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par

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TITRE

Score prédictif de rechute à 10 ans après une 1ère ligne de traitement dans le lymphome folliculaire.

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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
et de la probité dans l'exercice de la Médecine.
Je donnerai mes soins gratuits à l'indigent,
et n'exigerai jamais un salaire au-dessus de mon travail.
Admis dans l'intérieur des maisons, mes yeux
ne verront pas ce qui s'y passe, ma langue taira
les secrets qui me seront confiés et mon état ne servira pas
à corrompre les mœurs ni à favoriser le crime.
Respectueux et reconnaissant envers mes Maîtres,
je rendrai à leurs enfants
l'instruction que j'ai reçue de leurs pères.
Que les hommes m'accordent leur estime
si je suis fidèle à mes promesses.
Que je sois couvert d'opprobre
et méprisé de mes confrères
si j'y manque.

Relapse prediction score at 10 years post 1st line treatment in follicular lymphoma.

Summary :

Abstract:

Background: Follicular lymphoma (FL) is a disease recognized as incurable. Yet there are patients who do not relapse within 10 years of initial treatment. No prognostic score is available to determine relapse at 10 years after a first line of treatment in patients treated for FL. We investigated a single-center cohort for factors associated with the risk of relapse within 10 years in patients with FL.

Methods: In this retrospective study (inclusion between 2000 and 2010), 134 patients with FL at the University Hospital of Tours were included, 45 did not relapse after treatment versus 89 who relapsed before 10 years. For univariate analysis, Wilcoxon and Fisher statistics were used. The linear multinomial model was computed to weight the parameters and was validated using a split-sample strategy with 10 000 iterations. For the minimal model, the stepwise method was applied. Finally, a clinically implementable score based on minimal models is proposed.

Results: The univariate analysis shows that, for example, a complete response (p value <0.001), a stage I (p value=0.052) decrease the risk of relapse, and that a partial response (p value=0.019), a stage IV (p value=0.029), a "watch and wait" period (p value=0.040) and a spinal cord injury (p value=0.032) are associated with a higher risk of relapse. Different scores were created to explain relapse by data obtained at diagnosis, resulting in a simple score based on response to treatment and absolute monocyte count at diagnosis.

Conclusions: This score could be useful, after validation on an external cohort, for the follow-up of patients treated for FL, in order to adapt the duration and frequency of specialized follow-up.

Résumé :

Contexte : Le Lymphome folliculaire (LF) est une maladie reconnue comme incurable. Pourtant il existe des patients qui ne rechutent pas dans les 10 ans après la prise en charge initiale. Aucun score pronostique n'est disponible pour déterminer la rechute à 10 ans après une première ligne de traitement chez les patients traités pour un LF. Nous avons recherché dans une cohorte monocentrique des facteurs associés au risque de rechute dans les 10 ans chez des patients atteints de LF.

Méthodes : Dans cette étude rétrospective (inclusion entre 2000 et 2010), 134 patients atteints de LF au CHU de Tours ont été inclus, 45 n'ont pas rechuté après traitement contre 89 qui ont rechuté avant 10 ans. Pour l'analyse univariée, les statistiques de Wilcoxon et de Fisher ont été utilisées. Le modèle multinomial linéaire a été calculé pour pondérer les paramètres et a été validé en utilisant une stratégie d'échantillon fractionné avec 10 000 itérations. Pour le modèle minimal, la méthode « *stepwise* » a été appliquée. Enfin, un score cliniquement implémentable basé sur des modèles minimaux est proposé.

Résultats : L'analyse univariée montre que, par exemple, une réponse complète (p value <0.001), un stade I (p value=0,052) diminuent le risque de rechute, et qu'une réponse partielle (p value=0,019), un stade IV (p value=0,029), une période de « *watch and wait »* (p value=0.040) et une atteinte médullaire (p value=0,032) sont associés à un risque plus élevé de rechute. Différents scores ont été créés pour expliquer la rechute par les données obtenues au moment du diagnostic, aboutissant à un score simple, basé sur la réponse au traitement et le compte absolu de monocytes au moment du diagnostic.

Conclusions : Ce score pourrait être utile, après validation sur une cohorte externe, pour le suivi des patients traités pour LF, afin d'adapter la durée et la fréquence du suivi spécialisé.

I) Introduction:

Follicular lymphoma (FL) is one of the most common forms of indolent non-Hodgkin lymphoma with an estimated 3000 new cases diagnosed in France in 2018(1). FL is an incurable disease, but survival has improved over the past several decades. Recently, some authors have described a population of long-term responders (2).Thus the question of curability remains open.

Mean survival is currently 15 to 18 years, improvement being mainly attributed to the introduction of the anti-CD20 antibody Rituximab.(2–4) in relapse (5) and maintenance in relapse(6). Progression free survival has been improved by 1st line Rituximab adjunction and more recently the arrival of Obinutuzumab, a 2nd generation of anti-CD20(7).

Evaluation of prognosis is based on FLIPI & FLIPI 2, GELF scores (8–11). Recently, the m7-FLIPI score has been described, but is not currently used in routine because of the need for next generation sequencing data. Some papers demonstrated the prognostic impact of neutrophil/lymphocyte ratio (NLR) and lymphocyte/monocyte ratio (LMR) at diagnosis in B-cell non-Hodgkin's lymphoma, including follicular lymphoma(12,13).

However, there is no simple way to identify patients who are likely to be free of relapse after a prolonged time of remission. After a response to the first line of treatment, we would like to identify who are the long responders.

We hypothesize that initial bio-clinical factors of the disease, as well as treatment related information may help predict long-term relapse-free survival.

A retrospective study was conducted at the University Hospital of Tours on patients diagnosed with FL between 2000 and 2010 with a follow-up of more than 10 years, with the objective to identify such biomarkers.

II) Material and Methods:

Cohort description:

This retrospective study collected data between 2020/01/01 and 2010/12/31 in the University Hospital of Tours (n=641 patients). Inclusion criteria were patients with newly diagnosed follicular lymphoma (FL) at the Tours University hospital, treated by at least one line of treatment. Exclusion criteria included: non-FL NHL, lymphomas transformed at diagnosis, wait & watch for 10 years or more, insufficient follow-up, files with incomplete medical data or patients in spontaneous remission without treatment (Figure 1). 134 patients were included: 89 in the "Relapse within 10 years" (Relapse) group and 45 in the "No Relapse within 10 years" (No-Relapse) group.

The study was approved by "*Commission Nationale de l'Informatique et des Libertés* » (*registre des traitements informatiques du C.H.R.U. #2020_125*).

Statistical Analysis:

Data were analyzed using R version 4.0.4. Relevant clinical and pathological data collected at diagnosis or just before treatment are: age, gender, date of diagnosis, age at diagnosis, FLIPI & FLIPI 2 score(8,9), GELF score (14), histologic grade, stage, hemoglobin (g/L), absolute neutrophil count (ANC)(/mm^3), absolute lymphocytic count (ALC)(/mm^3), absolute monocyte count (AMC)(/mm^3), Neutrophil/Lymphocyte ratio (NLR), lymphocyte/monocyte ratio (LMR), LDH level higher than normal, extra-ganglionic involvement, site of extra-ganglionic involvement, number of affected lymph

node sites, osteo-medullary biopsy, Beta-2-microglobulin level, maximum normal value of Beta-2-microglobulin, presence of one node > 6cm, weight loss, fever, night sweats, watch & wait period (W&W), 3 nodes >3cm, 1 node >7cm, symptomatic splenomegaly, pain, effusion, date of treatment, type of treatment, date of evaluation, response to treatment maintenance, maintenance type, date of last dose of first line of treatment, relapse within 10 years, date of relapse, histology of relapse, transformation at relapse, treatment of relapse, date of last news, death, cause of death. For the ANC, ALC, AMC values we split (upper *vs.* lower of the median value). For NLR, LMR we analyzed as previously described(12,13).

Wilcoxon and Fisher test were computed for numerical and non-numerical values, respectively. NA values were omitted for statistical analyses.

Model construction

Multinomial logistic regressions were computed using multinom() function from nnet package(15). 10,000 iterations were performed, aiming to avoid over fitting the model(16)(41). For each iteration, two-thirds of the total number of subjects were randomly selected from the whole cohort do constitute a learning group, with the same proportion of patients from the Relapse group and the No-Relapse group as in the whole cohort.

In this learning group, multinomial model allowing the determination of weighting coefficients was calculated. Then, this model was applied to the test group (the remaining 44 patients not selected in the learning group). Efficiency of prediction was calculated in the test group, and models with more than 90% of efficiency were retains. The efficiency is defined as the ability of the model by in the learning group to correctly classify a sample of the “test” group (Figure 2).

A minimal model was selected using stepwise function from MASS package, with a forward strategy and BIC as criterion (17). Previously described split sampling strategy was applied to the minimal model. A minimal number of parameters were analyzed independently to build the proposed score.

III) Results:

134 patients treated between 2000/01/01 and 2010/12/31 were included in this study over the 641 initially analyzed, mainly due to differential diagnoses or diagnoses out of the hospital of Tours (Figure 1). Of these patients, 89 relapsed within 10 years of their first line of treatment and 45 were still in remission after their first line (Table 1). In overall population (n=134), median age was 57 years old, according with classical data(18).

The FLIPI score was equilibrated between low, intermediate and high level 33, 36 and 43 patients, respectively, representing 25%, 27% and 32% of the cohort (NA=21 patients, 16.0%). At least one GELF criterion is present in 103 patients (77.0% of the cohort). There were 60 histological grade 1 (44.7%), 46 grade 2 (34.3%) and 10 grade 3A (7.4%) (NA=11). In the Ann Arbor classification, there were 23 Stage I (17.0%), 11 Stage II (8.0%), 37 Stage III (28.0%) and 10 Stage IV (7.0%) (NA=18).

The median follow-up for all populations combined was 64.69 months (29.8 months in the relapse group *vs.* 145.6 months in the no-relapse group, Table 2). As expected, the median progression free survival (PFS) post 1st line is 43 months (23 months in the relapse groups *vs.* 141 months in the non-relapse groups).

Monoparametric analysis of numerical data fails to show any significant differences (Figure 3 and Table 1 and 2), the lowest p-value was for the FLIPI score (p value = 0.08, mean in relapse groups = 2.28, mean in no-relapse groups = 1.82).

Analysis of nominal data showed more Complete Response (CR) in the non-relapse (88.8%) *vs*. relapse group (46.0%, p value = $1.61.10^{-6}$), as well as more Stage 1 patients in no-relapse group (26.6% *vs* 12.3% respectively, p value=0.05). However, more Partial Response (PR) (15.7% *vs.* 2.22% p value = 0.019), more Stage 4 (53.9% *vs*. 33.3%, p value = 0.029), more patients with a watch & wait period (32.5% *vs*. 15.5% p value = 0.040) and more bone marrow involvement (47.2% *vs*. 26.6% p value = 0.032) in patients who relapsed than in those who did not, respectively (Figure 3 and Table 1 and 2). For the other parameters, there was no significant difference, although there seemed to be more patients relapsing after treatment with Alkylating agent monotherapy treatment (13.4% *vs*. 2.22% p value=0.060) and less relapse after sole radiation therapy (26.6% *vs*. 13.4% p value=0.093).

Aiming to avoid bias due to monoparametric approach, a multinomial model was built based on 46 parameters (Table S2). Covariance of numeric parameters were tested (Figure S1). These parameters were selected because of less than 30% of missing values in the initial data.

Weighted values (coefficients) were plotted (Figure 5), indicating that altogether, parameters could be useful for relapse prediction. Efficiency of this model, built with the median value of all efficient model (efficiency over 90%) indicates that the prediction efficiency in the total cohort is 92.4%. This first multiparametric approach describes an efficient model, but clinical application seems complex, even with data for all these parameters. To bypass these technical problems, a minimal model has been identify using stepwise analysis using BIC as criterion. This approach identifies only three majors parameters allowing the discrimination between no-relapse and relapse patients (Figure 6 and table S3) these parameters are Complete Response, Very Good Partial Response (VGPR) and AMC>400, the monocyte value at diagnosis

(monocytes values upper than 400/mm^3 implicates an AMC>400=YES). This model, less powerful than the complete model, shows an efficiency of 73.4%.

These three previously identified parameters have been numerically coded as follow:

CR (YES) = 3 points

CR (NO) = 0 point

VGPR (YES) = 0 point

VGPR (NO) = 1 point

AMC>400 (YES) = 1 point

AMC>400 (NO) = 0 point

This strategy allows the calculation of a value, from 0 point to 5 points (Figure 7 and Table 3). In the no relapse group at 10 years, 90% of the patients presents a score of 4-5 *vs*. 46% for relapse group. At the opposite, only 10% of non-relapse presents a score lower than 3 *vs*. 54% for the relapse group. This data indicates that with a simple and easily implementable strategy, our calculation can help to determine the follow-up of the patients after FL.

IV) Discussion:

The study finds some of the expected results such as the predictive impact of a complete remission post 1st line, a stage I or IV at diagnosis, a partial response but also a bone marrow involvement. Bone marrow involvement and stage already part of the FLIPI & FLIPI 2 scores.

Several other results are unexpected: a decreased risk of relapse if the histological grade is 3. Some studies describes that the impact of histological grading on patients' outcome in the rituximab plus doxorubicin containing chemotherapy era is negligible; and there is a tendency to "over-grade" FL. Moreover, results suggest that, at least

when doxorubicin-containing chemotherapy with an anti-CD20 monoclonal antibody is utilized, the outcome of patients with grade 3A FL is similar to that of patients with grade 1/2 disease(19,20).

The increased risk of relapse in patients who have had treatment with alkylating agents only (cyclophosphamide, chlorambucil) was predictable, these non-optimal, palliative treatments are routinely used only in frail patients, unable to receive the gold standard treatment.

As for the results on radiotherapy, although not significant in the study, there is a trend towards a decrease in the risk of relapse. this result should be interpreted with caution because the use of radiotherapy is limited to limited-stage follicular lymphoma (21), which has a better survival and PFS than advanced stages.

The population in this study appears to be younger than the population described by *Santé Publique France*. The median age at diagnosis in France is 65 years for men and 68 years for women(1). Sex ratio of the general population in France between 1990 and 2018: Men 54% *vs.* Woman 46% (as our study). For comparison with the PRIMA population(22), our population is composed of 24.6% FLIPI low level *vs.* 21%, intermediate level: 26.8% *vs.* 36% and high level: 32% *vs.* 43% respectively. It is possible that our study has a high number of "good FL" due to the design of the study, thus minimizing some results.

Probably the lack of significance for FLIPI is related to our statistical analysis by specific FLIPI level and not by level type low intermediate and high. This analysis could have worked with more statistical power. In addition, the FLIPI was shown to be correlated with the risk for progression before 24 months after treatment initiation, POD24, but no one has demonstrated it at 10 years(23).

Our analysis of FLIPI 2 lacks power due to a significant lack of systematic collection of $\beta_2$microglobulin at diagnosis.

We did not find a significant relationship between ALC, AMC and the risk of relapse. Stefaniuk et *al.* did an important review on ANC, ALC, AMC, NLR and LMR as new prognostic factors in Hematological Malignancies and particularly on FL(24).

Wilcox et *al.* found a positive correlation between OS and AMC (AMC cut off value has been calculated 0.57×10^9 cells/ L) (25). In contrast, Watanabe et *al.* found no such association with cut off value of $0{\cdot}34 \times 10^9$ cells/L(26). Marcheselli et *al.* observed that only AMC is a powerful predictor of PFS, and maybe OS in FL patients, treated with combination chemotherapy regimens, containing rituximab. AMC could be used as simple predictive factor, independently of the treatment regimen(27).

For ALC, Siddiqui et *al.* reported that an ALC ≤ 1.0×10^9 cells/l represented poor prognostic parameter for OS in FL, (most of all in patients with Grade 1 or 2 disease) (28).

Mohsen et *al.* reported that shorter OS and PFS were significantly associated with lower LMR when compared with those having higher LMR(13).

For NLR, in comparison with DLBCL (12), there is less evidence for prognostic value in FL, we did not find significant relationship, but this is similar to the study by Shing Fung Lee, Miguel Angel Luque-Fernandez (29) : LMR and NLR were evaluated as valuable prognostic factors. The best cut-off values were 3.20 for LMR and 2.18 for NLR. High LMR at diagnosis was associated with superior PFS (HR 0.31, 95% CI 0.13 to 0.71), as well as high NLR at relapse was associated with poorer post progression survival (HR 1.24, 95% CI 1.04 to 1.49).

LMR above 2 had longer time to treatment compared with those with LMR below 2. And 2-year PFS in patients treated with rituximab was superior in the LMR above 2 group(30).

Kumagai et *al.* evaluated the significance of ALC/AMC ratio in FL patients treated with rituximab-containing chemotherapy. It has been revealed that decreased ALC/AMC ratio was associated with inferior PFS (HR 2.714; 95% CI 1.060–6.948; p= 0.037) and was an independent poor prognostic factor. ALC/AMC ratio might be useful in selection of candidates for watch and wait strategy among FL patients(31).

Our data are vulnerable to operator dependent variability in the reading of a blood count between a technician and a machine with a higher accuracy for the machine (Rumke table). This could decrease the power of this study because not all CBCs are performed by the automated system for reading white cells.

In our study, we found a significant difference in favor of an increased risk of relapse at 10 years for patients who had a Watch & Wait period. Although European(32) and American guidelines(33) recommend watch and wait in advanced stage asymptomatic forms, with no treatment criteria, the question is still debated(34)(35). Rituximab monotherapy is considered as a treatment option for patients with asymptomatic, advanced-stage, low-tumour-burden follicular lymphoma (better time to start of new treatment)(36). We also add that it has already been described that in patients presenting with stage III/IV FL, median PFS following RChemo, is shorter when utilized after period of WW than at diagnosis(37).

It is likely that the lack of significance of the contribution of Rituximab or maintenance is related to a lack of power in our study. Some papers show an interest of maintenance only in patients with partial response post induction, on remission duration criteria, and

PFS. (R-CHOP or R-Bendamustine)(38). While maintenance rituximab appears to improve progression-free survival rates, toxicities, albeit tolerable, are increased and the effect on OS is to date unclear(6,39).

We would have liked to include in the score and analyses the effects of detection of BCL2/IgH+ cells by RQ-PCR on relapse. Indeed, it was shown that the detection of BCL2/IgH+ cells by RQ-PCR was correlated between tumor burden at diagnosis and achievement of clinical and molecular CR and EFS. And quantification of BCL2/IgH+ cells at diagnosis is an independent predictor of outcome. (40). Unfortunately, due to a lack of data, we were unable to include it in this study.

Before the realization of the scores, Figure 4 shows that our different parameters are not covariant with each other, thus avoiding a bias.

One of the strengths of this study is the predictive efficiency of the complete score: 92.35%. This score should be tested and optimized by adding data from other centers. For the moment, this score can only be adapted to a population of patients diagnosed in university hospitals between 2000 and 2010, within the French population.

For a routine use we have realized the score with minimal explanatory model with for parameter : AMC > 400/mm^3, Very Good Partial Response and Complete Response. It is an easy-to-use score with an efficiency of 73,4%.

The weaknesses of this study are the small number of patients, retrospective study, unicentric, with a great heterogeneity of treatment dating from the previous decade, with a representative population of a university hospital. There are several missing data reducing the power of the study (many data were not computerized or stored before 2009 at the University Hospital of Tours).

For the moment there is no score to predict the risk of relapse at 10 years. Such a score could help to personalize the surveillance modalities: increase or decrease the frequency of CT scans/PET scans and follow-up consultations according to the level of risk of recurrence. The increasing number of hematology consultations encourages rationalizing the number of follow-up consultations : less frequent monitoring or delegate a further follow-up to the general practitioner for low-risk patients could be considered.

Furthermore, announcing patients a low risk of recurrence could allow them to get closer to the notion of "cure", which could reassure them and help them project themselves into a disease-free future.

A larger study would be interesting to validate the score.

V) Conclusion:

The risk of relapse at 10 years after a 1st line of treatment in our study is well correlated to response to treatment (CR or PR) and to several independent predictive parameters at diagnosis (Stage 1, Stage 4, B.M.I and W&W period). We have created 2 scores: one complex but very efficient, another one simpler to use in routine but a little less efficient. We need to test these scores on another cohort to validate them.

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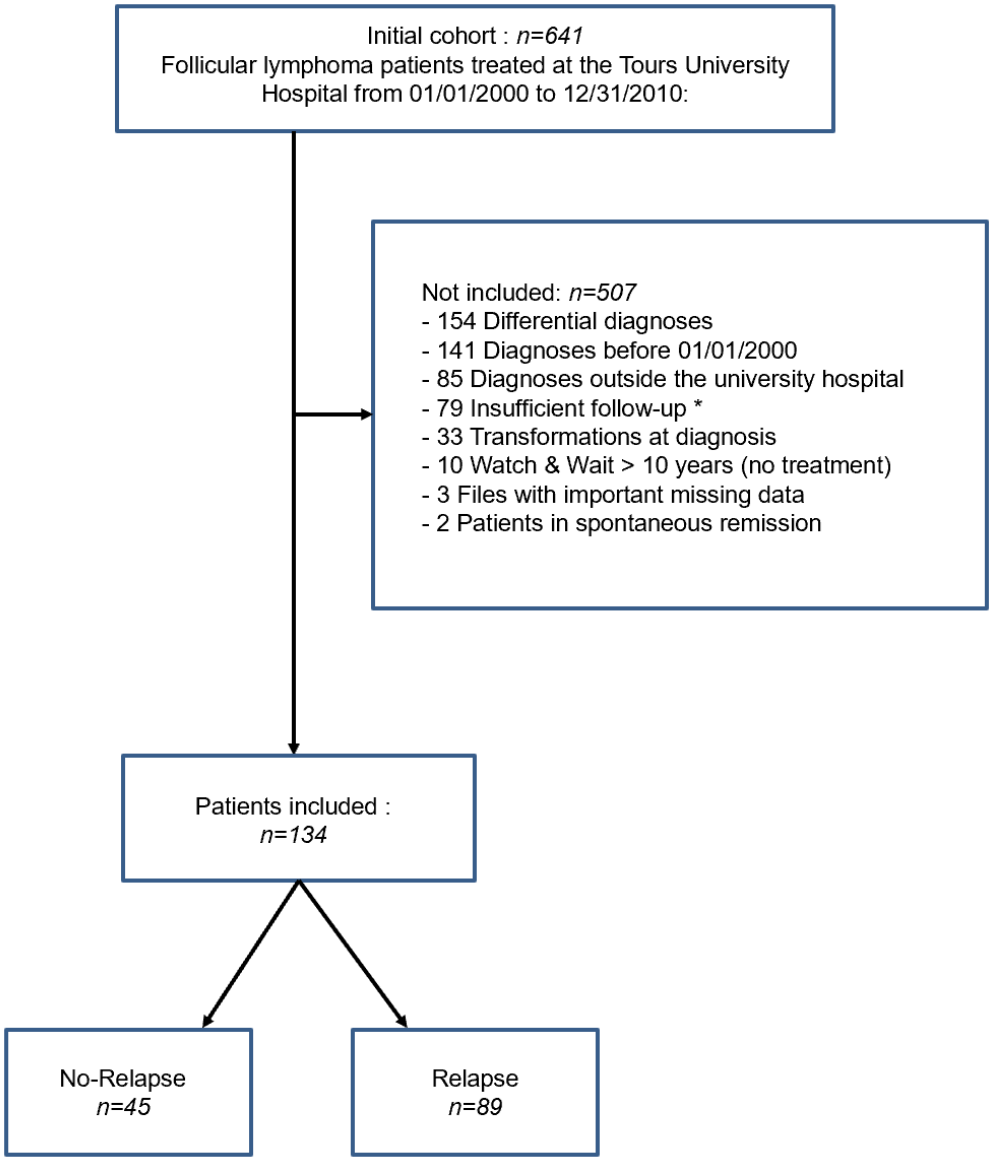
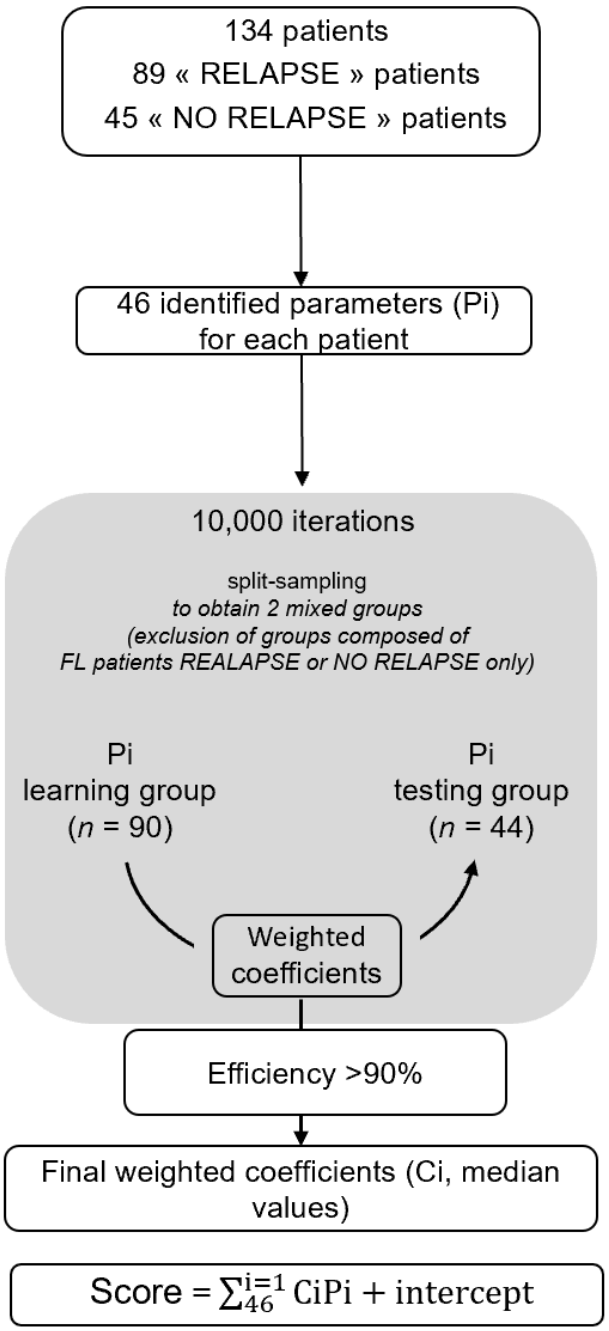
VII) Figures and tables

Figure 1: Flowchart of patients included in the studied cohort.



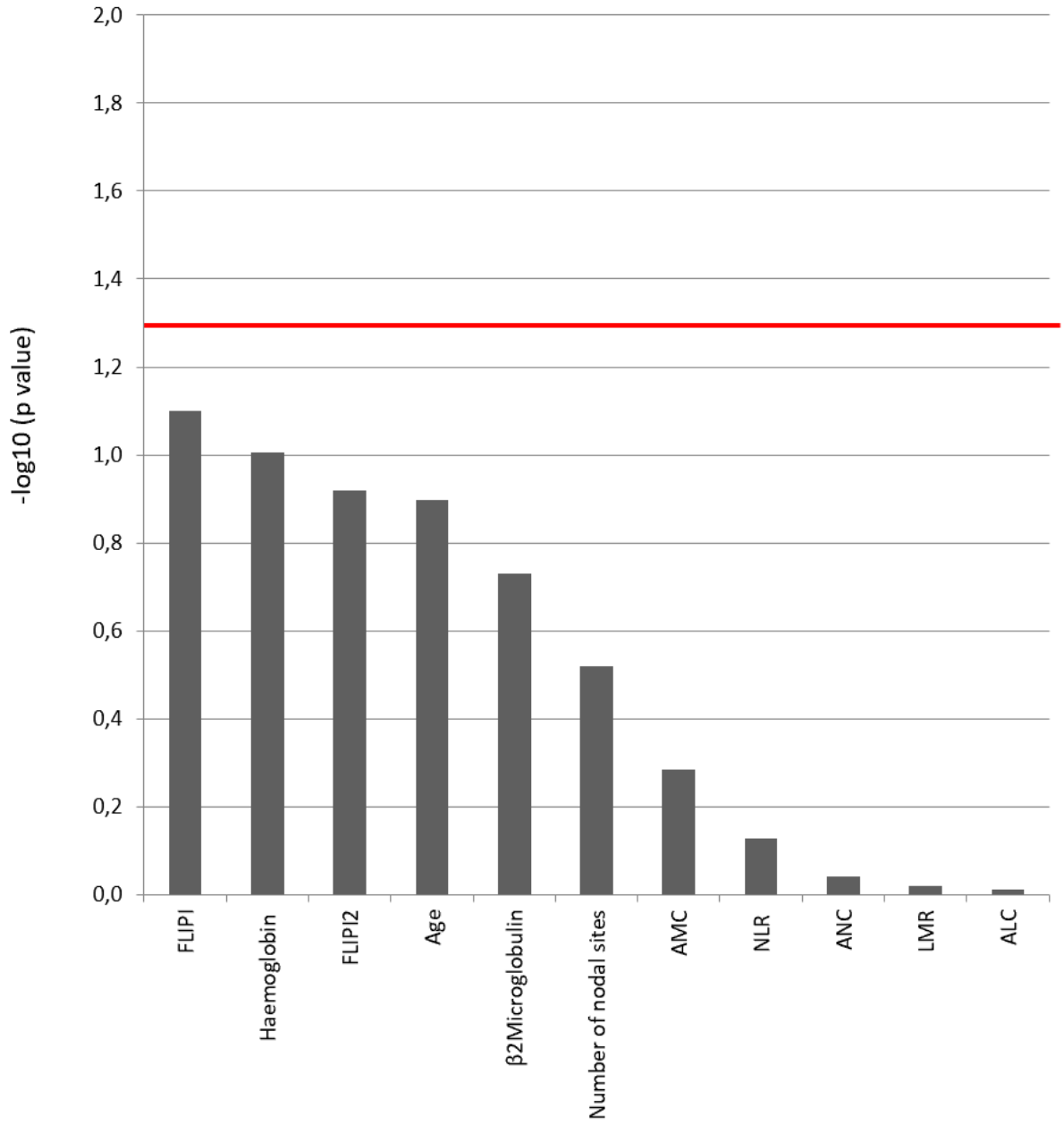
Initially, 641 patients were eligible for inclusion. Following exclusion criteria (pink square), 134 patients were included, split in 89 patients in the relapse group and 45 in the non-relapse group. * = lost to follow-up or ongoing follow-up under 10 years.

Figure 2: Analytic Pipeline allowing the determination of the score, based on split sampling strategy.



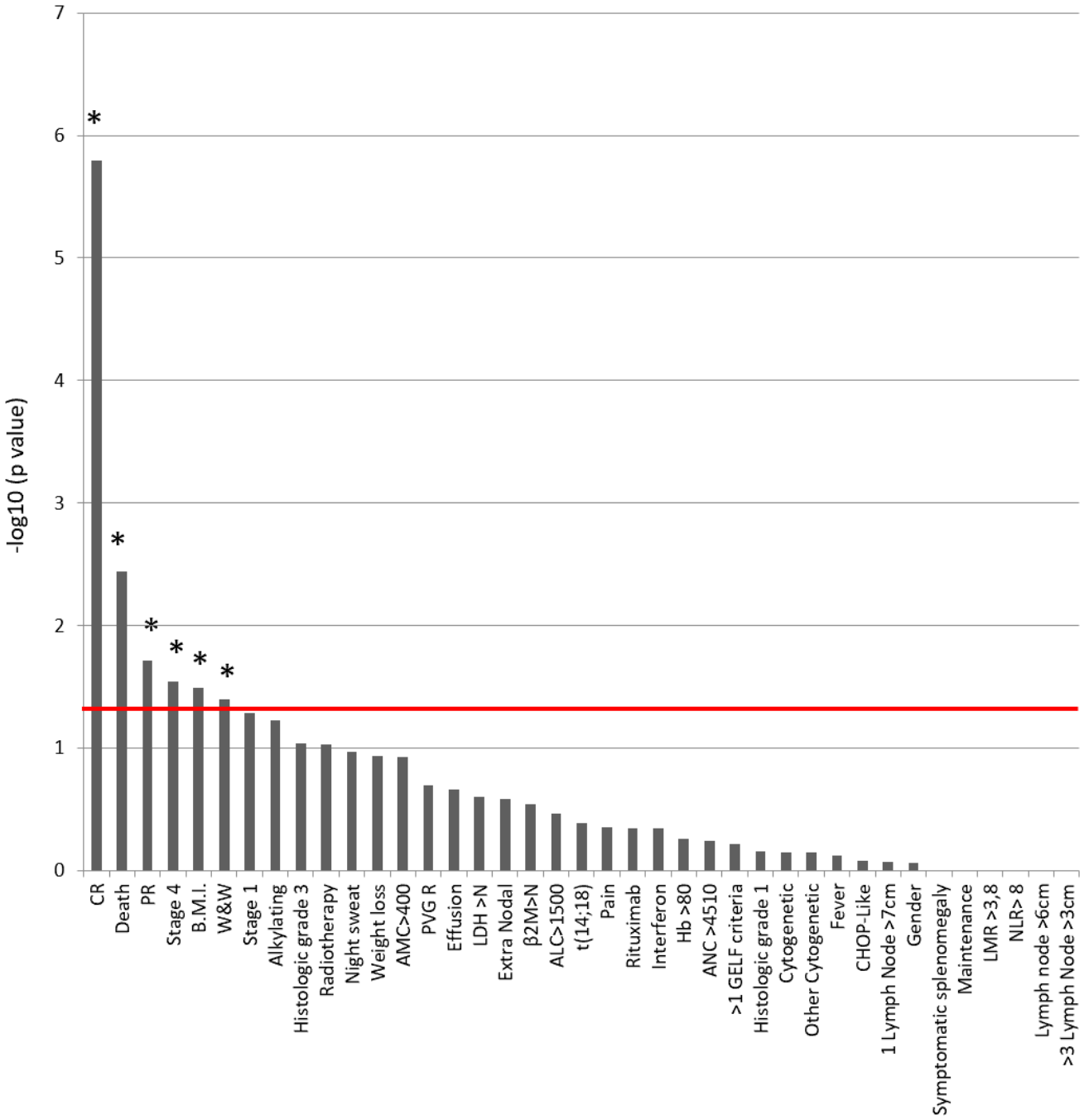
46 parameters for 134 patients were analyzed. 10,000models were built. For each model, 90 patients (60 from relapse group, 30 from non-relapse group) were used as learning group to build a multinomial model, that was tested in the other 44 patients (testing groups). All models allowing a good efficiency of prediction (<90%) were used for the final parameters determination.

Figure 3: Monoparametric analyses of numeric data fail to differentiate both relapse and no-relapse groups.



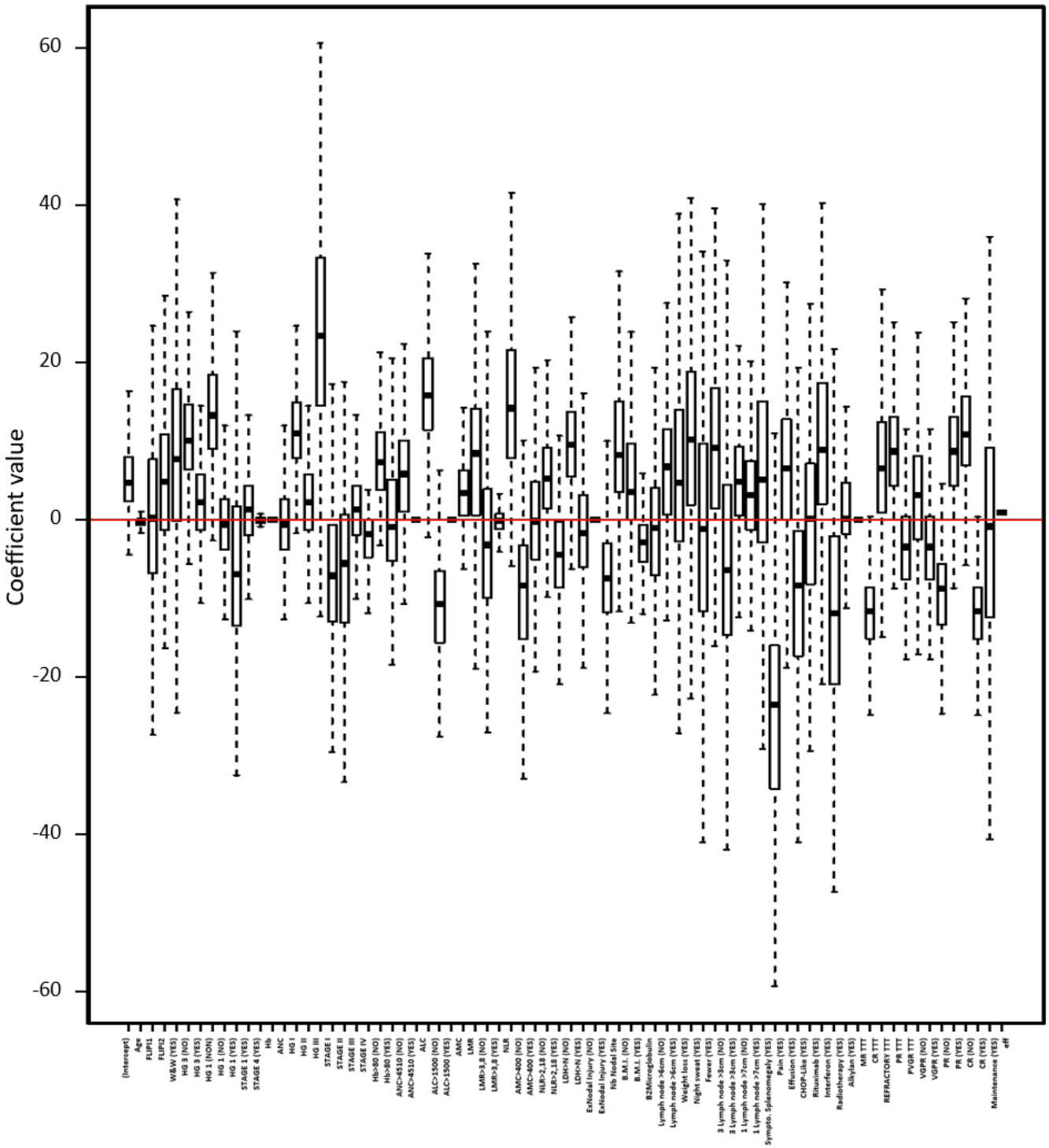
Wilcoxon test was computed for all numeric data including age, Hemoglobin at diagnosis, FLIPI score, aiming to identify a numeric indicator that could predict the relapse at 10 years. Unfortunately, no monoparametric analyses were sufficient to separate both groups. Horizontal red line (significant threshold): -log10(0.05). AMC= Absolute Monocyte Count, NLR=Neutrophil/Lymphocyte Ratio; ANC=Absolute Neutrophil Count; LMR= Lymphocyte/Monocyte Ratio; ALC = Absolute Lymphocytic Count,

Figure 4: Monoparametric analyses of non-numeric data shows differences between relapse and no-relapse groups.



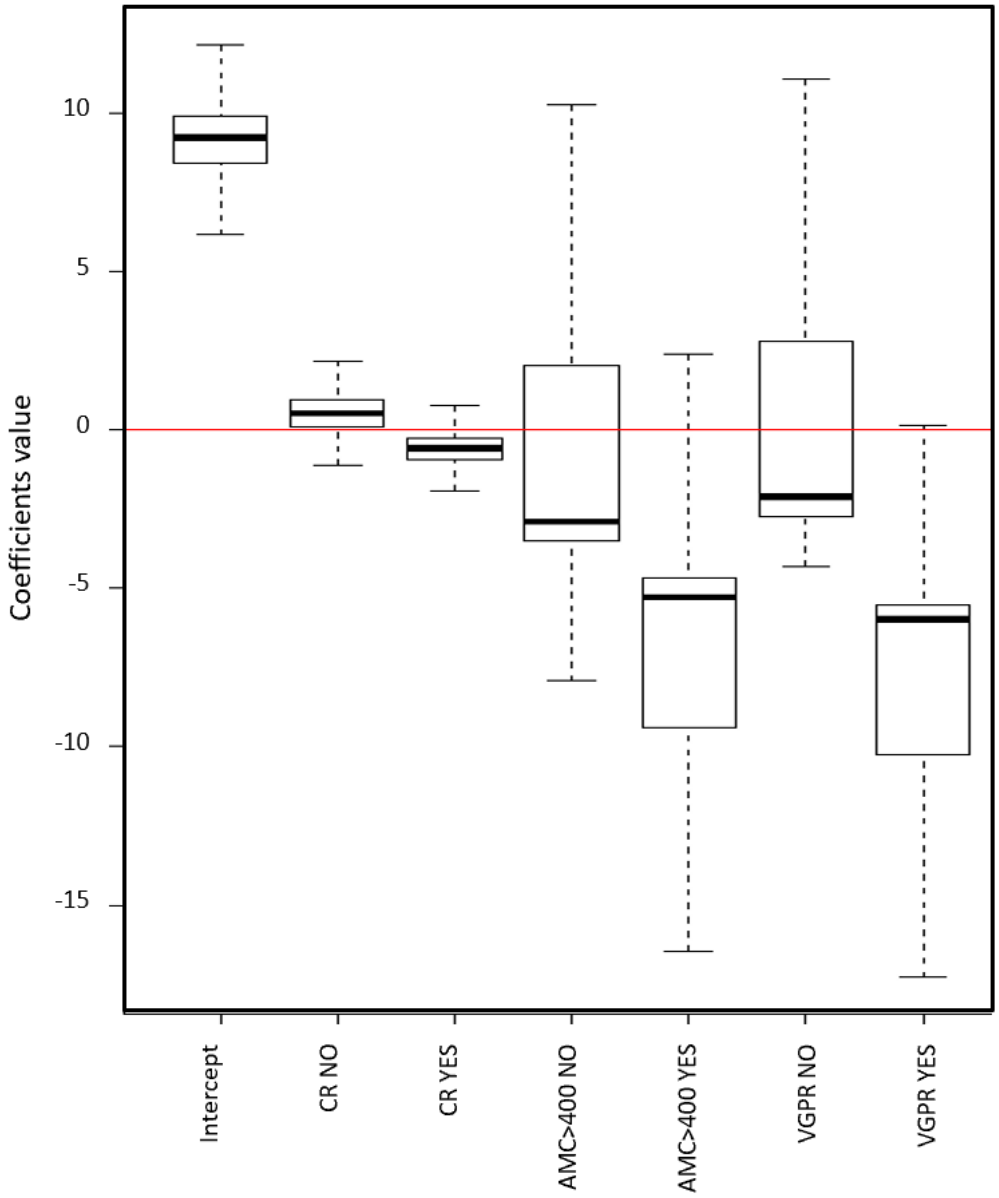
Fisher tests was calculated for all non-numeric parameters (n=39 parameters) and –log10(p value) were plotted. Six parameters (complete response (CR), Death occurrence, Partial Response (PR), Stage 4, Bone Marrow Involvement(B.M.I.) and Watch and Wait period are significantly different between groups, indicating that these elements could be of interest in case of monoparametric analyses. *: Significant difference, $p<0.05$. Horizontal red line (significant threshold): -log10(0.05). AMC>400= Absolute Monocyte Count>400mm^3; β2M= Beta-2-microglobulin; ALC>1500 = Absolute Lymphocytic Count>1500:mm3; ANC>4510=Absolute Neutrophil Count>4510/mm3; LMR>3.8= Lymphocyte/Monocyte Ratio>3.8; NLR>8= Neutrophil/Lymphocyte Ratio>8.

Figure 5: Coefficients of different parameters in the complete model.



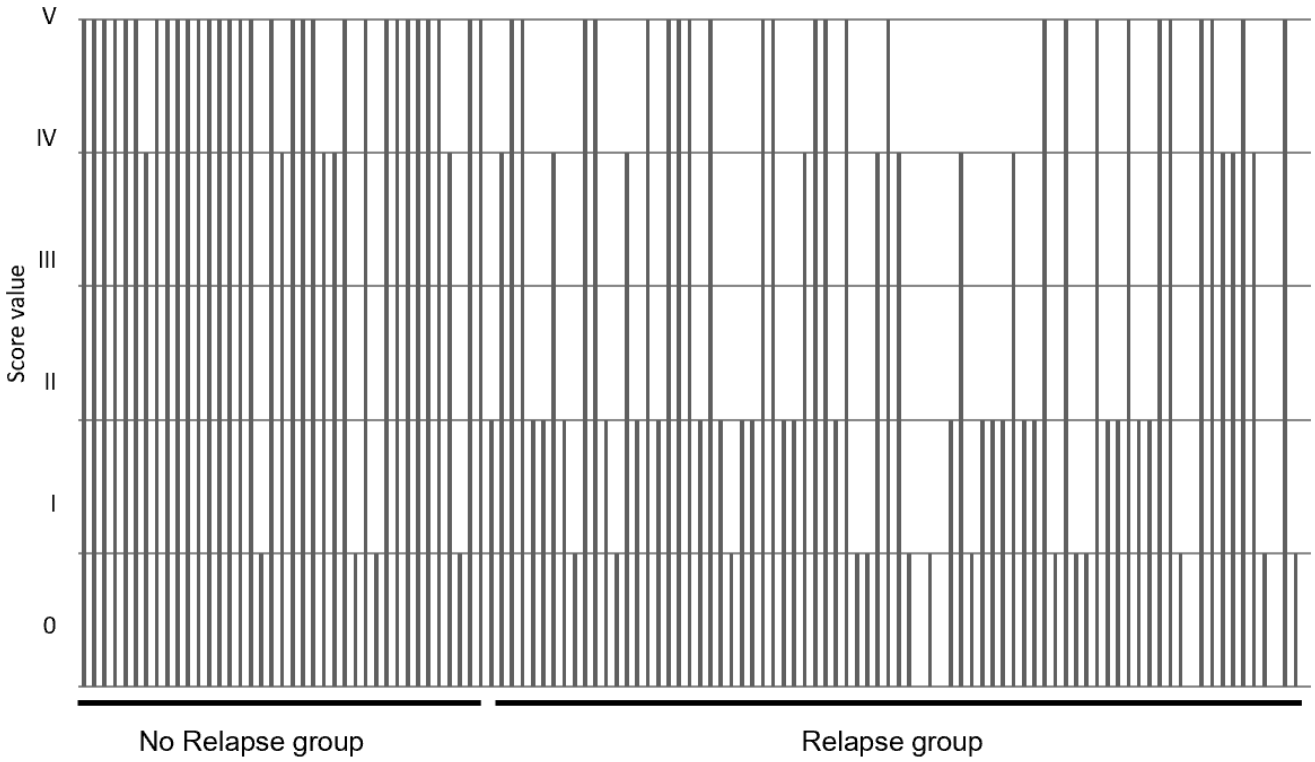
Weighting coefficients of parameters included in the multinomial model are plotted for each iteration (10,000), highlighting constant tendency for each parameter. Median of these coefficients allows an efficiency of 92.35% in the initial cohort. These data indicates that all parameters included in the complete model allow an efficient predictive ability to predict relapse in FL patients at 10 years, using split sampling strategy.

Figure 6: Coefficients values of different parameters in the minimal model.

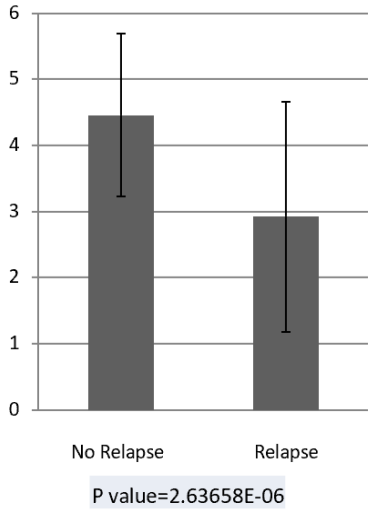


Stepwise analysis allows the identification of three parameters: Complete Response (CR), Very Good Partial Response (VGPR) and AMC>400 (AMC>400= Absolute Monocyte Count>400mm^3) that are sufficient to efficiently separate relapse *vs*. no relapse patients. The efficiency is 75.6% in the complete cohort. The weighting coefficients of these parameters are plotted as box plot.

Figure 7 : A): Distribution of patient scores according to relapse: on the left the NO RELAPSE group and on the right the RELAPSE group.

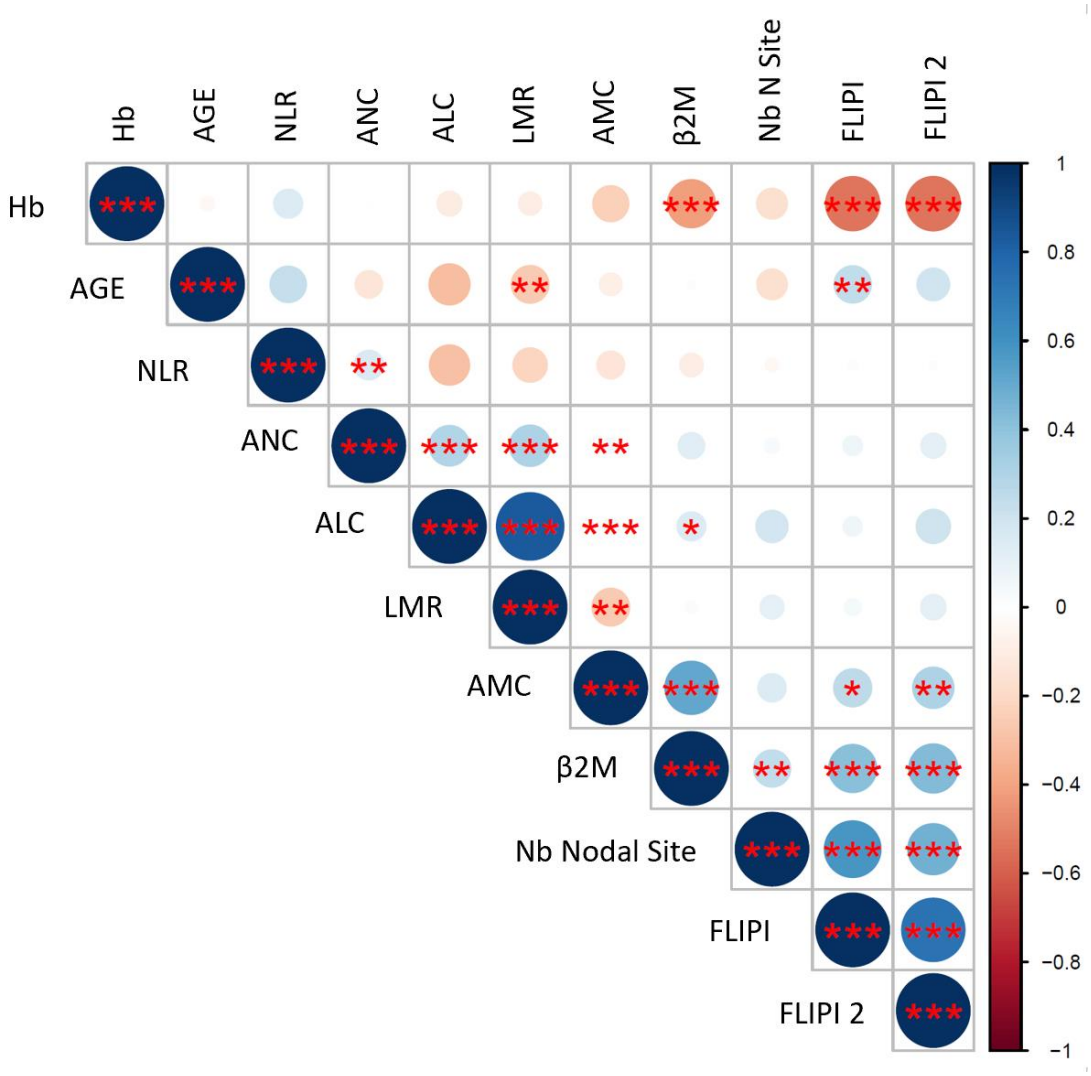


B) Statistical distribution with Wilcoxon test.



There is a statistical difference between the 2 groups on the distribution via the minimal score. (p value = $2.64.10^{-6}$).

Figure S1 : Study of the covariance between the numerical parameters.



No unexpected covariance was found. AMC= Absolute Monocyte Count, NLR=Neutrophil/Lymphocyte Ratio; ANC=Absolute Neutrophil Count; LMR= Lymphocyte/Monocyte Ratio; ALC = Absolute Lymphocytic Count, β2M = $\beta_2$microglobulin level.

Table 1: Parameters at diagnosis.

Parameters at diagnosis	All patients N=134	NA	RELAPSE Patients N= 89	NA	NO REALAPSE Patients N=45	NA	p value
Gender	**F**=63 *(47%)* **M**=71 *(53%)*		**F**=41 *(46,1%)* **M**=48 *(53,9%)*		**F**=22 *(48,9%)* **M**=23 *(51,1%)*		0.854
Age Median (Min;Max)	57.21 [28.4;84.1]		58.2 [32.9;84.1]		55.1 [28.4;75.8]		0.127
FLIPI1		21		14		7	0.079
Low	33 (*24.6%*)		17 (*19.1%*)		16 (*35.5%*)		
Intermediate	36 (*26.8%*)		26 (*29.2%*)		10 (*22.2%*)		
High	43 (*32.0%*)		31 (*34.8%*)		12 (*26.6%*)		
FLIPI2		59		43		16	0.120
Low	32 (*23.8%*)		18 (*20.2%*)		14 (*31.1%*)		
Intermediate	23 (*17.1%*)		13 (*14.6%*)		10 (*22.2%*)		
High	20 (*14.9%*)		15 (*16.8%*)		5 (*11.1%*)		
>1 GELF criteria	103 (*76.8%*)	11	70 (*78.6%*)	6	33 (*73.3%*)	4	0.604
Histologic grade	**I**=60; **II**=46; **III**=10	18	**I**=38; **II**=34; **III**=4	13	**I**=22; **II**=12; **III**=6	5	
Stage	**I**=23; **II**=11; **III**=37; **IV**=63		**I**=11; **II**=7; **III**=23; **IV**=48		**I**=12; **II**=4; **III**=14; **IV**=15		
Hb Median (Min;Max)	135.5 [78;160]	8	134.0 [78;160]	6	138 [83;160]	2	0.09
Hb>80g/L	124 (*92.5%*)		81 (*91%*)		43 (*95.5%*)		0.550
ANC Median (Min;Max)	4470 [1500;37200]	11	4515 [1500;37200]	7	4310 [2510;14470]	4	0.910
ANC >4510/mm3	60 (*44.7%*)		42 (*47.1%*)		18 (*40%*)		0.567
ALC Median (Min;Max)	1426 [130;29890]	10	1380 [130;29890]	7	1540 [340;4000]	3	0.974
ALC>1500/mm3	57 (*42.5%*)		35 (*39.3%*)		22 (*48.8%*)		0.342
AMC Median (Min;Max)	545 [40;3250]	12	580 [40;3250]	8	500 [170;1250]		0.519
AMC>400/mm3	94 (*70.1%*)		59 (*66.3%*)		35 (*77.7%*)		0.118
LMR Median (Min;Max)	2.7361 [0.16;91.97]	12	2.7021 [0.16 ;91.97]	8	2.8440 [0.57;12.80]	4	0.952
LMR >3.8	38 (*28.3%*)		25 (*28.8%*)		13 (*28.8%*)		1.00
NLR Median (Min;Max)	3.04 [0.07;93]	12	3.135 [0.07;93]	7	2.775 [1.04;18.32]	5	0.746
NLR>2.18	83 (*61.9%*)		56 (*62.9%*)		27 (*60%*)		1,000
LDH >N	74 (*55.2%*)		52 (*58.4%*)		22 (*48.8%*)		0.250
Extra Nodal injury	70 (*52.2%*)		52 (*58.4%*)		18 (*40.0%*)		0.257
Site Extra Nodal	**BONE MARROW**=40 **SKIN**=5 **TONSIL**=2 **BONE**=2 (Multiple site)=22		**BONE MARROW**=30 **SKIN**=2 **TONSIL**=2 **BONE**=2 (Multiple site)=17		**BONE MARROW**=10 **SKIN**=3 (Multiple site)=5		
Cytogenetic	89 (*66.4%*)		58 (*65.1%*)		31 (*68.8%*)		0.703
t(14;18)	6 (*4.4%*)		5 (*5.61%*)		1 (*2.22%*)		0.404
Number of Nodal Site							0.302
N<4	**0**=7; **1**=25; **2**=16; **3**=24;		**0**=4; **1**=15; **2**=9; **3**=18;		**0**=3; **1**=10; **2**=7; **3**=6;		
N≥4	**4**=17; **5**=21; **6**=24		**4**=12; **5**=14; **6**=17		**4**=5; **5**=7; **6**=7		
Bone marrow involvement	54 (*40.2%*)		42 (*47.2%*)		12 (*26.6%*)		0.032
β2Microglobulin Median (Min;Max)	2.280 [1.070 ;10.95]	43	2.460 [1.240;10.95]	32	1.970 [1.07;6]	11	0.187
β2M>N	42 (*31.3%*)		29 (*32.5%*)		13 (*28.8%*)		0.289
Lymph node >6cm	44 (*32.8%*)		29 (*32.5%*)		15 (*33.3%*)		1,000
Weight loss	18 (*13.4%*)		15 (*16.8%*)		3 (*6.6%*)		0.116
Night sweat	26 (*19.4%*)		21 (*23.5%*)		5 (*11.1%*)		0.106
Fever	11 (*8.2%*)		8 (*8.9%*)		3 (*6.6%*)		0.750
>3 Lymph Node >3cm	39 (*29.1%*)		26 (*29.2%*)		13 (*28.8%*)		1,000
1 Lymph Node >7cm	40 (*29.8%*)		26 (*29.2%*)		14 (*31.1%*)		0.839
Symptomatic splenomegaly	13 (*9.7%*)		9 (*10.1%*)		4 (*8.8%*)		1,000
Pain	45 (*33.5%*)		32 (*35.9%*)		13 (*28.8%*)		0.445
Effusion	13 (*9.7%*)		11 (*12.3%*)		2 (*4.4%*)		0.218
Watch&Wait	36 (*26.8%*)		29 (*32.5%*)		7 (*15.5%*)		0.040

GELF= Groupe d'Etude des Lymphomes Folliculaires, Hb = Hemoglobin level (g/L), ANC= Absolute Neutrophil Count (/mm^3), ALC= Absolute Lymphocyte Count(/mm^3), AMC= Absolute Monocyte Count(/mm^3), LMR=Lymphocyte/Monocyte Ratio, NLR= Neutrophil/Lymphocyte Ratio, β2M>N= $\beta_2$microglobulin level>normal of laboratory, LDH= lactate dehydrogenase, NA= Not available (Missing data).

Table 2: **Parameters Post 1st line treatment** :

Parameters Post 1st line treatment	All patients N=134	NA	RELAPSE Patients N=89	NA	NO REALAPSE Patients N=45	NA	pvalue
Type of treatment							
CHOP-Like	99 (*73.8%*)		65 (*73.0%*)		34 (*75.5%*)		0.837
RITUXIMAB	85 (*63.4%*)		54 (*60.6%*)		31 (*68.8%*)		0.448
INTERFERON	21 (*15.6%*)		16 (*17.9%*)		5 (*11.1%*)		0.451
RADIOTHERAPY	24 (*17.9%*)		12 (*13.4%*)		12 (*26.6%*)		0.093
ALKYLAN	13 (*9.7%*)		12 (*13.4%*)		1 (*2.22%*)		0.059
Treatment response:		2		2			
REFRACTORY	15		15				
SD	1		1				
VGPR	20 (*14.9%*)		16 (*17.9%*)		4 (*8.8%*)		0.202
PR	15 (*11.1%*)		14 (*15.7%*)		1 (*2.22%*)		0.019
CR	81 (*60.4%*)		41 (*46%*)		40 (*88.8%*)		$1.61x10^{-6}$
Maintenance	31 (*23.1%*)		21 (*23.6%*)		10 (*22.2%*)		1.00
Maintenance type							
ENDOXAN	2		1		1		
INTERFERON	15		12		3		
RITUXIMAB	14		8		6		
Relapse	89 (*66.4%*)		89				
Histology of the relapse	54		54				
Transformation	9		9				
Death	17		16 (*17,97%*)		1 (*2,22%*)		0.004
Median Duration of participation	64.69 [1.84;236.81]		29.86 [1.84;154.91]		145.6 [109.8;236.8]		
Median PFS	42.9897 [0.8542;218.64]		23.39 [0.8542;135.7536]		141.93 [63.34;218.64]		

VGPR= Very Good Partial Response, PR= Partial Response, CR= Complete Response, MR= Minimal Response, NA= Not available (Missing data), SD= Stable Disease.

Table 3: **Detail of the distribution of patients with the minimal score.**

Score value	No relapse	Relapse
V	30 (77%)	25 (32%)
IV	5 (13%)	11 (14%)
III	0 (0%)	0 (0%)
II	0 (0%)	24 (30%)
I	4 (10%)	14 (18%)
O	0 (0%)	5 (6%)

Supplementary Table 1: **P value. fold changes and means of all parametric parameters studied between relapse vs no relapse groups (Wilcoxon test)**

	p-value	log10(p-value)	Fold change	FC	mean Relapse group	mean no-relapse group
FLIPI	0.08	1.10	1.26	1.26	2.28	1.82
Hemoglobin	0.10	1.01	0.97	0.97	130.95	135.58
FLIPI2	0.12	0.92	1.34	1.34	1.89	1.41
Age	0.13	0.90	1.07	1.07	58.02	54.24
β_2Microglobulin	0.19	0.73	1.21	1.21	2.88	2.38
Number of nodal site	0.30	0.52	1.12	1.12	3.45	3.09
AMC	0.52	0.28	1.16	1.16	653.15	564.15
NLR	0.75	0.13	1.27	1.27	5.47	4.32
ANC	0.91	0.04	1.07	1.07	5 552.87	5 178.15
LMR	0.95	0.02	2.09	2.09	6.82	3.25
ALC	0.97	0.01	4.07	4.07	6 455.83	1 584.81

AMC=Absolute Monocyte Count(/mm^3), NLR=Neutrophil/Lymphocyte Ratio; ANC=Absolute Neutrophil Count(/mm^3), LMR=Lymphocyte/Monocyte Ratio, ALC=Absolute Lymphocyte Count(/mm^3).

Supplementary Table 2: **Coefficient's value. related to figure 4.**

Intercept	4.68
Age	-0.28
FLIPI	0.20
FLIPI2	4.86
W&W YES	7.66
HG 3 NO	10.04
HG 3 YES	2.21
HG 1 NO	13.25
HG 1 YES	-0.60
Stage 1 YES	-6.97
Stage 4 YES	1.28
HB	-0.06
ANC	0.00
HG.I	-0.60
HG.II	10.95
HG.III	2.21
Stage.I	23.34
Stage.II	-7.13
Stage.III	-5.56
Stage.IV	1.28
Hb>80 NO	-1.82
Hb>80 YES	7.31
ANC>4510 NO	-0.97
ANC>4510 YES	5.82
ALC	0.00
ALC>1500 NO	15.82
ALC>1500 YES	-10.72
AMC	0.04
LMR	3.41
LMR>3.8 NO	8.42
LMR>3.8 YES	-3.20
NLR	-0.15
AMC>400 NO	14.16
AMC>400 YES	-8.35
NLR>2.18 NO	-0.19
NLR>2.18 YES	5.17
LDH>N NO	-4.46
LDH>N YES	9.56
ExNodal Injury NO	-1.67
ExNodal Injury YES	0.00
Nb Nodal Site	-7.48
B.M.I. NO	8.24
B.M.I. YES	3.54
B2Microglobulin	-2.86
Lymph node>6cm NO	-1.10
Lymph node>6cm YES	6.73
Weight loss YES	4.65
Night sweat YES	10.17
Fewer YES	-1.16
3 Lymph node >3cm NO	9.15
3 Lymph node >3cm YES	-6.44
1 Lymph node >7cm NO	4.84
1 Lymph node >7cm YES	3.12
Sympto.Splenomegaly YES	5.14
PAIN YES	-23.53
Effusion YES	6.55
CHOP-like YES	-8.37
Rituximab YES	0.11
Interferon YES	8.92
Radiotherapy YES	-11.92
Alkylan YES	0.11
SD TTT	0.00
CR TTT	-11.69
Refractory TTT	6.56
PR TTT	8.69
PVGR TTT	-3.46
VGPR NO	3.10
VGPR YES	-3.46
PR NO	-8.76
PR YES	8.69
CR NO	10.82
CR YES	-11.69
Maintenance YES	-0.85

Supplementary Table 3: **Coefficient's value. related to figure 6.**

Intercept	9.21
CR NO	0.52
CR YES	-0.56
AMC>400 NO	-2.90
AMC>400 YES	-5.27
VGPR NO	-2.10
VGPR YES	-5.97

CR=Complete Response, VGPR= Very Good Partial Response, AMC>400=Absolute Monocyte Count>400mm^3

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MARC Maxime 42 pages – 6 tableaux – 8 figures

Contexte : Le Lymphome folliculaire (LF) est une maladie reconnue comme incurable. Pourtant il existe des patients qui ne rechutent pas dans les 10 ans après la prise en charge initiale. Aucun score pronostique n'est disponible pour déterminer la rechute à 10 ans après une première ligne de traitement chez les patients traités pour un lymphome folliculaire (LF). Nous avons recherché dans une cohorte monocentrique des facteurs associés au risque de rechute dans les 10 ans chez des patients atteints de LF.

Méthodes : Dans cette étude rétrospective (inclusion entre 2000 et 2010), 134 patients atteints de LF au CHU de Tours ont été inclus, 45 n'ont pas rechuté après traitement contre 89 qui ont rechuté avant 10 ans. Pour l'analyse univariée, les statistiques de Wilcoxon et de Fisher ont été utilisées. Le modèle multinomial linéaire a été calculé pour pondérer les paramètres et a été validé en utilisant une stratégie d'échantillon fractionné avec 10 000 itérations. Pour le modèle minimal, la méthode « *stepwise* » a été appliquée. Enfin, un score cliniquement implémentable basé sur des modèles minimaux est proposé.

Résultats : L'analyse univariée montre que, par exemple, une réponse complète (p value <0.001), un stade I (p value=0,052) diminuent le risque de rechute, et qu'une réponse partielle (p value=0,019), un stade IV (p value=0,029), une période de « *watch and wait* » (p value=0.040) et une atteinte médullaire (p value=0,032) sont associés à un risque plus élevé de rechute. Différents scores ont été créés pour expliquer la rechute par les données obtenues au moment du diagnostic, aboutissant à un score simple, basé sur la réponse au traitement et le compte absolu de monocytes au moment du diagnostic.

Conclusions : Ce score pourrait être utile, après validation sur une cohorte externe, pour le suivi des patients traités pour LF, afin d'adapter la durée et la fréquence du suivi spécialisé.

Mots clés : Lymphome folliculaire, rechute, score.

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