was based on age, stage, Hb, the number of nodal site areas, and LDH. Currently, FLIPI is a widely accepted tool for risk assessment of FL. However, the FLIPI has been built before the era of anti CD20 monoclonal antibodies and the initial cohort does not represent the present course of the disease. Besides, the FLIPI was based on retrospective analysis of archive data and

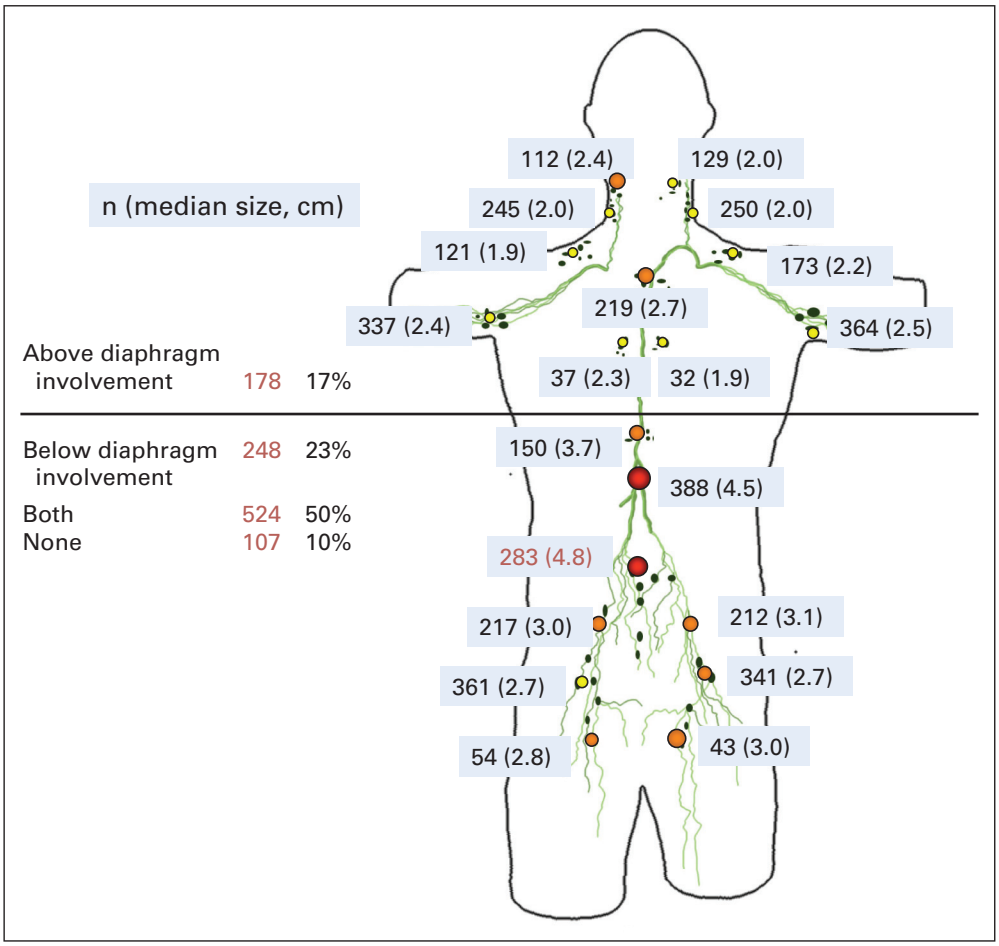

Fig 1. EasyStage mannequin summarizing nodal involvement distribution. Copyright 2004, Associazione Angela Serra per la ricerca sul cancro, Modena, Italy.

results were limited by selection of patients, missing data, and no inclusion of more recently reported parameters (ie, B2M). Finally, although overall survival (OS) should be the optimal end point, building an index with that end point is unrealistic in FL whereas progression-free survival (PFS) is a suitable surrogate. For all these reasons, in 2003 the International Follicular Lymphoma Prognostic Factor Project launched the F2 study, which was aimed at verifying whether a prospective collection of data would enable the development of a more accurate prognostic index. The F2 study was thus conceived to collect an exhaustive set of clinical, laboratory, pathologic, and therapeutic information for a large number of patients and in a very short period of time. In our current report, we present the results of this study, which involved 1,093 new FL cases registered between 2003 and 2005 among 69 European and American institutions.

PATIENTS AND METHODS

Patients

We considered adult patients with a new and histologically confirmed diagnosis of FL in accordance with the WHO 2001 classification eligible for the F2 study. Central pathology reviews were performed for the first 406 patients and a diagnosis of FL was confirmed in 98.3% of these patients. Grading discrepancies were recorded in 14.6% of patients. In particular, most of these discrepancies were between grade 2 and 3a, with a tendency of local pathologists to underscore grade 3a tumors. Given this very high confirmation rate, the diagnosis performed by the local pathologists was accepted for each of the remaining cases. Bone marrow involvement was established on the basis of the local pathology report of bone marrow biopsy. Tumor burden was calculated assuming that an enlarged lymph node has the shape of an egg; the volume of the node was thus estimated by the formula $0.5236 \times (\text{ØMax})^3 \times 0.6$.[2] Data on disease extension were collected using EasyStage (Associazione Angela Serra per la ricerca sul cancro, Modena, Italy; Pat. No. US 2004/0267573 A1-December 31, 2004), an interactive mannequin developed for registering nodal and extranodal sites. The sites and sizes of the involved nodes are summarized in Figure 1.

Initial treatment was defined according to the intention to treat principle. Watch and wait (WW) was defined as the decision not to treat patients and also by the absence of treatment within the first 3 months of follow-up.

This study was conducted in accordance with the Good Clinical Practice rules. Patient registrations were performed using a dedicated, secure Web site. Electronic case report forms were reviewed for accuracy by the respective local investigators.

Statistical Methods

For sample size definition, we assumed that each risk had a prevalence of at least 10%, the 5-year survival rate of the entire study population was 70%, and that the odds ratio would be 2 with, as compared to without, the risk factor. Under these conditions, there would be an 80% power to detect a statistically significant effect of the risk factor on outcome end points with a sample size of 750 patients. Because of the inter-relationship between risk factors, a total of 900 patients would be likely to yield similar power in a multivariate analysis, which allows for the effects of several risk factors. Response assessment was defined according to the criteria proposed by the

National Cancer Institute–sponsored International Working Group.[10] OS was measured from the date of diagnosis until death from any cause. PFS was measured from the date of diagnosis until either the date of disease progression or death from any cause.[11] OS was initially identified as the principal study end point. However, when accrual was completed, the F2 study population was characterized by an actuarial 5-year survival rate of 89% and not the assumed 70%. Given this scenario, the executive committee decided to adopt PFS instead of OS as the main trial efficacy end point.

PFS and OS were calculated using Kaplan-Meier estimators.[12] Comparison between categories was performed by means of the log-rank test.

Continuous biologic covariates were dichotomized according to usual clinical thresholds and the cutoff of the TB (50 mL) was chosen from a Cox proportional hazard regression spline analysis.[13] From the cubic smoothing spline, it appeared that the log of the hazard ratio changed abruptly when the value of TB is about 50 mL. However, as nodal TB was quite laborious to calculate, we searched for an additional parameter reflecting TB significance that was easier to determine. We found that nodal TB strongly correlates with the longest diameter of the largest involved node (LoDLIN). In linear regression the ln(LoDLIN) versus ln(TB) was equal to $0.416 + 0.330 \times \ln(TB)$, $R^2 = 0.933$. A TB value equal to 50 mL thus corresponded at the higher 95% CI limit to a value of 6 cm for the LoDLIN. Indeed, 97% of the cases in our current study cohort were classified into the same risk group (K statistics = 0.954; $P < .001$). Hence, LoDLIN replaced nodal TB in the final model.

The F2 model was built by means of a bootstrap screening with a backward elimination over the sample with complete observed covariates. These procedures were performed by means of a multivariate Cox proportional hazard model with a selection guide of $P = .10$.[14] The performance of the selected model was assessed by the error rate (1-c Harrell)[15] in an out-of-bootstrap sample that was used like a test data set. The procedure was repeated 1,000 times. Furthermore, the performance of the selected model was internally validated using Harrell's procedure.[16] All analyses were performed using Stata Statistical Software release 8.0 (StataCorp, College Station, TX). All P values were two sided.

RESULTS

Patient Characteristics and Treatments

Between January 2003 and May 2005, 1,093 patients (Fig 2) were registered. Thirty-six patients (3.3%) were subsequently excluded for the following reasons: no further information after registration (n = 20); revised histology (n = 8); diagnosis made before study start (n = 5); no compliance with inclusion criteria (n = 3). One hundred fifteen patients were addressed to a WW policy and were therefore withdrawn from model development, since events considered for PFS in the WW group and in the group of treated patients were not comparable. Start of therapy was coded as an event in WW group, while events registered in the group of patients treated for active disease were no response, relapse, progressive disease after therapy, and death from other causes than FL. This implies that the main end point considered (ie, PFS) was an irrelevant end point for WW patients. The characteristics of the 942 eligible patients included in this study cohort and their treatment details are summarized in Table 1. Overall, 826 patients received systemic therapy, 559 with rituximab and 267 without rituximab. With induction therapy, 684 patients (73%) achieved a complete response (CR), 95 patients (10%) achieved a partial response (PR) not requiring further therapy, 56 patients (6%) achieved a PR requiring further therapy, 74 patients (8%) did not respond, and 33 patients (3%) were lost to follow-up before any response assessment.

After a median follow-up of 38 months (range, 1 to 63) a total of 302 events were observed, including 68 disease progressions (34 after rituximab-containing therapy), 210 relapses, and 24 deaths not related to FL. The 3- and 5-year PFS rates were 68% (95% CI, 64% to 71%) and 40% (95% CI, 18% to 61%), respectively. The 3- and 5-year OS rates were 93% (95% CI, 91% to 95%) and 88% (95% CI, 82% to 92%), respectively (Fig 3). The analysis of the F2 population confirmed that FLIPI was highly predictive, giving a 3-year PFS of 78%, 68%, and 52% for patients at low risk (LR), intermediate risk (IR), and high risk (HR), respectively ($P < .00001$). FLIPI was highly predictive also in the group of patients treated with rituximab (PFS of 79%, 72%, and 53% for patients at LR, IR, and HR, respectively; $P < .00001$).

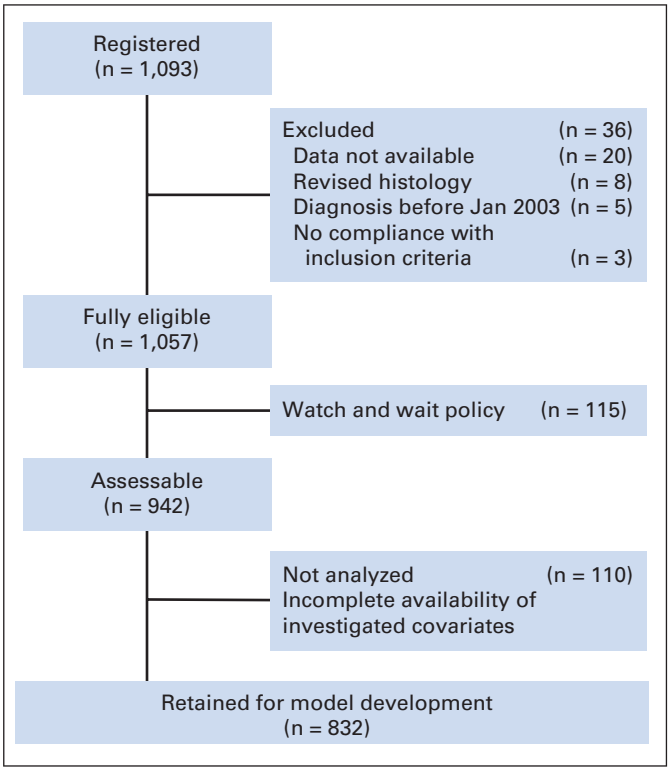

Fig 2. Flow chart of patients included in the analysis.

Prognostic Model Development

In univariate analysis, 12 variables had a statistically significant impact whereas four did not (Table 2). Performance status was significant, but not included in further analyses because of the low number of patients (4%) with a poor performance status. The remaining 11 variables were retained for further analyses in the group of 832 patients with complete data. A total of 261 events were observed, corresponding to an event/variable ratio of 24/1, a satisfactory ratio to perform the multivariate analysis.[17,18] A better compromise between the complexity of the model and the error in the out-of-bootstrap sample was obtained using models with five covariates. The five covariates with the highest inclusion frequencies from selection procedures were B2M higher than ULN, LoDLIN longer than 6 cm, BMI presence, Hb lower than 12 g/dL, and age older than 60 years.

Since the relative risk associated with each of the five factors was comparable, we constructed a risk score by simply summing the number of risk factors present in a single patient. Risk groups were defined by comparing the relative risk of disease progression in patients with each possible number of presenting risk factors and combining the

Table 1. Baseline Characteristics of the Assessable Patients (N = 942)

Characteristic	No.	%	Rituximab-Containing Regimens (%)
Median age, years	57		
≤ 60	537	57	
> 60	405	43	
Range	21-93		
Histologic grading			
1	266	28	
2	417	44	
3	230	24	
Unspecified	29	3	
Serum LDH (n = 932)			
≤ UNL	737	79	
> UNL	195	21	
Ann Arbor stage			
I-II	305	32	
III-IV	637	68	
No. of nodal sites			
0-4	741	79	
> 4	201	21	
Hemoglobin level g/dL			
≥ 12	777	82	
< 12	165	18	
Serum β_2-microglobulin (n = 848)			
≤ UNL	493	58	
> UNL	355	42	
Bcl-2 status (n = 605)			
Negative	298	49	
Positive	307	51	
LoDLIN, cm			
≤ 6	709	75	
> 6	233	25	
Bone marrow involvement (n = 927)			
Absence	552	60	
Presence	375	40	
No. of extranodal sites, including bone marrow			
0-1	833	88	
> 1	109	12	
ECOG performance status			
0-1	902	96	
> 1	40	4	
Systemic symptoms			
Absence	826	88	
Presence	116	12	
ESR, mm/h (n = 864)			
≤ 30	718	83	
> 30	146	17	
Serum albumin level, g/dL (n = 864)			
≥ 3.5	768	89	
< 3.5	96	11	
FLIPI (n = 932)			
0-1	428	46	
2	281	30	
3-5	222	24	
Treatment details			
Local	116	12	
Surgery	33	28	
Radiotherapy	26	22	
Surgery + radiotherapy	57	49	
Systemic	826	88	
Immunotherapy	47	6	100
Single agent	69	8	23
CVP	65	8	40
CHOP/CHOP like	401	49	73
Fludarabine-containing regimens	210	25	71
HDT	34	4	85
Rituximab-containing regimens	559	59	

NOTE. Because of rounding, percentages may not total 100. Bcl-2 status was assessed according to local adopted procedures.

Abbreviations: LDH, lactate dehydrogenase; UNL, upper limit of normal; LoDLIN, longest diameter of the largest involved node; ECOG, Eastern Cooperative Oncology Group; ESR, erythrocyte sedimentation rate; FLIPI, Follicular Lymphoma International Prognostic Index; CVP, cyclophosphamide, vincristine and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; HDT, high-dose therapy.

categories with a similar relative risk. Patients were then stratified according to the following three risk groups: score 0 (20%), LR; score 1 to 2 (53%), IR; score 3 to 5 (27%), HR (Table 3). The 3-year PFS resulted in 91%, 69%, and 51% for patients at LR, IR, and HR, respectively ($P < .00001$), and the 5-year PFS of 79%, 51%, and 20% in each risk category, respectively ($P < .00001$; Fig 4A).

Since elevated values of B2M had showed the higher inclusion frequencies in bootstrap procedure, we considered B2M the covariate with the most relevant prognostic weight. So, additional analyses were performed with the aim of incorporating B2M into the FLIPI instead of creating a new index. First, we assessed the prognostic value of a combination of FLIPI plus B2M more than UNL. Furthermore, we

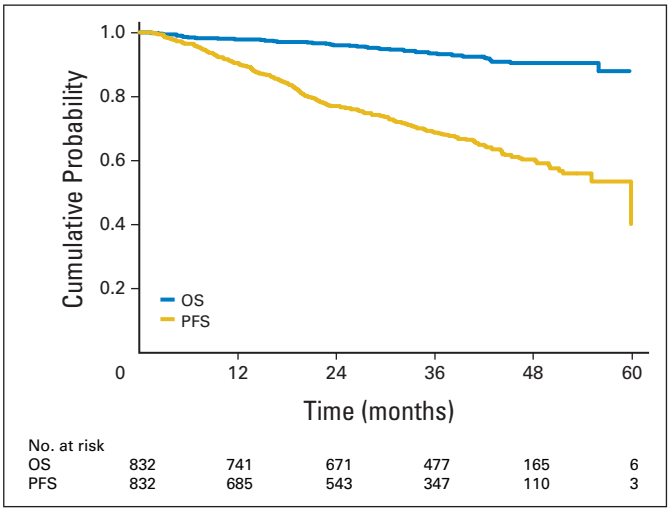

Fig 3. Overall survival and progression-free survival of 832 patients used for Follicular Lymphoma International Prognostic Index 2 development.

Table 2. Univariate and Multivariate Analysis of PFS

Variable	Adverse Factor	Patients (%)	PFS (%)		Cox PH Univariate (n = 942)		Final Model (n = 832)		
			3-Year	5-Year	HR	*P*	HR	SE	*P*
B2M	> UNL	42	58	21	2.04	< .001	1.50	0.20	.003
BMI	+	40	58	20	1.89	< .001	1.59	0.21	< .001
Hemoglobin, g/dL	< 12	18	52	42	1.88	< .001	1.51	0.22	.005
LoDLIN, cm	> 6	25	54	24	1.66	< .001	1.44	0.19	.006
Age, years	> 60	43	63	46	1.38	.006	1.41	0.18	.008
AA stage	III-IV	68	62	33	2.23	< .001			
PS*	> 1	4	51	32	2.05	.001			
NNS	> 4	21	56	30	1.88	< .001			
NES	> 1	12	54	38	1.75	.001			
B symptoms	+	12	53	42	1.65	.001			
LDH	> UNL	21	60	22	1.50	.002			
ESR, mm/h	> 30	17	63	25	1.28	.122			
Sex	Male	50	65	53	1.12	.326			
Bcl-2	+	51	67	53	1.08	.582			
Albumin, g/dL	< 3.5	11	67	49	1.03	.864			
Overall PFS			68	40					
Slope shrinkage								0.944	
Corrected c-Harrel								0.648	

NOTE. Slope shrinkage and corrected c-Harrel obtained after 1,000 bootstrap replications. Bcl-2 status was assessed according to local adopted procedures.
Abbreviations: PFS, progression-free survival; PH, proportional hazard; HR, hazard ratio; B2M, β2-microglobulin; UNL, upper limit of normal; BMI, bone marrow involvement; LoDLIN, longest diameter of the largest involved node; AA, Ann Arbor; PS, performance status; NNS, number of nodal sites; NES, number of extranodal sites; LDH, lactate dehydrogenase; ESR, erythrocyte sedimentation rate.
*PS not analyzed: low prevalence (4%) of patients with poor Eastern Cooperative Oncology Group (2 to 4).

tried to add B2M more than UNL to the five FLIPI factors. Finally, we explored the usefulness of a multivariate analysis adding B2M more than UNL to the 12 variables used for developing the original FLIPI. All of the above-mentioned approaches produced a less discriminating index compared to the FLIPI2 (Table 4).

The FLIPI2 was predictive also in the group of patients treated with rituximab (89%, 73%, and 57% for patients at LR, IR and HR, respectively; $P < .001$). Finally, the index proved to be a robust tool also for predicting survival. The 3-year survival rates were 99%, 96%, and 82% and the 5-year survival rates were 98%, 88%, and 77% for patients at LR, IR, and HR, respectively ($P < .0001$; Fig 4B).

External Validation

The predictive model was tested in an external validation sample of 231 cases enrolled in prospective clinical trials by Gruppo Italiano Studio Linfomi in the period 1998 to 2008, excluding cases of the period 2003 to 2005 already registered in the F2 study. The median follow-up was 40 months and 81 events for PFS were recorded. The annual PFS rate was 14.2% (95% CI, 11.4 to 17.7) similar to that of 12.4% (95% CI, 11.0 to 14.0) observed in the F2 study population.

According to FLIPI2, 42 patients (18%) were classified at LR, 143 (62%) at IR, and 46 (20%) at HR. The FLIPI2 was able to stratify this group of patients into the three risk groups with statistically different outcomes ($P = .0005$). The 5-year PFS was 76%, 46%, and 29% and the 5-year OS was 96%, 80%, and 59% in the LR, IR, and HR groups, respectively (Figs 4C and 4D).

DISCUSSION

The wide international cooperation and the prospective nature of this study allowed us to acquire valuable data in a very short period of time, and to construct a prognostic index incorporating the more promising known prognostic factors for FL. Moreover, the adoption of active

Table 3. Outcome and Relative Risk of Progression According to Risk Group as Defined by FLIPI2 (N = 832)

Risk Group	No. of Factors	Patients (%)	PFS					
			3-Year		5-Year			
			%	SE	%	SE	HR	95% CI
Low	0	20	90.9	2.4	79.5	5.0	1.00	—
Intermediate	1-2	53	69.3	2.4	51.2	5.7	3.19	2.00 to 5.15
High	3-5	27	51.3	3.7	18.8	13	5.76	3.53 to 9.40
High *v* intermediate							1.81	1.40 to 2.33

Abbreviations: FLIPI2, Follicular Lymphoma International Prognostic Index; PFS, progression-free survival; HR, hazard ratio.

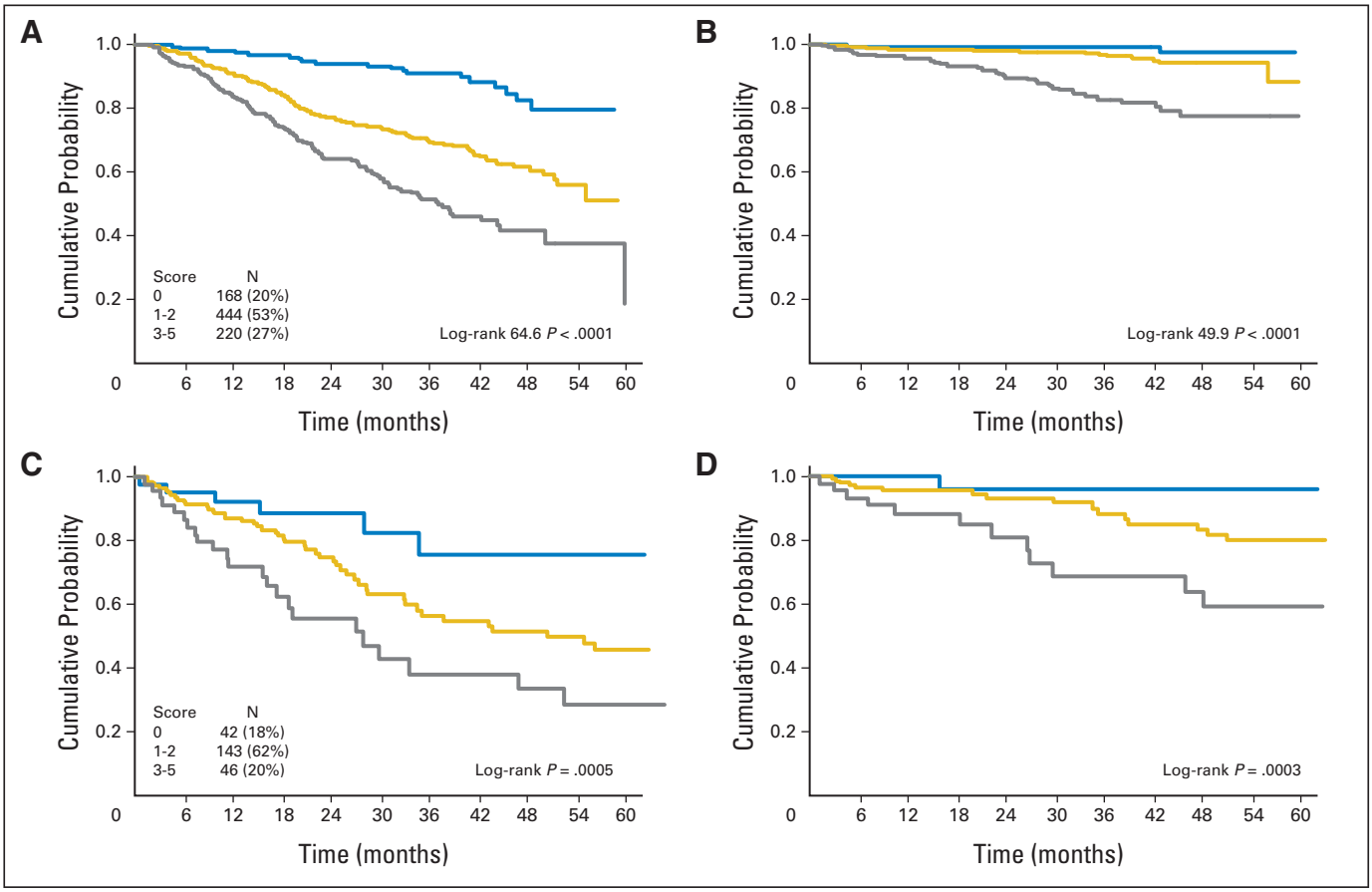

Fig 4. (A) Progression-free survival (PFS) and (B) overall survival (OS) of the training sample (832 patients) according to the Follicular Lymphoma International Prognostic Index 2 (FLIPI2); (C) PFS and (D) OS of the validation sample (231 patients) according to FLIPI2. FLIPI2: low risk, score 0; intermediate risk, score 1 to 2; high risk, score 3 to 5. Blue line, score 0; yellow line, score 1-2; grey line, score 3-5.

follow-up procedures permitted a careful analysis of different study end points, including response assessment, relapses, and causes of death. The availability of information regarding disease progression also allowed us to replace OS with PFS as the principal end point of the study. PFS was recently admitted as a primary efficacy end point, and is now considered the preferred end point in lymphoma clinical trials, especially those involving indolent subtypes such as FL.[11] PFS reflects tumor growth, and therefore can be interpreted earlier than the traditional OS end point. In addition, PFS is not confounded by the administration of subsequent therapy.

Table 4. Performances of Different Approaches Used for Improving FLIPI

Model	Log Rank	c-Harrell	D Royston	SE
FLIPI + B2M*	59.4	63.3	0.885	0.122
FLIPI recalculated†	57.8	63.2	0.841	0.118
FLIPI2	64.6	63.8	0.902	0.117

Abbreviations: FLIPI, Follicular Lymphoma International Prognostic Index; B2M, β2-microglobulin.

*A 6-parameter index was calculated on F2 study population, including all original FLIPI factors plus B2M.

†A new multivariate model was obtained using all 12 parameters used to build the original FLIPI index plus B2M on F2 study population. In the recalculated model B2M substituted LDH as independent prognostic factor, confirming independent prognostic role for age, stage, hemoglobin, and number of nodal sites.

The first aim of our current study was the validation of FLIPI which we found to be highly predictive also for patients treated with immunochemotherapy (ICHT).[19] The predictive value of FLIPI in terms of treatment outcome under the condition of a rituximab-containing regimen was reported previously by the German Low Grade Study Group for a cohort of 362 patients that had also been treated up-front with rituximab and CHOP.[20] Our second aim was to verify whether it would be possible to move forward to a new prognostic index focused on PFS. In order to better identify the variables that were more highly indicated for constructing the model, we collected information on all of the covariates already recognized by IPI, ILI, and FLIPI, and also those supposed to be relevant on the basis of published data. B2M, LoDLIN, BMI, Hb, and age were found to be the five most appropriate variables for building the prognostic index. Two parameters (Hb and age) have already been recognized by FLIPI, whereas B2M, LoDLIN, and BMI are essentially new.

Serum B2M emerged in our current analyses as a robust indicator, many years after it had been proposed as a promising prognostic factor in most lymphoproliferative disorders.[21-25] Of note, the prognostic value of B2M was found to be highly significant ($P < 10^{-4}$) in the univariate analysis undertaken in the FLIPI report but it was excluded from multivariate analysis because of the very high proportion of patients for whom this information was unavailable.[8] Baseline

serum B2M levels were further found to be an independent prognostic factor for FL patients, in addition to molecular response in a previous study[26] and, independent of FLIPI, in patients treated upfront with anthracycline-containing chemotherapy.[9] Based on our present results, we believe that serum B2M should now be included in the "main draw" of routine tests for newly diagnosed FL patients.

The second, and probably even more appealing, new parameter revealed by our multivariate analysis was the prognostic relevance of LoDLIN. This simple parameter represents a good surrogate for tumor burden, and retains the information provided in the FLIPI for the number of nodal sites, which is the most laborious factor to determine. It is noteworthy that the adverse impact of bulky disease was well recognized by most of the collaborators on the IPI, but the data could not be pooled effectively because nobody (Memorial Sloan-Kettering, Dana-Farber Cancer Institute, M. D. Anderson Cancer Center) had their data coded the same. FLIPI had similar issues. The importance of the prospective approach is evident from the way bulk could be successfully incorporated. The last new variable included in our final model was BMI. The presence or the extent of BMI in the final model may be due to the high proportion of cases without marrow infiltration, also reflecting the significant number of patients with localized disease in our study population. Similar rates of BMI have been recently reported by Friedberg et al[27] on behalf of the National LymphoCare study. In that observational study performed on 2,728 subjects diagnosed between 2004 and 2007 at 265 sites in United States, the rate of cases in stage IV was 37.1% only. BMI has already been found to be associated with poorer survival in indolent lymphomas[28,29] and the BMI variable has been included previously in the final model of peripheral t-cell lymphoma unspecified prognostic index.[30]

Before licensing FLIPI2 as a new product of the IFLPFP, we took care to assess a more conservative approach by incorporating B2M in some way into the FLIPI. All of these attempts produced positive results, but the FLIPI2 still maintained the best performance in all statistical analyses.

Several studies are currently investigating novel approaches for the identification of prognostic factors in FL and are mostly focused on the biology of the disease; these include for example the role of macrophages,[31] and the role of different molecular signatures of the FL cells,[32] and of the tumor microenvironement.[33] The interest of such studies is major as biologic factors are at the origin of the disease rather than a consequence as most clinical factors are. However, biologic factors are still far from being included in a prognostic model as their availability is limited and there is still much work to be done for reaching a consensus on their interpretation.

In conclusion, the F2 study demonstrates that a prospective web-based collection of data through a wide international cooperation is feasible and is a powerful instrument for investigating the prognosis of FL. Moreover, FLIPI2 is a simple prognostic index based on easily available clinical data and in the current era of ICHT may represent a promising new tool for the identification of patients with different risks of disease progression. This is particularly relevant considering the recent revolution in the treatment of patients with FL, with the adoption of ICHT as a novel and now standard initial treatment[34] and also as part of maintenance treatment for relapsing/progressing patients.[35]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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