Proposal and Validation of Prognostic Scoring Systems for IgG and IgA Monoclonal Gammopathies of Undetermined Significance

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Abstract

Purpose: The presenting clinico-hematologic features of 1,283 patients with IgG and IgA monoclonal gammopathies of undetermined significance (MGUS) were correlated with the frequency of evolution into multiple myeloma (MM).

Experimental Design: Two IgG MGUS populations were evaluated: a training sample (553 patients) and a test sample (378 patients); the IgA MGUS population consisted of 352 patients.

Results: Forty-seven of the 553 training group patients and 22 of 378 test group IgG patients developed MM after a median follow-up of 6.7 and 3.6 years, respectively. Multivariate analysis showed that serum monoclonal component (MC) levels of ≤1.5 g/dL, the absence of light-chain proteinuria and normal serum polyclonal immunoglobulin levels defined a prognostically favorable subset of patients, and could be used to stratify the patients into three groups at different 10-year risk of evolution (hazard ratio, 1.0, 5.04, 11.2; $P < 0.001$). This scoring system was validated in the test sample. Thirty of the 352 IgA patients developed MM after a median follow-up of 4.8 years, and multivariate analysis showed that hemoglobin levels of <12.5 g/dL and reduced serum polyclonal immunoglobulin correlated with progression. A pooled statistical analysis of all of the patients confirmed the validity of Mayo Clinic risk model showing that IgA class, serum MC levels, and light-chain proteinuria are the most important variables correlated with disease progression.

Conclusions: Using simple variables, we validated a prognostic model for IgG MGUS. Among the IgA cases, the possible prognostic role of hemoglobin emerged in addition to a decrease in normal immunoglobulin levels.

Monoclonal gammopathies of undetermined significance (MGUS) are the most common forms of plasma cell dyscrasia, with a prevalence of 3% in the general adult population ages >50 years. The incidence of MGUS increases with age, and is >5% in patients ages >70 years (1). By definition, serum monoclonal component (MC) concentrations are ≤3 g/dL and bone marrow plasma cell counts <10%; there is no related organ or tissue impairment and no evidence of multiple myeloma (MM), macroglobulinemia, amyloidosis, or other related plasma cell or lymphoproliferative disorders (2). As MGUS have a rate of malignant evolution of ~1% per year (3–6), it is important to identify the features at diagnosis that are capable of predicting neoplastic transformation. In a previous study of a limited series of IgG MGUS patients, we found that serum MC levels, the presence or absence of light-chain proteinuria, normal or decreased polyclonal immunoglobulin levels, and the percentage of bone marrow plasma cells were the most reliable variables in predicting different clinical outcomes (7). On the basis of these data, we also identified a subset of IgG MGUS patients at low risk of evolution for whom we proposed a noninvasive diagnostic approach, without bone marrow

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Translational Relevance

This study identifies subsets of monoclonal gammopathies of undetermined significance (MGUS) patients with different probabilities of malignant transformation into multiple myeloma on the basis of simple and easily measurable hematologic parameters, and allows the use of follow-up programs based on risk stratification.

The substantial number of patients and the significant number of progression events allowed us to divide the IgG MGUS population into two groups: a training sample, used to identify the prognostic variables to include in the scoring system, and an independent test sample to validate our data. Interestingly, our proposed risk stratification model also retained its prognostic value in the test sample. Moreover, a pooled statistical analysis of all of the patients confirmed the validity of Mayo Clinic risk model.

evaluation or skeletal radiology, and a less close follow-up. In the same study, we did not observe any higher propensity to progression in a series of IgA cases, in line with the findings of Cesana et al. (8) and Veneri et al. (9).

This study analyzed two series of IgA and IgG MGUS patients, with the aim of detecting the variables related to neoplastic evolution, in order to create (and validate for IgG MGUS) two distinct prognostic scoring systems. The Mayo Clinic prognostic model (10) was also tested in all of the patients as a whole.

Materials and Methods

Patients. The study involved 1,283 patients with IgG or IgA serum MC and MC protein levels of ≤3 g/dL in the absence of related organ or tissue impairment. Bone marrow examinations were done at diagnosis in 714 (56%) patients, all of whom had bone marrow plasma cell counts of ≤10%, thus completely satisfying the criteria of the International Myeloma Working Group for the diagnosis of MGUS (2). All of the patients with serum MC levels of >1.5 g/dL (316 patients) and 211 of 232 patients with mild anemia [hemoglobin (Hb) levels <12.5 and ≥10 g/dL at two consecutive assessments] underwent bone marrow evaluation. All of the patients required at least 12 mo of observation, according to our previous diagnostic criteria (7). Nine patients that evolved within 1 y were excluded from the study.

The IgG cases included a training sample (553 patients; M/F, 0.96; median age, 62 y; range, 23-89 y) and a test sample (378 patients; M/F, 0.98; median age, 61 y; range, 20-87 y). The training sample was an extension of our previously reported series (7) and consisted of patients that were referred to our institution between 1974 and 2006. This sample was used to identify the variables useful for defining a multiparametric prognostic model. The test sample, used to validate the statistical conclusions reached in the training group, included patients from seven Italian hematologic centers between 1976 and 2006: La Sapienza University, Rome (35%); A. Avogadro

Table 1. Characteristics of MGUS patients

	IgG				IgA	
	Training sample		Test sample			
	n	%	*n*	%	*n*	%
	553	**100**	**378**	**100**	**352**	**100**
Age at diagnosis, y						
≤50	133	24	84	22	69	20
51-60	141	26	83	22	74	21
61-70	157	28	124	33	109	31
71-89	122	22	87	23	110	28
Median age, y	61 (range, 20-87)		62 (range, 23-89)		64 (range, 24-93)	
Gender						
F	259	47	177	47	177	50
M	294	53	201	53	175	50
MC, mg/dL						
≤1.5	377	68	222	59	240	69
>1.5	176	32	156	41	108	31
Light-chain proteinuria						
Negative	487	88	343	91	281	92
Positive	66	12	35	9	26	8
Polyclonal immunoglobulin levels, g/dL						
Normal	459	83	302	80	198	70
Reduced	94	17	76	20	87	30
Serum Hb levels, g/dL						
≥12.5	473	86	298	79	274	78
<12.5 and >10.0	77	14	78	21	77	22
Period of recruitment						
1976-1985	99	18	5	1	32	9
1986-1989	229	41	45	12	94	27
1996-2004	225	41	256	68	198	56
2005-2006	—	—	72	19	28	8

Abbreviation: MC, serum monoclonal component; Hb, hemoglobin.

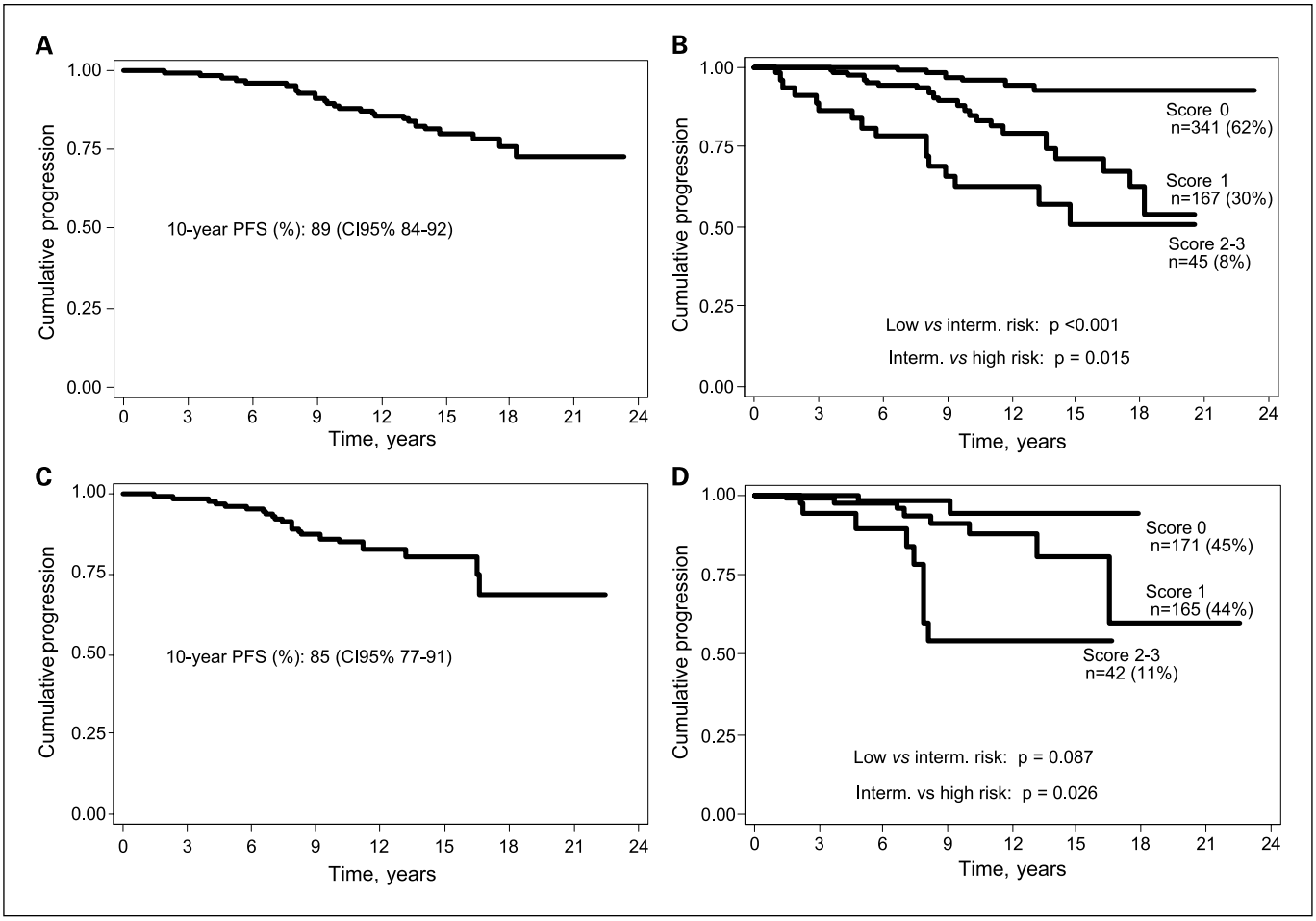

Fig. 1. Overall PFS and PFS stratified on the basis of the proposed score in the training (*A* and *B*) and validation sets of IgG MGUS patients (*C* and *D*). The score was built by giving one point for each of serum MC levels of >1.5 g/dL, low serum polyclonal immunoglobulin levels, and detectable light-chain proteinuria.

University of Piemonte Orientale, Novara (23%); Bianchi-Melacrino-Morelli Hospital, Reggio Calabria (16%); Campus Biomedico University, Rome (15%); Hematology II, San Martino Hospital, Genoa (7%); SS Antonio e Biagio and C. Arrigo Hospital, Alessandria (3%); and Centro di Riferimento Oncologico della Basilicata, Rionero in Volture (2%).

The IgA MGUS population consisted of 352 cases (M/F, 0.98; median age. 64 y; range, 24-93 y): 131 referred to our center and 221 to the other centers mentioned above. Table 1 shows the demographic and hematologic characteristics of the three populations.

In all three groups, in addition to the usual laboratory tests (serum calcium, liver and kidney function, β_2 microglobulin), we defined MC type by means of immunofixation and quantified it using serum protein-agarose gel electrophoresis. Serum polyclonal immunoglobulins were measured by means of nephelometry, and light-chain proteinuria was measured by means of cellulose-acetate electrophoresis. Under our conditions, the lowest level of light chain urine protein excretion considered evaluable was 100 mg/24 h. The usual laboratory tests and serum/urinary MC evaluations were done about twice a year for the first 2 y, and then, in the case of hematologic stability, once a year until the end of follow-up.

During the follow-up period, and in accordance with the International Myeloma Working Group criteria, bone marrow and complete skeletal X-ray examinations were done if related organ or tissue impairment appeared or MC or proteinuria levels significantly increased. Symptomatic and smouldering MM were defined on the basis of the International Myeloma Working Group criteria (2).

Statistical methods. Progression-free survival (PFS) was the end point for all the statistical analyses, and the rates of evolution to MM were estimated using Kaplan-Meier estimators (11). A prognostic model was built to fit a Cox proportional hazard model (12) using all of the variables affecting PFS at a P level of <0.01 in the univariate analysis of the training sample; the prognostic index was derived from the Cox proportional hazard analysis. The proportionality of the risks and overall model fit were graphically checked using scaled Schoenfeld (13) and Cox-Snell residuals; overfitting (shrinkage factor) and the stability of the regression coefficients were checked using Harrell's method (14). An external data set was used to validate the model and the score obtained in the training sample; the performance of the prognostic index was checked by means of the D index, a measure of prognostic separation for survival models (15). The scoring system was checked using the usual log-rank test and Harrell's concordance index (C-Harrell). All of the covariates were dichotomous, using previous published cutoff values (7). In the case of continuous covariates, the cutoff values were obtained by comparing distribution quartiles using the log-rank test. The crude rates are the ratios between the number of observed events and the overall duration of follow-up, expressed per 1,000 person-years. We did not plan a sample size, and all P values were based on two-sided testing.

Results

IgG MGUS training sample. The median duration of follow-up was 6.7 years (range, 1.0-27.2 years). Forty-seven of the 553

patients (crude rate 11 × 1,000 person-years) developed MM: 15 cases of indolent MM and 32 progressing to symptomatic MM. The 5-, 10-, and 15-year actuarial probabilities of PFS were 97%, 89%, and 80%, respectively (Fig. 1A). Table 2 shows the univariate Cox proportional hazard regression analysis of evolution to MM. Detectable light-chain proteinuria ($P < 0.001$), serum MC levels of >1.5 g/dL ($P < 0.001$), a decrease in serum polyclonal immunoglobulin ($P < 0.001$), and an age of >70 years ($P = 0.006$) were all significantly associated with evolution to MM. Multivariate analysis showed that the variables that significantly correlated with malignant transformation included MC levels of >1.5 g/dL ($P < 0.001$), low serum polyclonal immunoglobulin levels ($P < 0.002$), and detectable light-chain proteinuria ($P < 0.009$; Table 3). The model showed good calibration and discrimination [unbiased C-Harrell, 0.760; 95% confidence interval (95% CI), 0.693-0.826] and a shrinkage factor of 0.942; the regression coefficient indicated stability after 1,000 bootstrap replications. Although age was statistically significant, it was not included in the multiple regression because it has little clinical significance once serum MC and light-chain proteinuria levels are known.

Because the regression coefficients of these variables were not significantly different, we gave them one point each. Analysis of the PFS curves identified three prognostic subsets with significantly different 10-year risks of progression to MM: low risk (score = 0; 341 patients) with a hazard ratio (HR) of 1.0; intermediate risk (score = 1; 167 patients) with a HR of 5.04 ($P < 0.001$); and high risk (score = 2-3; 45 patients) with a HR of 11.2 ($P < 0.001$). The HR between the intermediate-risk and high-risk groups was 2.21 ($P = 0.015$). The 10-year probabilities of PFS in the low-risk ($n = 341$, 62%), intermediate-risk ($n = 167$, 30%), and high-risk ($n = 45$, 8%) groups were 95%, 86%, and 63%, and the 15-year probabilities were 92%, 72%, and 51%, respectively (Fig. 1B).

IgG MGUS test sample. The median duration of follow-up was 3.6 years (range, 1.0-24.7 years). Twenty-two of the 378 patients (crude rate 12 × 1,000 person-years) developed MM: 7 cases of indolent MM and 15 progressing to symptomatic MM. The 5-, 10-, and 15-year actuarial probabilities of PFS were 97%, 85%, and 80%, respectively (Fig. 1C). The PFS rates were not statistically different in the test and training samples ($P > 0.2$). Figure 1D shows that the scoring system distinguished two main groups with significantly different 10-year risks of progression to MM. The difference between the high-risk ($n = 42$; 11%) and low-risk ($n = 171$; 45%) groups was statistically significant ($P = 0.003$), as was that between the high-risk and intermediate-risk groups ($n = 165$; 44%; $P = 0.026$), whereas the low-risk and intermediate-risk groups showed a similar rate of progression ($P = 0.087$). The 10-year probabilities of PFS in the low-, intermediate-, and high-risk groups were 94%, 91%, and 54%, respectively. C-Harrell was 0.740 (95% CI, 0.613-0.867).

The model was also validated by comparing the D index using 1,000 bootstrap samples: it was developed on the training sample; its D index was estimated; and its performance was evaluated on the test sample. The D indices of the training and test samples were 1.492 (95% CI, 1.020-1.972) and 1.366 (95% CI, 0.553-2.179), respectively, and the 95% CI of the difference ranged from -0.608 to 0.360. The D index of the test sample was lower than that of the training sample (-0.126), but as the confidence intervals included zero, it can be concluded that there was no difference in the performance of the model. When the low-risk and intermediate-risk groups were pooled, the log-rank test gave P values of <0.001 for the training sample and 0.001 for the test sample.

Table 2. Univariate analysis of PFS in IgG MGUS training sample and IgA sample

Factor	10-y PFS (%)		HR (95% CI)		*P*	
	IgG	IgA	IgG	IgA	IgG	IgA
Age at diagnosis, y						
≤70	92	92	1.00	1.00		
>70	60	60	2.85 (1.36-5.98)	1.19 (0.47-3.01)	0.006	0.712
Gender						
F	90	90	1.00	1.00		
M	88	88	0.80 (0.46-1.43)	0.57 (0.27-1.20)	0.459	0.142
MC, g/dL						
≤1.5	94	94	1.00	1.00		
>1.5	79	79	4.34 (2.34-8.02)	1.68 (0.82-3.46)	<0.001	0.155
Light-chain proteinuria						
Negative	91	91	1.00	1.00		
Positive	66	66	3.82 (1.94-7.54)	2.68 (0.92-7.80)	<0.001	0.070
Polyclonal immunoglobulin levels, g/dL						
Normal	92	92	1.00	1.00		
Reduced	72	72	3.40 (1.87-6.18)	3.11 (1.43-6.78)	<0.001	0.004
Serum Hb level, g/dL						
≥12.5	89	89	1.00	1.00	—	—
<12.5 and >10.0	87	—	1.72 (0.88-3.45)	—	0.111	—
Continuous (13.5)*	—	—	—	0.72	—	0.001
<12.5	—	74	—	3.65 (1.78-7.50)	—	<0.001
Period of recruitment						
1976-1985	83	83	1.00	1.00		
1986-1995	91	91	0.61 (0.32-1.15)	0.72 (0.24-2.22)	0.128	0.572
1996-2004	98	98	0.70 (0.26-1.93)	1.39 (0.44-4.36)	0.496	0.572

*Median value.

Table 3. Multivariate analysis (Cox model) of evolution to MM in IgG training sample and IgA MGUS patients

IgG training sample

Factor	Coefficient	SE	HR	*P*	Boot-SE*	Boot-*P**
MC >1.5 g/dL	1.19	0.329	3.29	<0.001	0.359	0.001
Light-chain proteinuria	0.92	0.358	2.50	0.010	0.421	0.029
Serum pIg reduction	0.82	0.318	2.27	0.010	0.360	0.023
	Shrinkage factor, † 0.942; C-Harrell, † 0.760 (95% CI, 0.693-0.826)					
Score	*N*	%	HR	*P*		
Low (0)	341	62	1.00	—		
Intermediate (1)	167	30	5.04	<0.001		
High (2-3)	45	8	11.2	<0.001		

IgA patients

Factor	Coefficient	SE	HR	*P*	Boot-SE*	Boot-*P**
Hb <12.5 g/dL	0.94	0.403	2.57	0.019	0.445	0.037
Serum pIg reduction	1.01	0.402	2.76	0.011	0.444	0.020
	Shrinkage factor, † 0.919; C-Harrell, † 0.723 (95% CI, 0.626-0.820)					
Score	*N*	%	HR	*P*		
Low (0)	160	56	1.00	—		
High (1-2)	125	44	4.13	0.001		

Abbreviation: pIg, polyclonal immunoglobulin.
*More than 1,000 bootstrap replications.
† More than 250 bootstrap replications.

IgA MGUS group. The median duration of follow-up was 4.8 years (range, 1.0-24.1). Thirty of the 352 patients (crude rate 14 × 1,000 person-years) developed MM: 9 cases of indolent MM and 21 progressing to symptomatic MM. The 5-, 10-, and 15-year actuarial probabilities of PFS were 93%, 86%, and 81%, respectively (Fig. 2A). Table 2 shows the univariate Cox proportional hazard regression analysis of evolution to MM. Hb levels of <12.5 g/dL or Hb as a continuous variable (from a median of 13.5 g/dL; $P < 0.001$ for both), a decrease in polyclonal immunoglobulin ($P = 0.004$), and light-chain proteinuria ($P = 0.070$) were all significantly associated with the evolution into MM.

Multivariate analysis showed that Hb levels of <12.5 g/dL (HR, 2.57; $P = 0.019$) and a decrease in serum polyclonal immunoglobulin (HR, 2.76; $P = 0.011$) significantly correlated with disease progression. The model was built using 285 cases because of missing polyclonal immunoglobulin values for the rest of the sample, and had a marginal shrinkage factor (0.919), a good concordance index (unbiased C-Harrell, 0.723) and quite stable regression coefficients. Table 4 shows these data and the specific HRs. Because the HRs of these variables were not significantly different, we gave them one point each. Analysis of the PFS curves identified two prognostic subsets with significantly different 10-year risks of progression to MM: low risk (score =0; $n = 160$, 56%) with a HR of 1.0, and high risk with a HR of 4.13 (score >1; $n = 125$, 44%; $P = 0.001$; Fig. 2B).

Mayo Clinic risk model assessment. The prognostic significance of the Mayo Clinic risk stratification model for the

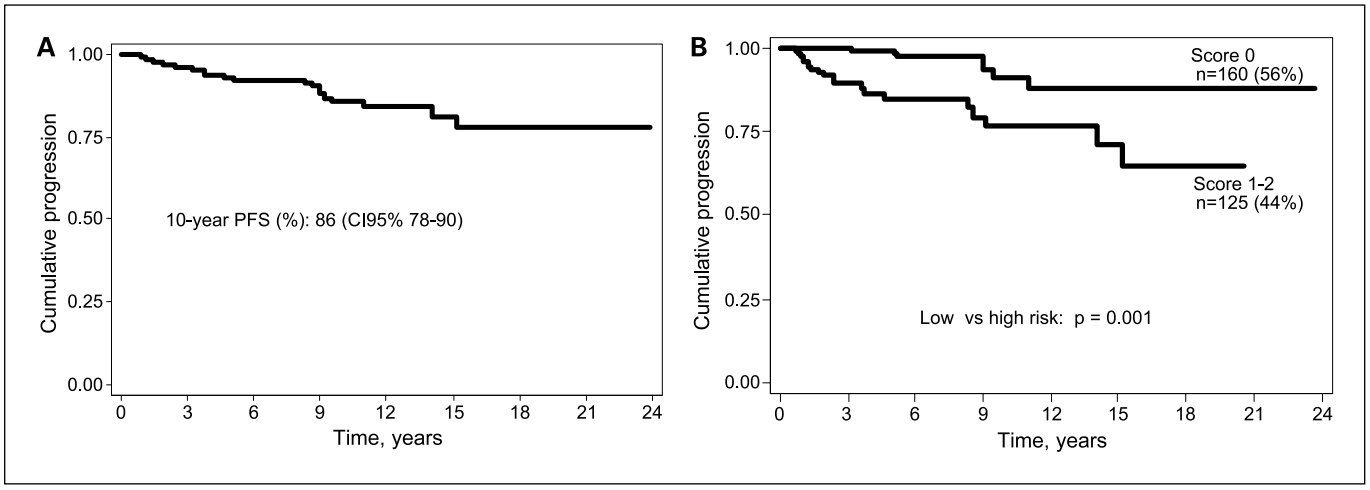

Fig. 2. Overall PFS and PFS stratified on the basis of the proposed score in IgA MGUS patients (*A* and *B*). One point each was given for Hb levels of <12.5 g/dL and a decrease in serum polyclonal immunoglobulin levels.

Table 4. Validation of risk stratification model proposed by Rajkumar et al. (10) for evolution to MM in pooled MGUS patients

Factor	Univariate Cox proportional hazard		Multivariate Cox proportional hazard	
	HR	*P*	HR	*P*
MC >1.5 g/dL	2.97	<0.001	2.98	<0.001
Light-chain proteinuria	3.34	<0.001	3.10	<0.001
IgA vs IgG MGUS	1.29	0.241	1.69	0.020
Risk levels	**No. of patients (%)**	**HR**	***P***	**10-y PFS (%)**
Low (0)	590 (48)	1.00	—	94
Low-intermediate (1)	511 (41)	3.79	<0.001	83
Intermediate-high (2)	129 (10)	6.23	<0.001	74
High (3)	5 (<1)	26.30	<0.001	40
Total	1,235			
C-Harrell, 0.64 (95% CI, 0.60-0.71)				

progression of MGUS (10) was evaluated in all 1,235 of our IgG and IgA patients as a whole. Its risk factors are IgG versus non-IgG MGUS, serum MC (≤1.5 or >1.5 g/dL), and unbalanced light chain production. Four risk groups were identified (with 0, 1, 2, or 3 variables) with significantly different HRs of progression: low risk (score = 0; 590 patients) with a HR of 1.0; low-intermediate risk (score = 1; 511 patients) with a HR of 3.79 ($P < 0.001$); intermediate-high risk (score = 2; 129 patients) with a HR of 6.23 ($P < 0.001$); and high risk (score = 3; 5 patients) with a HR of 26.3 ($P < 0.001$; Table 4). The same risk stratification model was tested in our IgG MGUS training (obviously excluding the immunoglobulin class variable) and identified three prognostic cohorts with significantly different 10-year risks of progression to MM: low risk (score = 0; 378 patients) with a HR of 1.0; intermediate risk (score = 1; 154 patients) with a HR of 4.42 ($P < 0.001$); and high risk (score = 2; 21 patients) with a HR of 10.4 ($P < 0.001$). The model was also validated in the IgG MGUS test sample. The high-risk group accounted for only 3.8% of the training sample and 2.1% of the test sample.

Discussion

This was a large-scale Italian multicenter MGUS study of patients with IgA and IgG MGUS; IgM MGUS were excluded because they are biologically different entities for which we have previously described a specific prognostic scoring model (16). Furthermore, as the question of differences in the outcomes of IgA and IgG MGUS is controversial, we evaluated the two series separately and together.

The substantial number of patients and the significant number of progression events allowed us to divide the IgG MGUS population into two groups: a training sample used to identify the prognostic variables to include in a scoring system, and an independent test sample used for validation purposes. The crude rates of progression in the two samples were not significantly different from each other (11 × 1,000 versus 12 × 1,000 person-years) and not particularly different from those observed in previously described series (although these also included IgM MGUS, which may have a different propensity to neoplastic transformation; refs. 4, 17). Multivariate analysis of our IgG cases showed that serum MC levels of ≤1.5 g/dL, the absence of light-chain proteinuria, and normal polyclonal serum immunoglobulin levels significantly correlated with no progression, and a scoring system including these hematologic variables at diagnosis was capable of stratifying the patients into subsets at significantly different risks of disease progression; the HRs in the intermediate-risk and high-risk subsets were 5.04 and 11.2, against the HR of 1.0 in the low-risk group.

The system was devised as a means of simplifying the management of essential clinical information, and its validity was confirmed in an independent series of IgG MGUS patients whose clinical and hematologic characteristics satisfied the study inclusion criteria. Interestingly, our proposed risk stratification model retained its prognostic value although the follow-up of the test sample was shorter and the number of patients progressing to MM was consequently smaller. The data clearly show that IgG MGUS are not homogeneous in terms of the risk of progression and that a subset of patients with a very low probability of malignant transformation can be identified.

The crude rate of evolution to MM in the group of patients with IgA MGUS was 14 × 1,000 person-years. The prognostically relevant variables at diagnosis proved to be low serum polyclonal immunoglobulin levels and Hb levels (as both a continuous and dichotomous variable), but we did not find any relationship between progression and serum MC levels or the presence of light-chain proteinuria. Although our series was larger than any previously reported IgA series, the number of cases evolving into malignancy did not allow us to create a validating group; however, we can propose a scoring system capable of identifying two subsets of low-risk and high-risk patients (HR, 1 and 4.13, respectively; $P = 0.001$) that may be useful for future studies of this rare MGUS.

The prognostic role of Hb at diagnosis is intriguing and not easily verified because of the lack of studies of selected IgA MGUS series. However, it has been described in IgM MGUS subsets in which discrete variations can be considered an early marker of evolution due to possible interference between erythropoiesis and pathologic B-cell clones (16). This interpretation is corroborated by the fact that the appearance of anemia in IgM MGUS is one of the most frequent signs of neoplastic progression. The relevance of low Hb levels in IgG and IgA plasma cell dyscrasias is confirmed by the fact that anemia is one feature of related organ or tissue impairment in MM, and our data suggest that a decrease in Hb levels may have particular prognostic significance in IgA MGUS. It does not

seem that the relevance of Hb was due to more advanced disease because the clinical and hematologic features of our IgA MGUS patients at diagnosis were comparable with those of the IgG MGUS subset.

We also tested the relevance of the Mayo Clinic prognostic model (10) in our total population as a whole, replacing free light chain with light-chain proteinuria as a marker of a light chain imbalance. This model identified four different risk groups, and confirmed the previously described worse prognosis of IgA MGUS (4, 17–19).

The prognostic role of unbalanced light chain production has been described at urinary level (7) and, more recently, serum level (10, 20). Our data confirm that a finding of excess light chains is a risk factor. Without making any merit judgements about the technical assays used to measure a light chain unbalance, they actually depend on their availability and feasibility in different institutions.

The Mayo Clinic model was also validated in our IgG MGUS subsets using a two-variable system (serum MC levels and light-chain proteinuria) that therefore identified three risk levels. However, the high-risk group accounted for only 3.8% of the training sample and 2.1% of the test sample, instead of the 8% and 11% selected by our own proposed score. Furthermore, our score performed better than that of the Mayo Clinic in the validation sample (C-Harrell, 73% versus 64%).

In conclusion, we identified predictors of progression to MM in a large series of IgG and IgA MGUS cases, evaluated separately and pooled together. In the whole casistic, the Mayo Clinic risk model confirmed its value. In our IgG MGUS series, we proposed and validated a prognostic model where the uninvolved serum immunoglobulin was shown to have an adjunctive prognostic role. We also found that Hb levels may play a prognostic role in IgA MGUS. Our findings may help to plan individualized follow-up programs based on risk stratification.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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