Follicular Lymphoma International Prognostic Project (FLIPP)

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Background: Among non-Hodgkin's Lymphoma, the pathological type "follicular" has a good prognosis. With most of the cases classified in the best prognostic group, the International Prognostic Index (IPI) developed for aggressive lymphomas is not appropriate for this pathological type. The absence of an adapted and widely accepted prognostic index increases the difficulty to routinely choose the most adapted treatment, and to specify inclusion criteria when designing clinical trials. Clinicians requested a simple and useful prognostic index for Follicular Lymphoma, with few components, summarising the effect of dichotomised prognostic variables.

Cases and Methods: The FLIPP was initiated by collecting data from 27 groups or centres in Europe, USA, and Hong-Kong. Inclusion criteria were: Follicular Lymphoma, diagnosed between 1985 and 1992, with a follow-up > 5 years. A group of 4167 patients was analysed. Based on clinical relevance and availability of the information, 11 parameters were selected. A proportional hazard model was fitted, retaining variables independently associated with overall survival. From this initial model, candidate 5-parameter sub-models were classified according to 2 criteria. –1- Score tests evaluated on 100 re-samples of the original dataset, –2- The Somer's D coefficient adapted by Harrell [1] for measuring concordance of observed and "expected" survival, optimism being corrected by bootstrap.

Results (1): Both backward or forward analyses retained 8 parameters in a model established on 1795 patients for whom these parameters were available.

Prognostic analysis. Initial model

Parameter	Adverse factor	p (wald)	RR	95 % CI
Sex	Males	0.001	1.33	1.14 – 1.56
Age	> 60	$<10^{-3}$	2.40	2.05 – 2.81
Ann Arbor stage (AA)	III – IV	$<10^{-3}$	1.66	1.26 – 2.19
Bone marrow (BM)	Involved	0.001	1.37	1.14 – 1.64
Number of nodal sites (Nsites)	> 4	0.001	1.32	1.11 – 1.56
Haemoglobin				
Lymphocytes				
LDH				

Score test evaluation

Variables included in model	rank	1	2	3	1+2+3
Age AA Nsites Haemoglobin LDH		24	19	16	59
Age BM Nsites Haemoglobin LDH		19	25	11	55
Age AA BM Ha					

Results (2): The 5-parameter sub-model selection led to retain: age, Ann Arbor, the number of nodal sites, Haemoglobin concentration, and LDH as the most predictive variables. On the 100 re-samples of the original dataset, this sub-model was classified 24 times with the best score and 59 times as one of the 3 highest score models. This model was the closest, in terms of individual prediction as measured by D [1], to the 8 parameter model.

D coefficient evaluation

Variables included in model	rank
Age AA NSites Haemoglobin LDH	1
Age AA BM Haemoglobin LDH	2
Age AA BM Nsites LDH	3
Age BM Nsites Lymphocytes LDH	4
Age AA Haemoglobin LDH Sex	5

Sex Age Haer

Sex Age Haer

Prognostic analysis. Final model

Parame			
Age			
Ann Arbor stage	III – IV	2.00	1.56 – 2.58
Number of nodal sites	> 4	1.39	1.18 – 1.64
Haemoglobin	< 12 g/dl	1.55	1.30 – 1.88

Results (3): These 5 parameters were retained to build a final prognostic model. Three groups of patients of different risk were defined according to the number of risk factors present.

FLIPP Index

Risk Group	Number of factors	% of patients (n = 1795)	5-year survival (%)	5-year survival (%)	RR
Good	0-1	36	91	71	1
Intermediate	2	37	78	51	2.3
Poor	>2	27	53	36	4.3

Conclusion: The previous approach was an efficient method fo
patients based on the presence/absence of maximum 5 indepen
original sample.

1. Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med* 1996;**5**:361-87