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A prognostic index predicting survival in transformed Waldenström macroglobulinemia

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ABSTRACT

Histological transformation into diffuse large B-cell lymphoma is a rare complication in patients with Waldenström macroglobulinemia (WM) and is usually associated with a poor prognosis. The objective of this study was to develop and validate a prognostic index for survival of patients with transformed WM. Through this multicenter, international collaborative effort, we developed a scoring system based on data from 133 patients with transformed WM who were evaluated between 1995 and 2016 (training cohort). Univariate and multivariate analyses were used to propose a prognostic index with 2-year survival after transformation as an endpoint. For external validation, a dataset of 67 patients was used to evaluate the performance of the model (validation cohort). By multivariate analysis, three adverse covariates were identified as independent predictors of 2-year survival after transformation: elevated serum lactate dehydrogenase (2 points), platelet count $<100x10^9$/L (1 point) and any previous treatment for WM (1 point). Three risk groups were defined: low-risk (0-1 point, 24% of patients), intermediate-risk (2-3 points, 59%; hazard ratio = 3.4) and high-risk (4 points, 17%; hazard ratio = 7.5). Two-year survival rates were 81%, 47%, and 21%, respectively (P<0.0001). This model appeared to be a better discriminant than either the International Prognostic Index or the revised International Prognostic Index. We validated this model in an independent cohort. This easy-to-compute scoring index is a robust tool that may allow identification of groups of transformed WM patients with different outcomes and could be used for improving the development of risk-adapted treatment strategies.

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Introduction

Waldenström macroglobulinemia (WM) is a rare B-cell lymphoproliferative disorder characterized by lymphoplasmacytic bone marrow infiltration and production of an IgM monoclonal component.[1] Histological transformation (HT) to diffuse large B-cell lymphoma (DLBCL) has been reported to occur in 2% to 10% of WM patients.[2,3] Most transformed patients present with high-risk features such as extranodal disease, elevated serum lactate dehydrogenase (LDH) levels and high International Prognostic Index (IPI) scores.[3,4] Patients who experience HT have an inferior survival compared to patients whose disease does not transform during its course.[3,5] Patients with transformed WM are mainly treated with strategies used in *de novo* DLBCL but cure rates are low, with a median survival from the time of HT ranging from 16 to 32 months.[3-5] However, as some patients experience prolonged survival, identifying those with high-risk features in order to select them for therapeutic intensification and/or novel agents is important. In a previous study of 77 patients, we identified elevated LDH and time to HT greater than 5 years as possible predictors of shorter survival[4] but there is a need to develop an accurate predictive model for overall survival in a larger cohort of patients with transformed WM.

Prognostic indices have been validated and are used routinely in aggressive non-Hodgkin lymphomas. The IPI was established in 1993 based on the clinical data of patients with *de novo* aggressive non-Hodgkin lymphoma treated with cyclophosphamide-doxorubicine-oncovin-prednisone (CHOP)-like chemotherapy.[6] The revised IPI (R-IPI) was proposed in 2006 for a more accurate prediction of outcome in the era of treatment with CHOP plus rituximab (R-CHOP).[7] However, data pertaining to the prognostic value of these scores in the setting of transformed WM are sparse. Moreover, a majority of patients with transformed WM (65% to 76%) present with high IPI scores, probably limiting the accuracy of the IPI in this setting.

The objectives of this large international collaborative study were to collect data on the characteristics of a large number of patients with transformed WM both at the time of the diagnosis of WM and at HT and to develop a prognostic index predicting survival following transformation, the transformed Waldenström International Prognostic Index (tWIPI). The final model was validated in an independent cohort of patients with transformed WM.

Methods

Patients and data collection for development of the prognostic model

Patients older than 18 years were included in the study if they had a diagnosis of WM and a concurrent or sequential histological diagnosis of DLBCL. The diagnosis of WM was based on criteria established in the Second International Workshop on WM.[8] Patients with a diagnosis of indolent lymphoma other than WM were excluded. Histological assessment of transformation was mandatory for being considered in this study. We retrospectively identified 133 patients diagnosed with HT between January 1995 and December 2016 from French Innovative Leukemia Organization (FILO) centers (France), the Dana-Farber Cancer Institute (Boston, MA, USA), University College London Hospitals (UK) and Nieuwegein (the Netherlands) (details of the centers are provided in *Online Supplementary Table S1*). This retrospective study was conducted in accordance with the Declaration

Table 1. Patients' characteristics at diagnosis of Waldenström macroglobulinemia and at transformation in the training and validation sets.

Variable	Training set	Validation set
Entire cohort	**n = 133**	**n = 67**
Median age, years	64 (range, 32-86)	63 (range, 27-82)
Sex male/female, ratio	75/58 (1.3/1)	42/25 (1.7/1)
Prior MGUS history	20 (15%)	4 (17%)
WM characteristics (concurrent WM and HT excluded)	**n = 116**	**n = 64**
Serum IgM level, g/L	17.7 (range, 1.4-66.7)	26 (range, 0.9-106)
IPSS score	n = 76	n = 43
0-1	31 (41%)	15 (40%)
2	30 (39%)	7 (18%)
≥ 3	15 (20%)	16 (42%)
Median number of regimens prior to HT	1 (range, 0-9)	1 (range, 0-9)
Therapies before HT	n = 98	n = 54
Chlorambucil	43 (44%)	15 (28%)
Fludarabine-based regimens	41 (42%)	16 (30%)
Bendamustine +/- rituximab	19 (19%)	6 (11%)
CHOP +/- rituximab	17 (17%)	11 (20%)
Bortezomib-based regimens	15 (15%)	7 (13%)
RCD	14 (14%)	12 (22%)
Ibrutinib	5 (5%)	1 (2%)
Autologous SCT	4 (3%)	0 (0%)
Rituximab (alone or in combination)	67 (50%)	41 (76%)
HT characteristics	**n = 133**	**n = 67**
Median age, years	68 (range, 33-89)	69 (range, 31-89)
PS (0-1/≥ 2)	59/48 (55%/45%)	30/18 (63%/37%)
B symptoms	56 (47%)	30 (49%)
Extranodal involvement	111 (86%)	46 (69%)
Serum IgM level, g/L	6.9 (range, 0-66.6)	6.3 (range, 0.3-43.9)
Absolute neutrophils, x 10^9/L	4.1 (range, 0.2-20.2)	3.6 (range, 0.4-12.3)
Absolute lymphocytes, x 10^9/L	0.9 (range, 0.1-56)	1.2 (range, 0.2-30)
Hemoglobin, g/L	104 (range, 46-155)	111 (range, 43-154)
Platelets, x 10^9/L	172 (range, 9-610)	186 (range, 8-576)
Elevated LDH	85 (72%)	37 (55%)
Albumin level < 3.5 g/dL	62 (56%)	30 (51%)
Stage III or IV	96 (86%)	43 (83%)
Median number of lines	1 (range, 0-5)	2 (range, 0-5)
First-line therapies after HT	n = 127	n = 63
CHOP-like regimen +/- rituximab	102 (80%)	42 (67%)
DHAP +/- rituximab	10 (8%)	3 (6%)
GEMOX +/- rituximab	3 (2%)	3 (6%)
Rituximab-containing regimen	110 (87%)	44 (70%)
Autologous SCT	20 (16%)	13 (21%)
Allogeneic SCT	6 (5%)	2 (3%)

MGUS: monoclonal gammopathy of undetermined significance; WM: Waldenström macroglobulinemia; HT: histological transformation; IPSS: International Prognostic Scoring System; CHOP: cyclophosphamide-doxorubicin-oncovin-prednisone; RCD: rituximab-cyclophosphamide-dexamethasone; PS: performance status; LDH: lactate dehydrogenase; DHAP: dexamethasone-cytarabine-cisplatin; GEMOX: gemzar-oxaliplatin.

of Helsinki and was approved by the institutional review board at each participating institution.

The clinical and disease characteristics considered as candidate prognostic factors were analyzed after reviewing medical records at the time of WM diagnosis and of HT. Variables considered as covariates for model building are detailed in the *Online Supplementary Methods*. In addition, the IPI and the R-IPI were assessed.[6,7] The presence of *MYD88*^{L265P} mutation was tested by allele-specific polymerase chain reaction on bone marrow samples at diagnosis of WM.[9]

Validation cohort

The data from 96 patients diagnosed between 1988 and 2018 and treated at the Mayo Clinic (Rochester, MN, USA), or in Athens (Greece), Salamanca (Spain), Amsterdam (the Netherlands) and Toulouse (France) were analyzed (*Online Supplementary Table S1*). Information on the three parameters of the tWIPI was available for 67 patients.

Statistical methods

The main endpoint of statistical analyses was 2-year overall survival calculated from the diagnosis of HT to the date of death or last follow-up. The survival curves were plotted using the Kaplan-Meier method and compared using the log-rank test for categorical variables. Univariate and multivariate analyses were performed using the Cox proportional hazards model. For continuous variables, the cutoffs were defined on the basis of published thresholds, for ease of clinical use. The multivariate Cox proportional hazards model included all variables with a *P*-value <0.10 by univariate analysis. A manual backward selection of covariates was used. The results were presented as hazard ratio (HR) and 95% confidence intervals (95% CI). A weighted risk score was assigned to each factor included in the final multivariable model. The prognostic score was then defined as the sum of single-risk parameters. Risk subgroups were pooled according to the number of patients within each category and the relative risk of death. The discriminatory value of the prognostic model and the score was assessed using concordance probability estimates by the Harrell concordance index (C-index).[10] Calibration was assessed using the May and Hosmer test for goodness-of-fit. An internal validation of both the model and score was performed using the bootstrap resampling method[11] (replication on 2,000 different samples drawn with replacement). External validation was performed in a second dataset of subjects. All tests of statistical significance were two-sided, and a *P*-value <0.05 was considered statistically significant. Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Patients' characteristics

The patients' characteristics are summarized in Table 1. Of the 133 patients, 17 (13%) were diagnosed at the time of initial diagnosis of WM. Fifty-six percent of patients were male and the median age at WM diagnosis was 64 years (range, 32-86 years). According to the International Prognostic Scoring System (IPSSWM)[12] when available, 31 patients (41%) were classified as low risk, 30 (39%) as intermediate risk and 15 (20%) as high risk. Following the diagnosis of WM, treatment was not initiated in 35 patients (26%) until the diagnosis of HT. The median number of lines of therapy for WM was one (range, 0-9). Half of the patients (n=67) had received rituximab alone or in combination for WM before HT.

The median time from WM diagnosis to HT was 4.3 years (range, 0-25 years). The median age at HT was 68 years (range, 33-89 years). Extranodal involvement by the DLBCL component was noted in 86% of patients. Serum LDH was elevated in 85 patients (72%). The first-line reg-

Table 2. Results of the univariate analysis of prognostic factors.

Characteristic	N. of patients (%)	2-year OS, %	P
Sex			
Male	75 (56)	54.7	0.64
Female	58 (44)	48.3	
Previous treatment for WM			
No	35 (26)	65.7	0.02
Yes	98 (74)	46.9	
Prior rituximab exposure			
No	66 (50)	57.6	0.01
Yes	67 (50)	46.3	
Time to transformation			
Less than 5 years	77 (58)	59.7	0.006
5 years or more	56 (42)	41.1	
Age at transformation			
65 years or less	44 (33)	45.5	0.61
More than 65 years	89 (67)	55.1	
Performance status (ECOG)			
0-1	59 (55)	50.9	0.22
More than 1	48 (45)	45.8	
B symptoms			
Absent	62 (53)	58.1	0.02
Present	56 (47)	41.1	
Extranodal involvement			
Absent	18 (14)	61.1	0.78
Present	111 (86)	51.4	
Ann-Arbor stage			
I-II	16 (14)	43.8	0.88
III-IV	96 (86)	49	
Leukocyte count			
4 x 10^9/L or more	56 (48)	46.4	0.73
Less than 4 x 10^9/L	61 (52)	55.6	
Hemoglobin level			
100 g/L or more	68 (57)	52.9	0.78
Less than 100 g/L	52 (43)	46.2	
Platelet count			
100 x 10^9/L or more	88 (75)	56.8	0.006
Less than 100 x 10^9/L	29 (25)	27.6	
Serum albumin			
35 g/L or more	48 (44)	54.2	0.80
Less than 35 g/L	62 (56)	50	
Serum LDH			
Less than or equal to ULN	33 (28)	78.8	0.001
Greater than ULN	85 (72)	42.4	
Serum β2-microglobulin			
Less than 3 mg/L	16 (28)	50	0.37
3 mg/L or more	41 (71)	53.7	

OS: overall survival; WM: Waldenström macroglobulinemia; ECOG: Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; ULN, upper limit of normal.

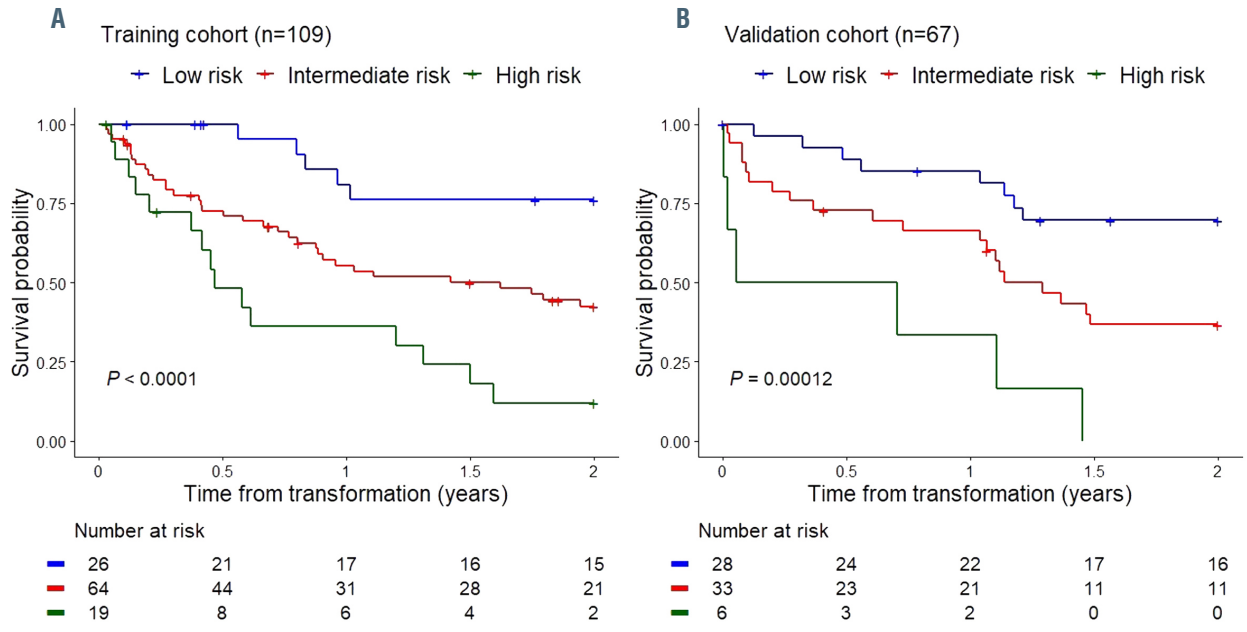

Figure 1. Kaplan-Meier curves for survival after transformation according to subgroups defined by the transformed Waldenström International Prognostic Index. (A) The model was built using three variables: previous treatment for Waldenström macroglobulinemia, lactate dehydrogenase at transformation and platelet count at transformation. It divided the cohort into three risk groups: low-, intermediate-, and high-risk with 2-year survival rates after transformation of 80.8%, 46.9% and 21.1%, respectively. (B) Validation cohort: 2-year survival after transformation of 71.4%, 39.4% and 0%, for the low-, intermediate-, and high-risk groups, respectively.

imens given at HT are listed in Table 1. The median number of lines of therapy given for HT was one (range, 0-5). The majority of patients (80%) were treated with first-line regimens used in *de novo* DLBCL (CHOP +/- rituximab). Rituximab was part of the first-line treatment for HT in 110 patients (87%).

The median follow-up for all patients was 6.4 years (range, 0.1-33.7 years) after the diagnosis of WM and 2.3 years (range, 0-16.6 years) after HT. The median overall survival after HT was 19 months (95% CI: 12-31 months) (*Online Supplementary Figure S1A*). When we divided the cohort into two groups on the basis of the date of diagnosis of HT (using three cutoffs: 2004, 2008 and 2012), we did not observe any significant differences in terms of survival (*data not shown*). At the date of last follow-up, 83 patients (62%) had died. The majority of deaths were related to progressive disease (75%) or infections (14%).

Prognostic factors

In univariate analysis, six variables that were associated with lower 2-year survival after HT were identified for inclusion in multivariate analyses: previous treatment for WM (P=0.02), prior exposure to rituximab (P=0.01), time to transformation more than or equal to 5 years (P=0.006), elevated LDH (P=0.001), B symptoms (P=0.02) and platelet count less than $100x10^9$/L (P=0.006) (*Online Supplementary Figure S2*). Age and Eastern Cooperative Oncology Group performance status at HT were of no significant prognostic value. Among other variables included in the IPI, Ann Arbor stage III and IV and extranodal involvement were not only very common (86% for both) but also not associated with worse outcome. Serum IgM level at transformation was of no significant prognostic value (P=0.51). The prognostic values of the clinical and biological characteristics for survival at transformation are reported in Table 2.

Development of the prognostic model and the scoring system

In multivariate analysis, independent factors for 2-year survival after HT were elevated serum LDH (P=0.003; HR=3.6; 95% CI: 1.53-8.50), platelet count less than $100x10^9$/L (P=0.03; HR=1.8; 95% CI: 1.04-3.19) and previous treatment for WM (P=0.04; HR=2; 95% CI: 1.04-3.94) (Table 3). Bootstrapping of the multivariable model showed good internal validity. The May and Hosmer goodness-of-fit test did not identify any calibrations issues (P>0.6 for each stratum) and the model's Harrell C-index was 0.75 (CI 95%: 0.65-0.84). The prognostic model comprised these three variables all available for 109 patients. Based on the relative hazard ratios, platelet count $<100x10^9$/L and previous treatment for WM were scored with 1 point and elevated serum LDH with 2 points. As a result, there were groups of patients with scores ranking from 0 to 4. Patients with score 0 were combined with those with score 1 because they were too few to constitute a separate risk group. Patients with scores of 2 and 3 were combined because they both corresponded to a group with an intermediate prognosis. The tWIPI was thus created and comprised three risk categories: low (0-1 point, 24% of patients), intermediate (2-3 points, 59%) and high (4 points, 17%). The 2-year survival rates were 81%, 47% and 21%, respectively (P<0.0001). The distribution of patients into these three groups and hazard ratios are shown in Table 4. The survival curves are shown in Figure 1A. The prognostic index displayed high model performances, as assessed by concordance probability estimates. The Harrell C-index was 0.75 (95% CI: 0.66-0.85). The May and Hosmer goodness-of-fit test did not identify any calibrations issues (P>0.7 for each stratum). Excluding patients with concurrent disease (WM and DLBCL), the model also identified three risk groups with significant different 2-year survivals and displayed good discrimination

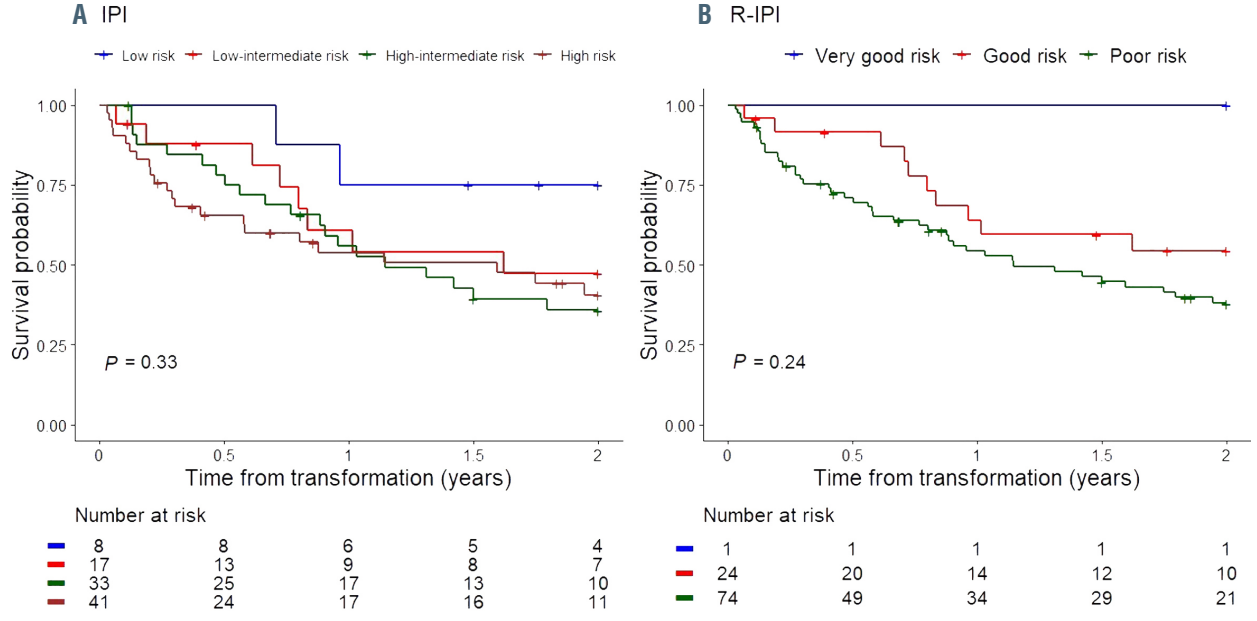

Figure 2. Kaplan-Meier curves for survival after transformation according to risk group as defined by (A) the International Prognostic Index (IPI) and (B) the revised IPI (R-IPI).

Table 3. Results of the Cox regression analysis: final prognostic model.

Variable	Adverse factor	Hazard ratio	95% CI	P
Previous treatment for WM	≥ 1	2	1.04-3.94	0.04
Platelet count at HT	< 100 x 10^9/L	1.8	1.04-3.19	0.03
LDH at HT	> ULN	3.6	1.53-8.50	0.003

95% CI: confidence interval; WM: Waldenström macroglobulinemia; HT: histological transformation; LDH: lactate dehydrogenase; ULN: upper limit of normal.

Table 4. The transformed Waldenström International Prognostic Index: outcome and relative risk of death according to risk group.

Risk group	Score	N. of patients (%)	2-year OS %	Median survival, months	HR	95% CI
Low	0-1	26 (24)	80.8	NR	1.0	NA
Intermediate	2-3	64 (59)	46.9	16.8	3.4	1.3-8.7
High	4	19 (17)	21.1	4.8	7.5	2.7-20.7

OS: overall survival; HR: hazard ratio; 95% CI: 95% confidence interval; NR: not reached; NA: not applicable.

and calibration properties (*Online Supplementary Figure S3A* and *Online Supplementary Table S2A*).

Comparison with the International Prognostic Index and its revised form

Complete information for the parameters of the IPI (age, serum LDH level, performance status, Ann Arbor stage and number of extranodal sites of disease) was available for 99 of the 109 patients used to build the tWIPI. The distribution of patients into the four IPI and the three R-IPI risk groups is shown in *Online Supplementary Table S3*. Neither the IPI nor the R-IPI was able to discriminate subgroups of patients with significantly different survival outcomes (*P*=0.33 and 0.24, respectively) (Figure 2).

External validation

We applied the tWIPI to 67 other patients with transformed WM. The median follow-up from WM diagnosis and from HT was 8.8 (range, 0.2-20.8) and 3.1 years (range, 0-13.4) respectively. The main clinical characteristics of this cohort are shown in Table 1. The median survival after HT was 18 months (95% CI: 13 months – not reached) (*Online Supplementary Figure S1B*). The model successfully divided the cohort into three groups with 2-year survival rates of 71%, 39% and 0% for the low-, intermediate- and high-risk groups, respectively (*P*=0.0001) (Figure 1B). The prognostic significance of the tWIPI in the external cohort demonstrated good performance for discrimination. The Harrell C-index was 0.79 (95% CI: 0.64-0.92). The May and Hosmer goodness-of-fit test did not identify any calibrations issues (*P*>0.8 for each stratum). In the same way as for the training cohort, the results were similar when patients with concurrent disease were excluded (*Online Supplementary Figure S3B* and *Online Supplementary Table S2B*).

Impact of *MYD88* mutation status on survival after transformation

By combining the training and the validation cohorts, we were able to analyze 64 patients with available data on *MYD88* mutation status at the time of WM. Forty-

three patients (67%) carried a *MYD88*^{L265P} mutation and 21 (33%) had wild-type (WT) alleles. The characteristics of the subset of patients for whom *MYD88* mutation results were available and those for whom the status was not known (n=136) were comparable, except for a shorter time to transformation in the cohort with known *MYD88*^{L265P} mutation status. The 2-year survival rates after HT were 67% and 49% in patients with *MYD88*^{WT} and *MYD88*^{L265P}, respectively (P=0.018) (*Online Supplementary Figure S4*).

Discussion

The prognosis of transformed indolent lymphomas is historically poor despite combination chemoimmunotherapy, especially in chronic lymphocytic leukemia (Richter syndrome) and WM.[4,13] Characterization of adverse prognostic factors in this setting is important for identifying specific risk groups and comparing different therapeutic approaches. There is no specific prognostic score for transformed WM and the existing scores such as the IPI appear not to discern prognosis appropriately.

We developed an easy-to-use prognostic index relying on a model with three risk groups defined by the presence, or not, of one or more of the following parameters: previous treatment for WM, serum LDH level and platelet count at the time of HT. Previous treatment for WM is typically associated with prior exposure to rituximab and a prolonged time to transformation. This parameter could reflect chemo-resistance and/or immunological impairment related to the disease and its previous treatment. Serum LDH level is a well-established prognostic factor both in hematologic malignancies and solid tumors.[14-17] Its prognostic role has been validated in both WM and DLBCL, being one of the variables included in the revised IPSSWM and the IPI, respectively.[6,18] Low platelet count, also part of the IPSSWM, is usually associated with a poor prognosis in hematologic malignancies[12,19] and could reflect a critical level of bone marrow involvement. For development of the prognostic score, only pretreatment characteristics were considered. Nevertheless, despite the retrospective nature of the study, first-line treatments at HT were quite uniform with a majority of patients being treated with R-CHOP chemoimmunotherapy, similarly to *de novo* DLBCL. This is unlikely to have influenced the analysis.

Using this index, we were able to separate patients with transformed WM into three risk groups. In patients with a good prognosis (score 0-1), the 2-year survival rate was 81%. This indicates that the standard R-CHOP regimen could lead to prolonged control of the high-grade component in a majority of these patients. In the intermediate-risk group (score 2-3), less than half of the patients were alive after 2 years. In this group, the role of consolidative therapies such as high-dose therapy with stem cell transplantation in younger patients or association with targeted therapies would be interesting to investigate. For patients in the high-risk group (score 4), the outcome was very poor with a 2-year survival of 21%. Innovative therapies are required and these patients should be directed to clinical trials with new agents. Chimeric antigen receptor (CAR) T-cell therapies have been shown to be effective and to lead to durable responses in relapsed/refractory DLBCL including transformed follicular lymphomas.[20-22] The potential effectiveness of CAR T-cell therapy in transformed WM has recently been suggested based on one case report with complete response maintained at 1 year.[23] Clinical trials are needed to evaluate the place of CAR T-cell therapy in WM and transformed WM.

An important finding of our study is that the IPI and the R-IPI do not seem appropriate to identify patients with significantly different outcomes in the particular setting of transformed WM. Application of the IPI in our cohort was not able to separate the intermediate-risk and high-risk groups, most patients with transformed WM falling in the high-intermediate or the high-risk category. In addition, of the IPI risk factors, only serum LDH level showed prognostic relevance in univariate analyses. The IPI and the R-IPI have been studied in other transformed lymphomas such as transformed follicular lymphoma and marginal zone lymphoma and could predict survival.[24,25] A Richter syndrome prognostic score has been proposed and is based on five adverse risk factors.[13] Interestingly, the three variables of our score are part of the Richter syndrome score.

We performed internal validation by bootstrap[11] and confirmed marked stability of the model developed. Despite the rarity of the disease, we were able to validate the prognostic index in an independent cohort of patients with transformed WM. Our model displayed good discrimination properties in the validation cohort, identifying three risk groups with similar 2-year survival after transformation to the ones in the training set. This external validation confirms the robustness and the reproducibility of the tWIPI.

Advances in the biology of WM have demonstrated the role of mutation status in outcome prediction. The *MYD88*^{L265P} mutation is found in 95% of WM patients and represents an important diagnostic marker.[26] *MYD88*^{WT} WM patients seem to have a worse outcome and a higher incidence of DLBCL events.[5,27] In our study, molecular parameters were available only for one-third of the patients and so could not be included in the initial analysis. By combining the two cohorts, we could analyze 64 patients and found that patients with *MYD88*^{L265P} mutation had a significantly lower 2-year survival rate after transformation compared to patients with *MYD88*^{WT} disease. Although this finding should be confirmed by multivariate analysis in a larger cohort of patients, it is in line with previous studies showing that *MYD88* mutations are associated with worse survival in de novo DLBCL.[28-30]

Our study has some limitations. First, the majority of patients were exposed to chlorambucil and/or fludarabine-based regimen as therapy for WM. Half of the patients received rituximab alone or in combination and very few patients were treated with Bruton tyrosine kinase inhibitors such as ibrutinib. The tWIPI warrants further validation in a cohort of patients with transformed WM treated with more contemporary regimens at the time of WM. Secondly, in the present study, we were not able to assess the clonal relationship between the original WM and DLBCL. It is known that the occurrence of DLBCL in WM can result from HT or arise as a *de novo*, not clonally related lymphoma.[31] This phenomenon has been widely described in Richter syndrome in which *de novo* DLBCL usually carries a better prognosis (median survival of 5 years *vs.* 8-16 months for clonally

related DLBCL transformation).[32] Nevertheless, one strength of our study was the strict and homogeneous definition of transformation by restricting inclusion to histologically documented transformation.

In conclusion, through this large multicenter study aimed at identifying factors predicting survival in transformed WM, we developed a prognostic model and validated it in an independent series of patients. Retrospective and prospective international multicenter studies are needed to define the optimal therapeutic strategies for transformed WM. Our prognostic score could help physicians individualize treatment strategy and improve the management of patients with transformed WM by selecting the most appropriate treatment.

Disclosures

No conflicts of interest to disclose.

Contributions

ED, LK, AD, and JJC designed the study; ED, SZ, EK, SD, RG, CT, BH, ET, CP, JPA, TG, GI, JMV, SG, JD, SL, and JB collected patients' clinical data; ED and LK performed the statistical analysis; ED, LK, AD and JJC wrote the manuscript, all authors contributed to analyzing and interpreting the data and provided final approval of the manuscript.

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References

1. Swerdlow SH, Berger F, Pileri SA, et al. Lymphoplasmacytic lymphoma. In: Swerdlow SH, Campo E, Harris NL, et al., editors. WHO Classification of Tumours of Haematopoietic and Lymphoïd Tissues. Lyon, Franc. IARC 2008. pp. 194-195.
2. Leblond V, Johnson S, Chevret S, et al. Results of a randomized trial of chlorambucil versus fludarabine for patients with untreated Waldenström macroglobulinemia, marginal zone lymphoma, or lymphoplasmacytic lymphoma. J Clin Oncol. 2013; 31(3):301-307.
3. Castillo JJ, Gustine J, Meid K, et al. Histological transformation to diffuse large B-cell lymphoma in patients with Waldenström macroglobulinemia. Am J Hematol. 2016;91(10):1032-1035.
4. Durot E, Tomowiak C, Michallet AS, et al. Transformed Waldenström macroglobulinaemia: clinical presentation and outcome. A multi-institutional retrospective study of 77 cases of the French Innovative Leukemia Organization (FILO). Br J Haematol. 2017; 179(3):439-448.
5. Zanwar S, Abeykoon JP, Durot E, et al. Impact of MYD88 L265P mutation status on histological transformation of Waldenström macroglobulinemia. Am J Hematol. 2020;95(3):274-281.
6. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med. 1993;329(14):987-994.
7. Sehn LH, Berry B, Chhanabhai M, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood. 2007;109(5):1857-1861.
8. Owen RG, Treon SP, Al-Katib A, et al. Clinicopathological definition of Waldenstrom's macroglobulinemia: consensus panel recommendations from the Second International Workshop on Waldenstrom's Macroglobulinemia. Semin Oncol. 2003;30(2):110-115.
9. Xu L, Hunter ZR, Yang G, et al. MYD88 L265P in Waldenstrom macroglobulinemia, immunoglobulin M monoclonal gammopathy, and other B cell lymphoproliferative disorders using conventional and quantitative allele-specific polymerase chain reaction. Blood. 2013;121(11):2051-2058.
10. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med. 1996;15(4):361-387.
11. Efron B, Tibshirani RJ. An Introduction to the Boostrap. Vol. 57: Chapman and Hall/CRC. 1994.
12. Morel P, Duhamel A, Gobbi P, et al. International prognostic scoring system for Waldenstrom macroglobulinemia. Blood. 2009;113(18):4163-4170.
13. Tsimberidou AM, O'Brien S, Khouri I, et al. Clinical outcomes and prognostic factors in patients with Richter's syndrome treated with chemotherapy or chemoimmunotherapy with or without stem-cell transplantation. J Clin Oncol. 2006;24(15):2343-2351.
14. Solal-Céligny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood. 2004;104(5):1258-1265.
15. Hoster E, Dreyling M, Klapper W, et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. Blood. 2008;111(2):558-565.
16. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for Multiple Myeloma: a report from International Myeloma Working Group. J Clin Oncol. 2015;33(26):2863-2869.
17. Manola J, Atkins M, Ibrahim J, et al. Prognostic factors in metastatic melanoma: a pooled analysis of Eastern Cooperative Oncology Group trials. J Clin Oncol. 2000; 18(22):3782-3793.
18. Kastritis E, Morel P, Duhamel A, et al. A revised international prognostic score system for Waldenström's macroglobulinemia. Leukemia. 2019;33(11):2654-2661.
19. Ochi Y, Kazuma Y, Hiramoto N, et al. Utility of a simple prognostic stratification based on platelet counts and serum albumin levels in elderly patients with diffuse large B cell lymphoma. Ann Hematol. 2017; 96(1):1-8.
20. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017;377(26):2531-2544.
21. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicenter, phase 1-2 trial. Lancet Oncol. 2019; 20(1):31-42.
22. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2019;380(1):45-56.
23. Bansal R, Jurcic JG, Sawas A, et al. Chimeric antigen receptor T cells for treatment of transformed Waldenström macroglobulinemia. Leuk Lymphoma. 2020;61(2):465-468.
24. Alonso-Alvarez S, Magnano L, Alcoceba M, et al. Risk of, and survival following, histological transformation in follicular lymphoma in the rituximab era. A retrospective multicentre study by the Spanish GELTAMO group. Br J Haematol. 2017; 178(5):699-708.
25. Alderuccio JP, Zhao W, Desai A, et al. Risk factors for transformation to higher-grade lymphoma and its impact on survival in a large cohort of patients with marginal zone lymphoma from a single institution. J Clin Oncol. 2018 Oct 12. [Epub ahead of print]
26. Treon SP, Xu L, Yang G, et al. MYD88 L265P somatic mutation in Waldenström's macroglobulinemia. N Engl J Med. 2012; 367(9):826-833.
27. Treon SP, Gustine J, Xu L, et al. MYD88 wild-type Waldenstrom macroglobulinaemia: differential diagnosis, risk of histological transformation, and overall survival. Br J Haematol. 2018;180(3):374-380.
28. Rovira J, Karube K, Valera A, et al. MYD88 L265P mutations, but no other variants, identify a subpopulation of DLBCL patients of activated B-cell origin, extranodal involvement, and poor outcome. Clin Cancer Res. 2016;22(11):2755-2764.
29. Dubois S, Viailly PJ, Bohers E, et al. Biological and clinical relevance of associated genomic alterations in MYD88 L265P and non-L265P-mutated diffuse large B-cell lymphoma: analysis of 361 cases. Clin Cancer Res. 2017;23(9):2232-2244.
30. Schmitz R, Wright GW, Huang DW, et al. Genetics and pathogenesis of diffuse large B-cell lymphoma. N Engl J Med. 2018; 378(15):1396-1407.
31. Talaulikar D, Biscoe A, Lim JH, et al. Genetic analysis of diffuse large B-cell lymphoma occurring in cases with antecedent Waldenström macroglobulinaemia reveals different patterns of clonal evolution. Br J Haematol. 2019;185(4):767-770.
32. Rossi D, Spina V, Gaidano G. Biology and treatment of Richter syndrome. Blood. 2018;131(25):2761-2772.