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International prognostic scoring system for Waldenström's Macroglobulinemia

Short title: Prognostic index for Waldenström Macroglobulinemia

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ABSTRACT

Recently, many new drugs have been developed for the treatment of Waldenström's macroglobulinemia (WM). In order to optimize the treatment according to the prognosis and to facilitate the comparison of trials we developed an international scoring system for WM (ISSWM) in a series of 587 patients with clearly defined criteria for diagnosis and for initiation of treatment. With a median follow-up of 64 months, the median survival after treatment initiation was 87 months. Five adverse covariates were identified: age >65 years, hemoglobin ≤11·5 g/dL, platelet count ≤100 x 10^9/L, ß2-microglobulin >3 mg/L and serum monoclonal protein concentration >7.0 g/dL. Low risk patients (27% of patients) presented with ≤1 adverse characteristic and age ≤65 years, intermediate risk patients (38%) with 2 adverse characteristics or only age >65 years and high risk patients (35%) with >2 adverse characteristics. Five-year survival rates were 87%, 68% and 36% respectively (p<0·0001). The ISSWM retained its prognostic significance in subgroups defined by age ≤65 years, >65 years, treatment with alkylating agent, and purine analogue. Thus, the combination of age, ß2-microglobulin, monoclonal protein concentration and blood counts may provide a means to design risk-adapted studies. However, independent validation and new biological markers may enhance its significance.

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INTRODUCTION

Waldenström macroglobulinemia (WM) is a lymphoproliferative disorder characterized by production of serum monoclonal immunoglobulin (Ig) M, lymphoplasmacytic bone marrow infiltration[1-3] and a unique gene expression profile, compared to chronic lymphocytic leukemia and multiple myeloma.[4,5] Median survival ranged between 60 and 120 months.[6-9] While approximately one-fourth of patients are asymptomatic and diagnosed by chance,[7,9] most are symptomatic and therefore require treatment in order to control symptoms related to tumor burden, such as anemia, organomegaly or hyperviscosity,[1-3] or to IgM characteristics. Mortality of asymptomatic patients was not significantly different from that expected in the general population, whereas the standard mortality ratio of patients with symptomatic WM was significantly higher (5.4) [10]. Until recently, first-line therapy of WM was based on single-agent therapy with alkylating agents, nucleoside analogues or rituximab.[1-3] During the last 5 years, improved response rates were reported with the combination of 2 or 3 of these drugs or RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone);[11,12] however, follow-up is usually limited. Encouraging results have also been reported with allogeneic or autologous stem cell transplantation[2,3] in advanced phase, or bortezomib,[13] lenalidomide,[14] and thalidomide[2,3,11]. In the absence of randomized trial results and recognized system for comparing different series of patients, treatment recommendations of the 3rd International Workshop suggested that individual patient considerations should be weighed in making the choice of a first-line agent.[11] Therefore, agreement in the treatment algorithm of WM patients would be greatly facilitated by the availability of a simple and accurate prognostic index for overall survival similar to the International

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Prognostic Index (IPI) for aggressive NHL,[15] the Follicular Lymphoma IPI,[16] or the International Staging System for Multiple Myeloma (ISSMM).[17]

In retrospective analyses, advanced age,[6-9,18-22] low hemoglobin concentration,[6-9,19-22] low platelet count,[6-8,18-21] low albumin concentration,[7,8,19,22] and elevated serum β2-microglobulin [7-9,19,20] were constantly associated with a poor clinical outcome. Other adverse characteristics found in 3 or more studies were: leucopenia,[6,7,20] high concentration of serum IgM paraprotein,[7,9,22] the pattern or the percentage of bone marrow infiltration,[18,19,23] a poor performance status,[18,20] and the presence of constitutional symptoms.[6,9,19,21] From these analyses few prognostic indices have been proposed, but none of them have been widely accepted and used. Finally, in most series both asymptomatic and symptomatic patients have been included.

Therefore, 7 cooperative groups or institutions decided to join their data in order to design a prognostically meaningful international scoring system for WM patients requiring therapy (ISSWM) because of a symptomatic disease, according to the Athens workshop recommendations[24]

METHODS

Patients and design of the study

The marked difference of outcome between symptomatic and asymptomatic patients and the identification of internationally validated criteria for initiating therapy prompted us to focus on symptomatic patients requiring a first-line therapy. The design of the study is presented below.

Inclusion criteria

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Inclusion criteria were as follows: (1) proven WM according to the 2nd International Workshop recommendations.[25] All patients presented with serum monoclonal IgM and bone marrow lymphoplasmacytic infiltrate >20% either on bone marrow smears or on trephine biopsy. (2) Symptomatic disease at the time of initiation of therapy, namely: presence of constitutional symptoms (weakness, fatigue, recurrent fever, night sweats, or weight loss), cytopenia defined by a disease-related hemoglobin ≤10.0 g/dL, platelet count <100 x 10^9/L, bulky and/or symptomatic lymphadenopathy, splenomegaly or hepatomegaly, symptomatic hyperviscosity syndrome or IgM-related symptoms defined by severe neuropathy, symptomatic nephropathy, systemic amyloidosis, symptomatic cryoglobulinemia, or cold-agglutinin disease[24]. (3) Complete clinical and biological evaluation, comprising serum β2-microglobulin, at the time of the initiation of therapy in at least 95% of the observations provided by each institution, with no more than 2 missing covariates in incomplete observations. (4) Initiation of therapy and diagnosis before January 2002. This analysis was a retrospective study that relied on patients included in several trials conducted according to legal guidelines in each country with IRB approval at the time of study. Consent for this study was part of the informed consent given for these trials in accordance with the Declaration of Helsinki.

Endpoint

In order to design a prognostically meaningful scoring system for choosing first-line therapy in symptomatic WM patients requiring treatment, the main endpoint was overall survival from initiation of first-line therapy to the stopping date, the date of last follow-up or the date of death if they occurred earlier. Experts defined as objective of the study, the identification in the series of at least 25% high-risk patients with a median survival of 4 years or less.

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Sample size estimates

Sample sizes were calculated following the available recommendations, as reported in the Data Supplements. The number of patients needed was estimated to be 600. Given the rarity of the disease, only internal validation was carried out, because at least 450 additional patients were estimated necessary for external validation of the final model.

Data collection

Clinical and biologic characteristics

Because of the necessity for multivariate analyses of observations with all covariates available, a limited number of variables was selected using a consensus method in order to build a simple and practical model.[26] Thus, all covariates identified as prognostic factors in at least two previous studies at the time of the design were selected, and the final questionnaire gathered the following variables: age, gender, treatment initiation criteria listed above, the time from diagnosis to treatment initiation, and the following characteristics assessed at the time of treatment initiation: the presence of splenomegaly, hepatomegaly, lymphadenopathy, hemoglobin concentration, platelet, white blood cell, absolute lymphocyte, absolute neutrophil counts, monoclonal (M) protein concentration estimated by densitometry, albumin, and β2-microglobulin concentrations, the latter being expressed as an absolute value and the ratio of the measured value to the upper limit of normal for the institution.

Validation of the data

By June 2004, 661 observations from 7 institutions or groups were submitted for potential inclusion. Validation rested on a descriptive analysis of data for the identification of values out of range. A checklist of 35 controls was applied through a SAS procedure and 894 queries were sent to investigators. In addition, using a

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classification analysis (by means of the SAS fastclus procedure), 6 observations appeared very different from the others and they have been completely verified. At the end of this process, 587 observations were suitable for the statistical analyses. Seventy-four observations were not validated because of the lack of consistency of the data (25 patients) or initiation of therapy after January 1st, 2002 (15 patients) or submission by one institution of incomplete clinical evaluation at the time of the initiation of therapy in a significant percentage of the observations, according to inclusion criteria detailed above. The data of this center have been completely excluded (34 patients). The survival of these 74 patients was not different from that of other patients (p=0.10).

Statistical analyses

Statistical analysis was performed by means of SAS software (SAS Institute Inc Cary, NC 25513) and S-PLUS (Insightful Corp, Seattle, WA 98109). All tests of statistical significance were two-sided, and statistical significance was defined as $P \leq .05$. Descriptive statistics included all clinical and demographic characteristics and time values. Results were expressed by the means and standard deviations (SD) for continuous variables, the frequencies and percentages for categorical variables. The relationship between the different covariates was investigated using Pearson correlation coefficient for numeric variables and chi-square test otherwise.

Identification of covariates and their cut-off (univariate analysis)

For qualitative variables, survival and SD were estimated by the method of Kaplan and Meier, and compared by use of the log rank test.[27] The prognostic value of continuous variables was assessed using the Cox proportional hazards model. The final decisions on the choice of the covariates to be included in multivariate analyses, the use of a cut-off and the choice of its value were taken by all authors during a

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meeting, on the basis of the Cox proportional hazards model, tests of the assumption of its underlying hypothesis, the p value of univariate test, the statistical significance of the previously reported cut-off values in the present series, the results of Fisher algorithm,[28] recursive partitioning analysis[29] (a brief technical description of these methods is given in the Data Supplements) and the necessity, for clinical practice, to build a model based on a small number of covariates.[26]

Identification of the prognostic model

Multivariate Cox proportional hazard survival analysis was performed on all selected covariates, after transformation if required (full model). The simplification of this full model was done with the stepwise selection at the level p=0·15. The stability of the selected model was investigated using the bootstrap resampling method.[30]

The result of this method was compared with the stepdown reduction method[31] (see the Data Supplements for more technical information). Finally, the set of selected covariates was compared with that identified by a regression tree survival analysis.[29]

Correlations between the selected prognostic factors were assessed (see the Data Supplements).

Identification of the prognostic staging system

Risk subgroups identified by each possible combination of presenting risk factors were compared using the relative risk of death. These subgroups were pooled according to the number of patients within each category and the relative risk of death.

Validation

The prognostic model was validated using cross validation analysis and the staging model with the measure of separation (see the Data Supplements). This parameter is used to compare several prognostic classifications without calibration.

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RESULTS

Initial characteristics and clinical course

The main characteristics of the 587 symptomatic patients available for the final analysis are reported in Table 1. All these characteristics were recorded at the time of initiation of treatment. Sixty-nine percent of these patients were treated at diagnosis and 31% of patients became symptomatic and received therapy 4 to 164 months later. Criteria for initiation of therapy, as defined above, included cytopenia, constitutional symptoms, organomegaly, hyperviscosity and IgM-related symptoms, which pertained to 51%, 44%, 35%, 31% and 13%, respectively. With a median follow-up of 64 months (range, 6 to 182 months) in surviving patients, 266 patients (45%) had died at the stopping date and the median survival after treatment initiation was 87 months (95% confidence interval: 79-103 months, Figure 1A). There was no difference in survival according to the type of therapy applied (p=0·3)**.**

Univariate analysis of survival prognostic factors

Using univariate survival analyses, 7 adverse characteristics were identified for inclusion in multivariate analyses: age >65 years, platelet count ≤100 $x10^9$/L, β2-microglobulin >3 mg/L, Hb ≤11.5 g/dL, M-protein concentration >7.0 g/dL (estimated by densitometry), granulocytes ≤1.5 $x10^9$/L and albumin ≤3.5 g/dL. (For details on the choice of the covariates and cut-off values see the Data Supplements).

The prognostic values of the clinical characteristics at the time of initiation of first-line therapy for subsequent survival are shown in Table 2. Low platelet count and high M-protein concentration were highly significant, although they identified only small patient subsets of 9% and 7%, respectively. The presence of bulky adenopathy,

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splenomegaly or hepatomegaly had no prognostic value for survival after first-line therapy.

Development of the scoring system

Multivariate analysis selected the 5 covariates reported in Table 3**.** The correlations among the covariates were low (less than 0·3, see the Data Supplements). Using the combination of age, hemoglobin, platelet count, β2-microglobulin and M-protein concentration estimated by densitometry, low-risk was defined by the presence of ≤1 adverse characteristic and age ≤65 years, high-risk by the presence of ≥3 adverse characteristics; the remaining patients with 2 adverse characteristics or age >65 years belonged to an intermediate-risk group. The ISSWM was thus created with 3 risk groups: low, intermediate and high, comprising 27%, 38% and 35% of patients with 5-year survival rates of 87%, 68% and 36% ($p<0·0001$). The distribution of patients into these 3 groups and hazard ratios are shown in Table 4. The survival curves are shown in Figure 1B.

Validation of the scoring system and comparisons with previous systems

The goodness of fit of the 5 covariates prognostic system was validated: The cross validation covariate was associated with a beta value of 0·93, close to 1.

Estimate of the separation parameter, D, was 1·21. This value is far higher than the separation estimated with the inclusion of only one of the 5 characteristics (the D value ranged from 0.20 to 1.1 for the 5 covariates, $p<0·0001$ with paired t test for each characteristics). All these parameters demonstrate the excellent validation of the model. This is further confirmed by the following verifications.

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Age. Since age influences the choice of some treatment options, such as high-dose therapy, we analyzed whether the ISSWM system applies equally to young (Figure 2A) and older patients requiring therapy (Figure 2B). Although older patients (e.g., > 65 years) have poorer survival than younger patients, the ISSWM system applied to both subgroups.

Treatment type. Again, the ISSWM system discriminated similarly in the subgroup of 367 patients treated with alkylating agent and in the subgroup of 195 patients treated with purine analogue, as shown in Figures 2C and 2D respectively.

Patients treated for IgM related disorder only. We specifically addressed the prognostic value of ISSWM in these 20 patients because they required therapy but they differed from the majority of other patients by the absence of symptoms and signs related to the bulk of the disease. The ISSWM was found significant (p=0.01) because it identified 3 high-risk patients with shorter survival after treatment initiation.

Comparisons with previous scoring systems. The ISSWM system split the 12 subgroups defined by the Morel, Merlini, Ghobrial or Dhodapkar systems ($p \leq 0.0001$ except in 4 subgroups: with p value between 0.01 and 0.04). Conversely, log-rank test was significant in subgroups identified by ISSWM only when the Dhodapkar system was assessed in ISSWM low-risk patients (p=0.01).

DISCUSSION

Alkylating agents, purine analogues,[2,3] the anti-CD20 monoclonal antibody rituximab,[2,3] intensive therapy with autologous stem cell transplantation and allogeneic stem cell transplantation[2,3] have been used for the treatment of symptomatic patients with WM. Then, improved response rates were reported with the combination of 2 to 3[11,12] of these single drugs or RCHOP.[11] Encouraging results,

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despite toxicities, have also been observed with bortezomib,[13] lenalidomide[14] and thalidomide,[2,3,11] in few preliminary series. Considering the large number of new treatment options currently available, evaluations at best in the setting of stratified randomized studies and at least with a simple prognostic system for describing the characteristics of these series are urgently required in order to allow meaningful comparison of the results of different trials. Thus, an international prognostic system would be very helpful. In addition, such system would guide the identification of patients in whom these therapies are warranted.

This task was greatly facilitated by the definition of the criteria for the diagnosis of WM[18] and for starting treatment,[19] thus providing a solid base for an international project, which allowed the collection of a large and multicenter database of patients with this rare disease. The main initial clinical and hematological characteristics of patients with WM in the present series were in agreement with previous reports. These studies estimated median age between 64 and 71 years and identified male predominance, anemia, thrombocytopenia, leucopenia, lymphocytosis, and organomegaly, respectively in 38 to 85%, 16 to 22%, 4% to 20%, 7% to 18%, and 25% to 53% of patients.[6-9,18,20,22,23]

According to the design of the study, several clinical characteristics had not been included in the present statistical analysis because their prognostic value had been reported only in a limited number of studies. This was the case for a high concentration of lactate dehydrogenase,[23] and an elevated concentration of C-reactive protein,[22] However, the importance of these variables will need to be explored in future attempts to improve the ISSWM.

The scoring system reported here includes parameters related to patient characteristic (age), and disease burden (hemoglobin, platelet count, β2-

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microglobulin and M-protein concentrations). The cut-off value identified for hemoglobin level was similar to the values reported previously. This value (11·5 g/dL) was rather high, probably because the prognostic value of hemoglobin level reflects not only the consequence of the disease on the bone marrow function, but also the increase in plasma volume related to splenomegaly or the serum monoclonal IgM concentration. The prognostic significance of very high concentrations of M-protein, estimated by densitometry,[19] had been rarely addressed previously.[32] Prognostic analysis was based only on pretreatment variables. Nevertheless, it is unlikely that the treatments given during the period of inclusion have significantly changed the natural history of the disease. All the parameters of the ISSWM have been included in other prognostic indices. They are routinely evaluated in WM patients. This will allow the comparison of the distribution of patients and the survival curves of many other series and will further evaluate the accuracy of the ISSWM.

Our data have some limitations. Due to the rarity of this disease, we could not validate the scoring system in an independent series of patients. Nevertheless, cross-validation and bootstrapping of the separation parameter were performed for internal validation. In addition, the discriminating power of ISSWM persisted in subgroups of patients defined by previous scoring systems. Notably, the recent validation of the present scoring system in an independent series of patients treated with rituximab alone or in combination with dexamethasone and cyclophosphamide as first-line therapy,[33] further supports its validity. Thus ISSWM may be helpful in comparing results of new combination therapies with alkylating agents, purine analogues and rituximab. Since overall survival has been considered to be an appropriate endpoint with new agents whose success depends more on keeping the tumor stable, ISSWM should be useful for comparing the efficacy of these agents in

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the future.[34] Cause-specific survival may be another standard for evaluating outcome of patients. However, in the multicenter setting it appears unlikely, that reliable information could be obtained about cause of death. In addition, the prognostic value of the present ISSWM for cause-specific survival has been recently demonstrated.[33]

The ISSWM specifically focussed on symptomatic patients who require therapy by contrast with asymptomatic patients. This design allowed us to analyze a more homogeneous patient population. Thus, ISSWM may be used for selecting treatment in individual patients. In patients with a good prognosis (0-1 adverse factor), the median survival is 12 years. This indicates that optimal treatment in these patients must avoid toxicity and preserve quality of life. However, all low-risk patients are ≤65 years of age, therefore there is a need for improving survival, using new combination therapy without toxicity. In contrast, high-risk patients have a median survival less than 4 years. Innovative approaches are required for these patients. New treatment options, including bortezomib, thalidomide, lenalidomide in combination with dexamethasone or rituximab may hopefully improve the results achieved with single agent regimen. However, all these approaches have been evaluated only in phase 2 studies. Unlike findings reported in other B-cell malignancies distinct from WM,[4,5] at present, no data suggests that new targeted therapies may overcome an adverse prognostic factor in WM, especially the clinical characteristics included in ISSWM. Therefore the present scoring system may be useful in the near future for defining the role of new treatment approaches by comparing results obtained in risk-subgroups of patients. Furthermore, it may facilitate the identification of different subsets of the disease, based on cytogenetic and molecular markers. These new markers may efficiently improve ISSWM.

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Although an external validation in a large and independent series of uniformly treated patients is still expected to allow a broad application of ISSWM, we conclude that the combination of age, β2-microglobulin, M-protein concentration and blood counts, might allow risk-adapted treatment decisions in individual patients with WM, stratification and comparison of clinical trials. In addition ISSWM provides a provisional basis for identifying new biological prognostic markers.

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Authorship

Pierre Morel, designed research, performed research, collected data, analyzed and interpreted data, performed statistical analysis, wrote the manuscript.

Paolo Gobbi, designed research, performed research, collected data, analyzed and interpreted data, performed statistical analysis.

Alain Duhamel, designed research, performed research, analyzed and interpreted data, performed statistical analysis, wrote the manuscript.

Meletios Dimopoulos, designed research, performed research, collected data, analyzed and interpreted data, wrote the manuscript.

Madhav Dhodapkar, designed research, collected data, analyzed and interpreted data, wrote the manuscript.

Jason McCoy, collected data.

John Crowley, collected data.

Enrique Ocio, collected data, analyzed and interpreted data.

Ramon Garcia-Sanz, collected data, analyzed and interpreted data.

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Steve Treon, designed research, performed research.

Veronique Leblond, collected data, analyzed and interpreted data, wrote the manuscript.

Robert Kyle, designed research, collected data, analyzed and interpreted data, wrote the manuscript.

Bart Barlogie designed research, collected data, wrote the manuscript.

Giampaolo Merlini designed research, performed research, collected data, analyzed and interpreted data, wrote the manuscript.

All authors declare no competing financial interests

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Table 1. Clinical characteristics at the time of initiation of therapy in 587 patients with symptomatic Waldenström macroglobulinemia

Characteristics	**Median (standard Deviation)**	**N° (%)**
Patients		587
Age (years)	67 (11)	
Hemoglobin (g/dL)	10.4 (2·1)	
Platelet count (10^9/L)	210 (119)	
Absolute neutrophil count (10^9/L)	3.35 (2·6)	
Serum albumin (g/dL)	3.7 (1·6)	
Serum monoclonal protein (g/dL)	3.2 (2·1)	
Serum β2-microglobulin (mg/L)	3.2 (2·3)	
Bulky adenopathy		117 (20)
Splenomegaly		94 (16)
Hepatomegaly		62 (11)
Criteria for treatment initiation		
Cytopenia		300 (51)
Single criteria		81
In association		219
Organomegaly		207 (35)
Single criteria		0
In association		207
Hyperviscosity		183 (31)
Single criteria		47
In association		136
Constitutional symptoms		255 (44)
Single criteria		42
In association		213
IgM related symptoms		77 (13)
Single criteria		20
In association		57
Treatment regimen		
Alkylating agent		369 (62·8)
Fludarabine alone		189 (32·2)
Fludarabine plus alkylating agent		6 (1)
Rituximab		23 (4)

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Table 2. Characteristics at the time of initiation of first-line therapy and their associated survival in 587 patients with symptomatic Waldenström macroglobulinemia

Characteristics	No of patients (%)		Median survival	95%CI	p value
Gender					
Male	373	(64%)	85	65-98	
Female	212	(36%)	89	79-110	0·74
Age					
Less than or equal to 65	254	(43%)	141	120-53	
Greater than 65	333	(57%)	56	49-63	<0·0001
Criteria for treatment initiation					
Cytopenia †					
Absent	285	(49%)	92	84-20	
Present	300	(51%)	77	60-90	0·03
Organomegaly †					
Absent	380	(65%)	89	79-106	
Present	207	(35%)	80	64-143	0·84
IgM related symptoms †					
Absent	506	(87%)	84	74-98	
Present	77	(13%)	94	87-174	0·27
Hyperviscosity †					
Absent	401	(69%)	85	79-103	
Present	183	(31%)	80	57-117	0·35
Constitutional symptoms †					
Absent	323	(56%)	89	79-110	
Present	255	(44%)	85	60-119	0·18
Time from diagnosis to treatment initiation					
Less than 4 months	406	(83%)	89	79-118	
Greater than or equal to 4 months	181	(17%)	85	54-106	0·14
Hemoglobin (g/dL) †					
Less than or equal to 11.5	381	(65%)	123	110-179	
Greater than 11.5	205	(35%)	72	62-84	<0·0001
Platelet count (10^9/L) †					
Less than or equal to 100	54	(9%)	51	32-59	
Greater than 100	531	(91%)	90	83-116	<0·0001
Absolute Neutrophil Count (10^9/L) †					
Less than or equal to 1.5	53	(9%)	46	27-74	
Greater than 1.5	512	(91%)	89	80-103	0·0018
Serum monoclonal protein (g/dL) †					
Less than or equal to 7.0	541	(93%)	90	82-110	
Greater than 7.0	43	(7%)	49	37-62	0·0016
Serum albumin (g/dL) †					
Less than or equal to 3.5	197	(36%)	79	55-89	
Greater than 3.5	354	(64%)	106	92-137	0·0012
Serum β2-microglobulin (mg/L)					
Less than or equal to 3	251	(44%)	122	103-141	
Greater than 3	326	(56%)	63	55-83	<0·0001
Treatment					
Alkylating agents	369	(63%)	85	74-103	
Fludarabine (alone or in combination)	195	(33%)	85	61-NR	
Rituximab	23	(4%)	NR	30-NR	0·30

Percentages in parentheses. CI: confidence interval. † Data were unavailable for some patients

Table 3. Results of multivariate analyses: Final prognostic model

Variable before Treatment initiation	Parameter Estimate	Standard Error	Hazard Ratio	95% confidence interval
Age >65 years	1·02687	0·14402	2·792	2·11 - 1·70
Hemoglobin ≤11.5 g/dL	0·37574	0·15491	1·456	1·07 - 1·97
Platelet count ≤100 x10^9/L	0·67804	0·19472	1·970	1·35 - 2·89
β2-microglobulin >3 mg/L	0·49382	0·13986	1·639	1·25 - 2·16
Monoclonal IgM conc. >7.0 g/dL	0·53163	0·20429	1·702	1·14 - 2·54

Abbreviations: conc: concentration.

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Table 4. The new International Prognostic Scoring System for symptomatic Waldenström Macroglobulinemia requiring therapy

Stratum	**Score**	**Total number of patients (%)**	**Failed**	**median survival**	**Percent 0·95 LCL**	**0·95 UCL**	**Hazard** ratio
Low	0 or 1 (except age)	155 (27)	38	142·5	120·3	- 195·7	1
Intermediate	age or 2	216 (38)	87	98·6	81·7	- 137·2	2·36
High	≥3	203 (35)	134	43·5	36·6	- 55·1	6·61

LCL: lower confidence limit, UCL: upper confidence limit

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Legends to the Figures

Figure 1. Survival after first-treatment initiation of the whole population of symptomatic patients and survival after first-treatment initiation according to subgroups defined by the International scoring system (ISSWM). A: Kaplan-Meier estimates of the survival after first treatment initiation of the patient population (solid), along with pointwise 95% confidence intervals. B: survival after first treatment initiation according to the ISSWM.

Figure 2. International Staging System (ISSWM); staging by age and treatment: A is patient's age ≤65 years; B is patient's age >65 years; C is standard-alkylating based chemotherapy and D is purine analogue therapy. P values were $p<0.0001$ for each plot. See text for discussion.

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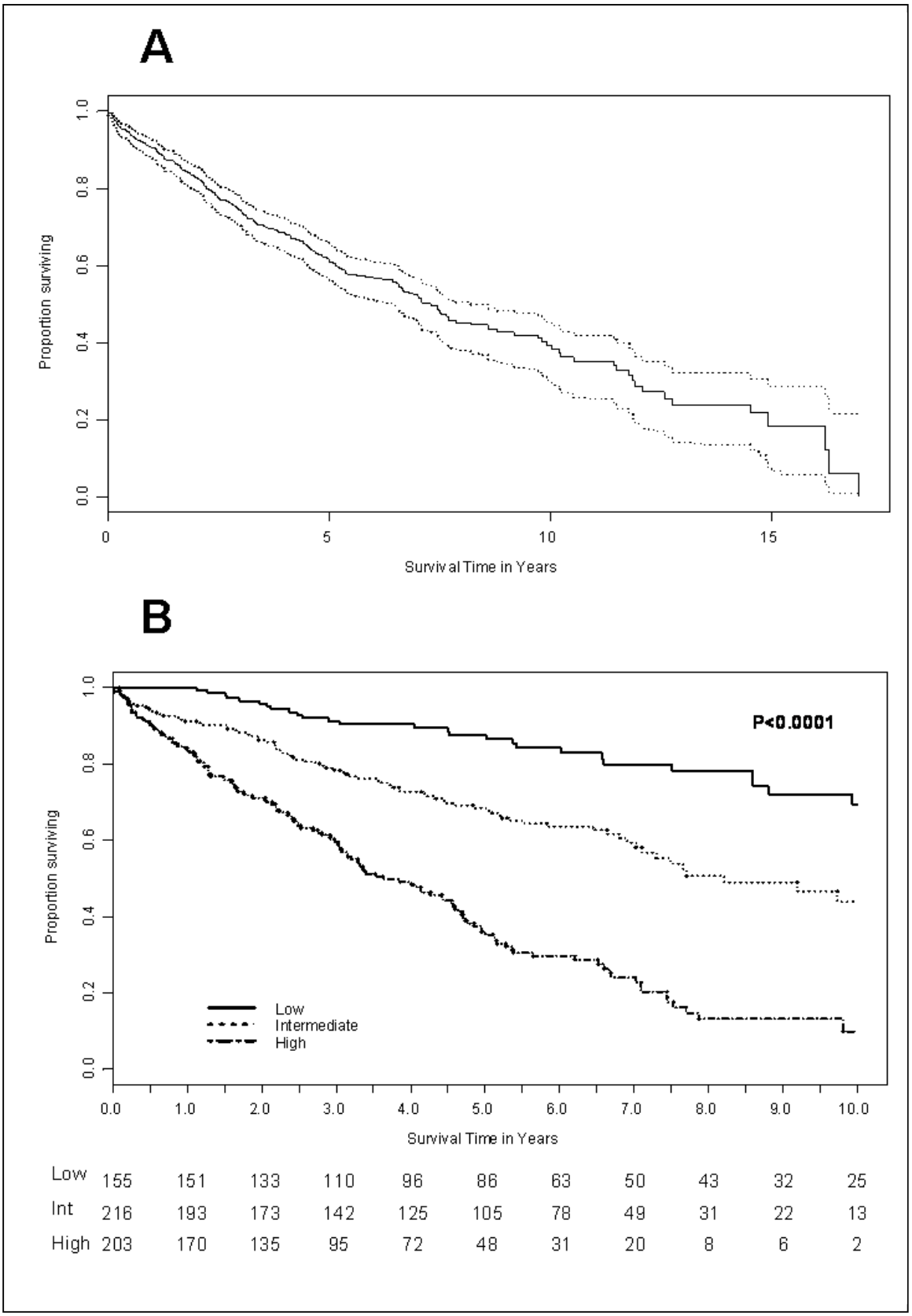

Figure 1

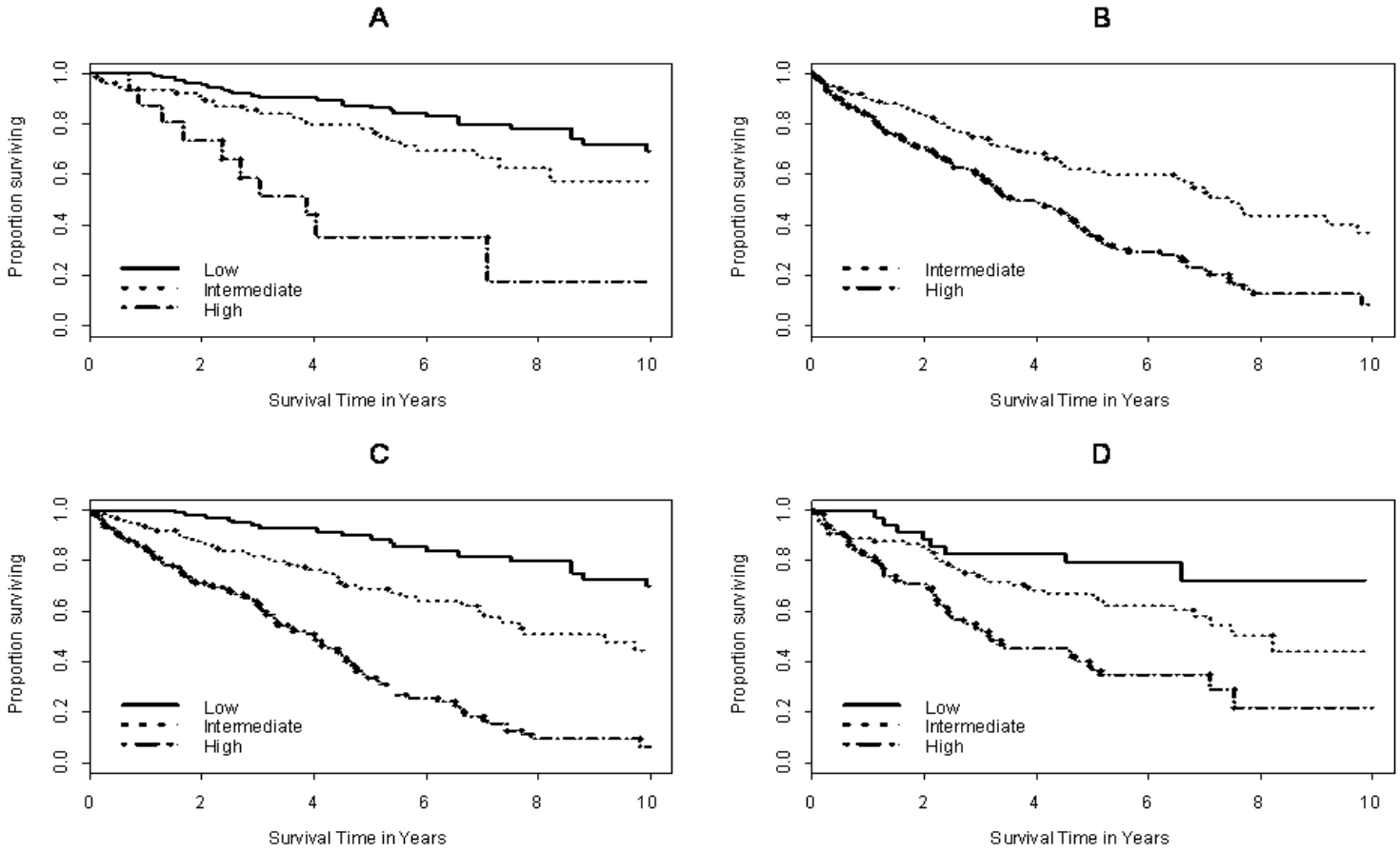

Figure 2

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