

## International and Italian prognostic indices in follicular lymphoma

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**Background and Objectives.** The International Prognostic Index (IPI), initially designed for aggressive lymphomas, has been successfully used in patients with follicular lymphoma (FL). The Italian Lymphoma Intergroup (ILI) created a new prognostic index specific for FL. The aim of this study was to compare which of these two indices is more useful when applied to a large group of FL patients.

**Design and Methods.** Both indices, IPI (age >60 years, extranodal involvement  $\geq 2$  sites, elevated lactate dehydrogenase, ECOG  $\geq 2$ , stage  $\geq 3$ ) and ILI (age >60 years, extranodal involvement  $\geq 2$  sites, elevated lactate dehydrogenase, male sex, B symptoms, erythrocyte sedimentation rate  $\geq 30$  mm 1<sup>st</sup> hour) were calculated in a group of 398 FL patients. Overall survival (OS) and progression-free survival (PFS) associated with each prognostic group were calculated according to the Kaplan-Meier method.

**Results.** The overall concordance between both indices was 73%. According to the IPI 122 patients (31%) were in the higher risk group, whereas according to the ILI index 132 (33%) were; concordance between the high risk groups was 66%. The 10-years OS and PFS rates after applying the IPI system were 73% and 37%, respectively, in the low risk groups; 47% and 26%, in the intermediate risk groups and 25% and 2%, in the high risk groups (log-rank=69.2 and 41.3, respectively;  $p < 0.0001$ ). According to ILI index the 10-year OS and PFS were 60% and 34%, respectively, in the low risk groups; 59% and 30%, in the intermediate risk groups and 17% and 0%, in the high risk groups (log-rank=86.6 and 58.5, respectively;  $p < 0.0001$ ).

**Interpretation and Conclusions.** Both the IPI and ILI index, are useful for classifying FL patients into different risk groups. Although it seems that the ILI index has a higher discriminating power among groups, significant differences were not observed in identifying FL patients with a poor outcome.

**Key words:** follicular lymphoma, prognostic index, survival.

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Follicular lymphoma (FL) represents approximately 25% of all adult non-Hodgkin's lymphomas (NHL) in Western countries.<sup>1</sup> During the last decade, more intensive therapeutic approaches have been used in an attempt to increase overall and disease-free survival in this type of lymphoma, considered as indolent but not curable with conventional treatment. For this reason, it is important to identify patients with a poor prognosis who would be candidates to receive experimental treatments.<sup>2-7</sup> A number of prognostic indices have been used in FL patients.<sup>8-11</sup> The *International Prognostic Index* (IPI), initially designed for aggressive lymphomas, has been successfully applied in patients with FL.<sup>12,13</sup> However, the IPI seems to have a limited discriminatory power in FL, because most patients are allocated into the favorable or the intermediate risk groups. Recently, the Italian Lymphoma Intergroup (ILI) described a new prognostic index specific for FL and hypothetically more useful than IPI at discriminating high risk patients.<sup>14</sup> The ILI prognostic system is composed of three variables also used in IPI, in addition to three simple parameters usually measured in patients with lymphoma. The aim of this study was to validate both indices in a large group of patients with FL and to determine which one of them more accurately discriminated poor prognosis patients.

### Design and Methods

#### Patients' characteristics

Four hundred and thirty-seven patients with a histologically confirmed diagnosis of grade I or II FL according to the WHO classification, consecutively diagnosed in five Barcelona hospitals (Hospital Clínic, Hospital Santa Creu i Sant Pau, Hospital Durán i Reynals [Hospitalet de Llobregat], Hospital Germans Trias i Pujol [Badalona] and Hospital del Mar) between January 1976 and December 2001 were initially considered for this study. Data were available to calculate the IPI and the ILI index in 398. The clinical characteristics of patients at diagnosis are shown in Table 1. The median follow-up of the series lasted 60 months (range: 1-292). Stage at diagnosis was determined in all patients by clinical evaluation, chest and abdomen computed tomography and bone marrow biopsy. Patients received several first-line treatments: 18 patients (5%) did not receive any treatment according to a watch-and-wait strategy; 33 patients (8%) were treated with radiotherapy and/or surgery alone; 55 patients (14%) with a single alkylat-

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**Table 1. Clinical characteristics of patients.**

N <sup>o</sup>	398
Age, median (range)	56 (19-88)
≤ 60 years	249 (62%)
Sex	
Female	209 (48%)
Male	189 (52%)
Ann Arbor stage	
I-II	85 (21%)
III-IV	313 (79%)
Bone marrow involvement	234 (59%)
B symptoms	99 (25%)
Performance status (ECOG)	
0-1	330 (83%)
≥2	68 (17%)
Extranodal involvement (≥ 2 sites)	139 (35%)
Increased serum LDH level	88 (22%)
ESR <sup>1</sup> (≥ 30 mm at 1 <sup>st</sup> hour)	105 (26%)
First line treatment	
Watch and wait	18 (5%)
Single alkylating agent	55 (14%)
CT <sup>2</sup> without anthracyclines	70 (18%)
CHOP/CNOP	222 (55%)
Surgery and/or radiotherapy	33 (8%)
Response <sup>3</sup>	
Complete response	187 (50%)
Partial response	142 (38%)
Non response/progression	42 (12%)

<sup>1</sup>ESR: erythrocyte sedimentation rate; <sup>2</sup>CT: chemotherapy; <sup>3</sup>Response: 9 treated patients were not evaluable for response.

ing agent (cyclophosphamide or chlorambucil); 70 patients (18%) with a combination chemotherapy regimen without an anthracycline (basically cyclophosphamide, vincristine and prednisone and 19 patients were treated with regimens containing purine analogs) and 222 patients (55%) with a chemotherapy regimen with an anthracycline (CHOP/CNOP). Response to treatment was assessed 3 months after the end of therapy, and during follow-up patients were evaluated every 4 months. One hundred and eighty-seven patients (50%) achieved a complete response (CR) and 38% (n=142) a partial response (PR) with initial therapy.

#### Calculation of the IPI and ILI indices

The IPI was calculated according to the International Non-Hodgkin's Lymphoma Prognostic Factors Project.<sup>11</sup> The variables used were age (≤60 vs > 60 years), performance status (Eastern Cooperative Oncology Group [ECOG] 0 or 1 vs ≥ 2), Ann Arbor stage (I to II vs III to IV), extranodal involvement (< 2 vs ≥ 2 sites) and serum lactate dehydrogenase (LDH) level (normal vs high). Three risk groups were defined by the IPI: score 0-1, low risk;

score 2, intermediate risk; score ≥3, high risk (we combined the high-intermediate and high risk groups of IPI in a single high risk group to establish comparisons between the two indices).

The ILI index was calculated as detailed by the Italian Lymphoma Intergroup.<sup>14</sup> Six variables were used to construct this index, three of which are also included in the IPI (age, extranodal involvement and LDH level). The other three variables considered were presence of B symptoms, male sex and erythrocyte sedimentation rate (ESR) ≥ 30 mm at 1<sup>st</sup> hour. Three risk groups were defined within the ILI index: patients with none or one unfavorable variable were considered at low risk, those with two variables at intermediate risk, and those with 3 or more adverse variables were considered at high risk.

#### Statistical analysis

Overall survival (OS) and progression-free survival (PFS) curves were calculated for each risk category according to the Kaplan-Meier method. PFS was calculated for all treated patients from the beginning of the therapy to the time of disease progression, relapse or death. Survival curves were compared using the log rank test. All data were analyzed by the Statistical Package for the Social Sciences (SPSS®). The limit of statistical significance for all analyses was defined as  $p \leq 0.05$ .

#### Results

##### Application of the IPI and ILI indices

Table 2 shows the patients' distribution according to risk group after applying the IPI and the ILI index. Overall concordance between both classification systems was 73%: 290 patients were allocated to the same risk group. The concordance between the low risk groups was 70%; that between the intermediate risk groups was only 31% and that between the high risk groups was 66%. The IPI and ILI index identified a similar number of high risk patients, 122 (31%) and 132 patients (33%), respectively. Among the 249 patients sixty years old or younger, 36 (14%) were classified in the high risk group according to the IPI, and 42 (17%) were included in the high risk group according to the ILI index.

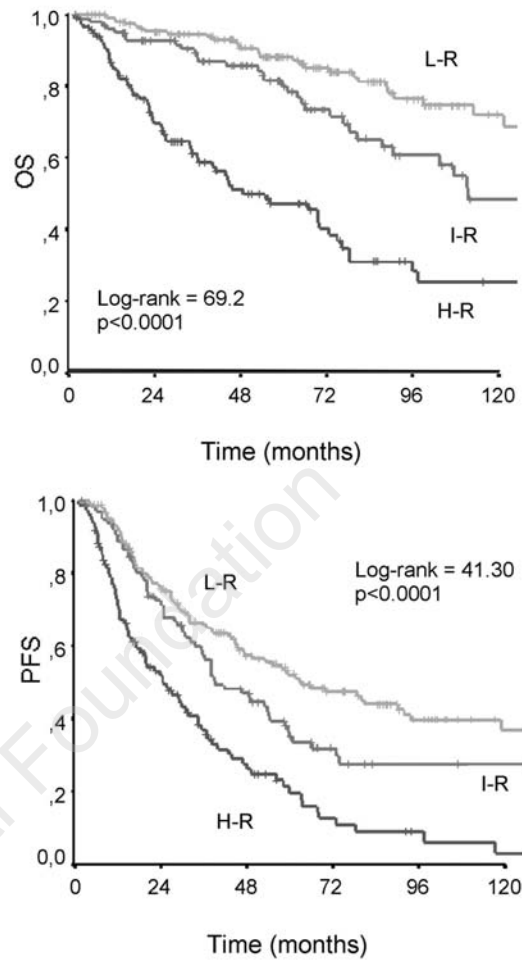
##### Survival

Survival data for the whole population and for each risk group are summarized in Table 3, and OS and PFS curves according to the IPI and the ILI index are shown in Figures 1 and 2. With the IPI system, three groups of patients with statistically different OS and PFS were distinguished. The 5- and 10-years OS rates were 89% and 73%, respectively, in the low risk group; 78% and 48% in the intermediate risk group and 47% and 25% in the high risk group (log-rank test, 69.2;  $p < 0.0001$ ).

**Table 2. Prognostic indices and patients' distribution according to risk.**

<b>International Prognostic Index (IPI)</b>	
Age > 60 years	
Extranodal involvement ≥ 2	
Serum LDH level	
ECOG ≥ 2	
Stage ≥ 3	
Low risk 0-1	165 (41%)
Intermediate risk 2	111 (28%)
High risk 3-5	122 (31%)
<b>Italian Lymphoma Intergroup (ILI) Index</b>	
Age > 60 years	
Extranodal involvement ≥ 2	
Serum LDH level	
Male sex	
Presence of B symptoms	
ESR ≥ 30 mm 1 <sup>st</sup> hour	
Low risk 0-1	178 (45%)
Intermediate risk 2	88 (22%)
High risk ≥ 3	132 (33%)

<sup>1</sup>Intermediate-high and high risk groups according to the IPI were considered as a single risk group.



**Figure 1. OS and PFS curves according to IPI risk groups. L-R: low risk; I-R: intermediate-risk; H-R: high risk.**

**Table 3. Survival data for all patients and risk groups.**

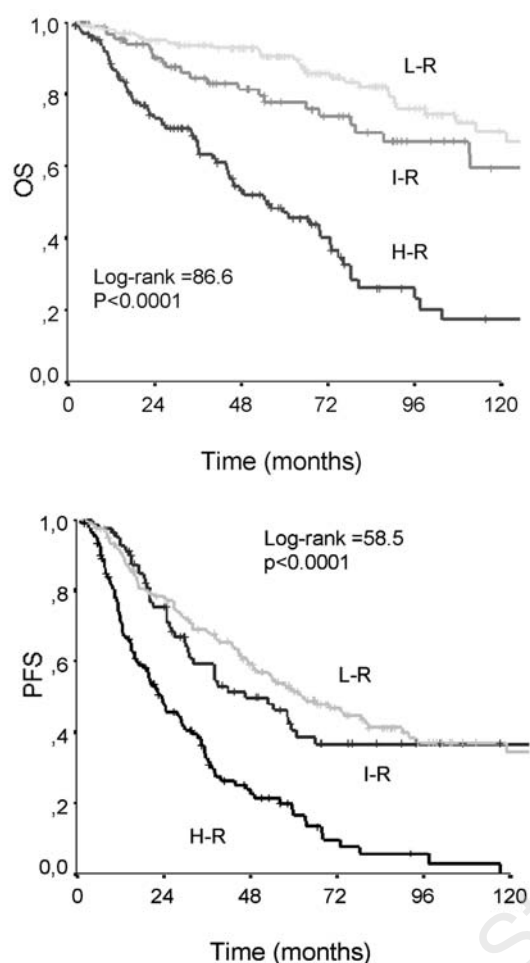
Prognostic Index	OS		PFS (%)	
	5 years (%)	10 years (%)	5 years (%)	10 years (%)
Whole group	73	51	61	49
<b>IPI</b>				
Low risk	89	73	53	37
Intermediate risk	78	47	33	26
High risk	47	25	21	2
<b>ILI Index</b>				
Low risk	90	69	51	34
Intermediate risk	78	59	40	30
High risk	46	17	18	0

Differences in OS and PFS between each risk group were statistically significant ( $p < 0.0001$ ) in both prognostic systems.

Referring to time to progression for patients who achieved CR, the 5-years PFS for the low risk group was 53%, for the intermediate risk group 33% and for the high risk group 21% (log-rank test, 41.3;  $p < 0.0001$ ).

The ILI index also defined three groups of patients. The OS at 5 and 10 years from diagnosis for each ILI risk group was as follows: low risk, 90% and 69%, respectively; intermediate risk, 78% and 59%, and high risk, 46% and 17% (log-rank test, 86.6;  $p < 0.0001$ ). The 5-year PFS of patients in CR after initial therapy was 51% for patients at low risk; 40% for patients at intermediate risk and 15% for patients at high risk (log-rank test, 58.5;  $p < 0.0001$ ).

No differences were observed between treatments received by patients included in each high risk group



**Figure 2.** OS and PFS curves according to ILI risk groups. L-R: low risk; I-R: intermediate risk; H-R: high risk.

according to the IPI and ILI index. Most high risk patients were treated with chemotherapy regimens including an anthracycline, CHOP/CNOP (50% and 58%, respectively) and other chemotherapy regimens without anthracyclines (25% and 19%, respectively).

## Discussion

In this report we applied two different prognostic indices (i.e., the IPI and the ILI index) to a group of FL patients in order to validate these prognostic systems and to determine which was more accurate in identifying poor prognosis patients. More than 75% of FL patients present with advanced stage (III-IV) disease at diagnosis, but there is a great heterogeneity in outcome among individual patients.<sup>15</sup> Given the poor results obtained with conventional

treatment more intensive therapies, such as high-dose therapy followed by hematopoietic stem cell rescue or allogeneic transplantation, are increasingly being used in patients with FL.<sup>2-7</sup> In order to select reasonable candidates for these more intensive –and also more toxic–treatments, prognosis must be very carefully assessed. Several studies have been addressed to identify prognostic factors associated with poor survival in patients with low-grade lymphomas.<sup>9,16-19</sup> Some prognostic models based on these factors have been proposed.<sup>8-10</sup> Nevertheless, none of them has been widely accepted. The IPI, initially designed for use in aggressive lymphomas, is easy to apply in clinical practice.<sup>11</sup> The IPI is also useful when applied to low-grade lymphomas<sup>12,13</sup> because it adequately separates groups of patients with different responses to treatment and with different survival probabilities. One important criticism to the application of the IPI to patients with FL is that only a low percentage of them (about 8-11%) get included in the high risk group. The ILI index is similar to the IPI and is also easy to calculate, but may identify a larger number of poor prognosis patients than does the IPI.<sup>14</sup>

Our analysis was based on OS and PFS as the most reliable parameters in prognostic analysis in FL.<sup>18</sup> The IPI and ILI systems were useful to distribute FL patients into three groups with statistically different survivals. Nevertheless, on the basis of the log-rank test values, it seems that the ILI index has a higher discriminatory power among groups, as indeed was previously reported by the Italian Lymphoma Intergroup.<sup>14</sup> The percentage of patients included in high risk groups after applying both indices was very similar (31% and 33%) and the OS at 5 and 10 years for these groups was really poor. Patients sixty years old or younger were classified similarly by both indices into high risk groups, 14% vs 17%. Both the IPI and the ILI index were also applied to a series of FL patients including some grade III FL in a previous study, and the conclusion was that the ILI index was better fitted to grade I-II FL patients while the IPI showed a better discrimination among grade III patients. In this study the 5- and 10-year OS for high risk patients, as defined by the IPI, were 43% and 22% and 25% and 0% for those at high risk according to the ILI index.<sup>19</sup> In our study, grade III FL patients were not included.

Prognostic indices could be complemented with other prognostic variables such as the level of  $\beta 2$  microglobulin. An elevated serum  $\beta 2$  microglobulin level is associated with a lower CR rate and shorter time-to-treatment failure in low grade lymphomas.<sup>20</sup> Recently, several biological parameters have been analyzed in order to investigate their relevance as prognostic parameters in NHL; some of these do seem to play an important role: type of bcl-2 rearrangement,<sup>21,22</sup> levels of soluble ICAM-1,<sup>23</sup> vascular endothelial growth factor level<sup>24</sup> and

increase of soluble CD23 and tumor necrosis factor  $\alpha$ .<sup>25</sup> Some of these parameters may be included in future prognostic systems. In conclusion, both the IPI and the ILI index are useful for classifying FL patients into risk groups with different survivals, and although it seems that the ILI index has a higher discriminatory power among groups, significant differences in identifying FL patients with a poor outcome were not found.

At the time of writing this study, another new prognostic index, specific for FL patients, has been described by the *Follicular Lymphoma International Prognostic Project* (FLIPP).<sup>26</sup> The index includes, besides age ( $\geq 60$  years), stage at diagnosis (III-IV) and elevated LDH level, the number of nodal involvement sites ( $\geq 5$  nodal sites) and hemoglobin level ( $<120$  g/L). The index defines three groups of FL patients with different survival rates. The high risk group according to this new index showed a 5- and 10-year OS of 52.5% and 35.5%, respectively (better outcome than high risk patients identified by the IPI and the ILI index in our study). The FLIPP index needs to be compared with the IPI and the ILI index in the future.

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