

# Progression Risk Stratification of Asymptomatic Waldenström Macroglobulinemia

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**BACKGROUND** Waldenström macroglobulinemia (WM) is preceded by asymptomatic WM (AWM), for which the risk of progression to overt disease is not well defined.

**METHODS** We studied 439 patients with AWM, who were diagnosed and observed at Dana-Farber Cancer Institute between 1992 and 2014.

**RESULTS** During the 23-year study period, with a median follow-up of 7.8 years, 317 patients progressed to symptomatic WM (72%). Immunoglobulin M 4,500 mg/dL or greater, bone marrow lymphoplasmacytic infiltration 70% or greater,  $\beta$ 2-microglobulin 4.0 mg/dL or greater, and albumin 3.5 g/dL or less were all identified as independent predictors of disease progression. To assess progression risk in patients with AWM, we trained and cross-validated a proportional hazards model using bone marrow infiltration, immunoglobulin M, albumin, and beta-2 microglobulin values as continuous measures. The model divided the cohort into three distinct risk groups: a high-risk group with a median time to progression (TTP) of 1.8 years, an intermediate-risk group with a median TTP of 4.8 years, and a low-risk group with a median TTP of 9.3 years. We validated this model in two external cohorts, demonstrating robustness and generalizability. For clinical applicability, we made the model available as a Web page application ([www.awmrisk.com](http://www.awmrisk.com)). By combining two cohorts, we were powered to identify wild type MYD88 as an independent predictor of progression (hazard ratio, 2.7).

**CONCLUSION** This classification system is positioned to inform patient monitoring and care and, for the first time to our knowledge, to identify patients with high-risk AWM who may need closer follow-up or benefit from early intervention.

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## INTRODUCTION

Waldenström macroglobulinemia (WM) is a low-grade non-Hodgkin lymphoplasmacytic lymphoma of the bone marrow (BM), characterized by production of monoclonal immunoglobulin M (IgM) protein.<sup>1,2</sup> WM is a rare malignancy with an incidence of 3.4 per million among the male population and 1.7 per million among the female population in the United States, and an incidence of 7.3 and 4.2 per million for males and females, respectively, in Europe.<sup>3-6</sup>

The phenotype of these clonal lymphoplasmacytic cells suggests that they are derived from IgM memory B cells that have undergone somatic hypermutation, but not isotype switching.<sup>7-9</sup> Approximately 90% to 95% of patients with WM carry the MYD88 L265P mutation, whereas 40% carry mutations in CXCR4.<sup>10-12</sup>

WM is preceded by an early precursor stage named IgM monoclonal gammopathy of undetermined significance (IgM MGUS) and a later stage known as smoldering WM (SWM).<sup>13,14</sup> Both stages are asymptomatic,

although SWM exhibits an increased risk of progression, which warrants closer follow-up and monitoring.<sup>15</sup> According to previous reports, 1.5% of patients with IgM MGUS and 12% of patients with SWM progress to WM per year, and the rate decreases with the years of follow-up.<sup>10,11,13,14</sup> Currently, treatment initiation is recommended in the presence of symptoms, including symptomatic lymphadenopathy or splenomegaly, constitutional symptoms, anemia with a hemoglobin level of 10 g/dL or less, platelet count less than  $100 \times 10^9/L$ , hyperviscosity syndrome, symptomatic peripheral neuropathy, and symptomatic cryoglobulinemia.<sup>16,17</sup>

Nonetheless, it has been challenging to distinguish the asymptomatic patients who will progress from those who will not. A revised stratification is needed, yet the rarity of the disease and the ensuing scarcity of data represent a practical challenge. We assembled the largest cohort of patients with AWM (including IgM MGUS and SWM) to date with the aim of identifying risk factors for disease progression and generating an evidence-based risk stratification system to help

## ASSOCIATED CONTENT

### Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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clinicians improve the management of patients with this rare malignancy and identify those who need closer follow-up.

## METHODS

### Primary Cohort

After institutional review board approval, we identified all patients with WM who had been diagnosed and observed at Dana-Farber Cancer Institute from November 1992 to December 2014 (Data Supplement). The cutoff date for follow-up was January 2018. Only patients with AWM at the time of diagnosis were included in this cohort to identify risk factors for disease progression. We defined patients with AWM as those who had morphologic findings of lymphoplasmacytic lymphoma in the BM and monoclonal IgM protein, encompassing both IgM MGUS and SWM stages.<sup>2</sup> Exclusion criteria are provided in the Data Supplement. Clinical data were analyzed after reviewing medical records and death certificates. Survival status, cause of death, and disease progression were identified at the end of follow-up from the National Death Index and the patients' medical records.

### Validation Cohorts

Two different AWM cohorts were used for external validation. The first cohort was diagnosed and observed at Mayo Clinic, Rochester, MN, between 1996 and 2013. The second cohort was diagnosed and observed at the Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Greece, between 1995 and 2014. Baseline characteristics of these cohorts are listed in the Data Supplement.

### End Points

The primary end point of the study was progression to symptomatic WM that required treatment. Symptomatic WM was defined according to the criteria for treatment initiation by consensus panel recommendations from the Second International Workshop on Waldenström Macroglobulinemia.<sup>16-18</sup>

### Risk Factors

Possible risk factors for disease progression were identified a priori and extracted from medical records. The presence of *MYD88* L265P mutation was tested by allele-specific polymerase chain reaction on BM samples.<sup>11</sup> All data were collected at the time of diagnosis.

### Statistical Analysis

The primary end point with respect to progression to symptomatic WM was calculated in terms of the cumulative probability of progression. Time to progression (TTP) was calculated from the date of diagnosis to the date of the first assessment showing evidence of symptomatic disease and requiring treatment. Data for patients who died before

disease progression, did not have disease progression during the study period or were lost to follow-up before progression were censored. For survival analysis, the Kaplan-Meier method was used to estimate the cumulative incidence of progression, and differences between the curves were tested by log-rank test. Disease-specific survival was calculated where patients whose death was deemed unrelated to WM or its complications were censored. A multivariable Cox proportional hazards model was used to identify risk factors for disease progression among patients with AWM.

## RESULTS

### Patient Baseline Characteristics

We identified 439 patients who were diagnosed with AWM at Dana-Farber Cancer Institute; 273 (62.2%) were men and 166 (37.8%) were women. The median age at WM diagnosis was 61 (range, 26 to 91) years. Forty-one patients (9.3%) had a family history of WM. All baseline characteristics are listed in [Table 1](#).

### Disease Progression

During the 23-year study period and a median follow-up of 7.8 years, 317 patients (72.2%) experienced disease progression. The median TTP from AWM diagnosis to symptomatic WM was 3.9 years (95% CI, 3.2 to 4.6 years). The probability of disease progression within 2 years was 30.8% (95% CI, 26.7% to 35.3%), as shown in [Figure 1A](#).

To ensure there was no bias in TTP estimates because of changes in patient management during the study period of 23 years, we divided our cohort into two groups on the basis of the date of diagnosis (patients diagnosed between 1992 and 2003 and patients diagnosed between 2004 and 2014) and tested for a difference in TTP. No difference was observed between these two groups (log-rank test,  $P = .1$ ; Data Supplement).

The 2-year progression rate was 63.6% (95% CI, 49.7% to 77.4%) for patients with IgM 4,500 mg/dL or greater and 25.7% (95% CI, 21.5% to 30.6%) for those with lower levels. The risk of progression was 45.5 and 15.1 events per 100 person-years, respectively (log-rank test,  $P < .001$ ; [Fig 1B](#)).

The 2-year progression rate for patients with BM lymphoplasmacytic infiltration of 70% or greater was 61.0% (95% CI, 52.0% to 70.1%) and 20.6% (95% CI, 16.6% to 25.4%) for those with lower infiltration levels. The risk of progression was 37.5 and 13.6 events per 100 person-years, respectively ( $P < .001$ ; [Fig 1C](#)).

The 2-year risk of progression among patients with  $\beta 2$ -microglobulin of 4.0 mg/dL or greater was 65.3% (95% CI, 42.2% to 87.1%), whereas it was 28.1% (95% CI, 22.6% to 34.6%) in those with lower levels ( $P < .001$ ; [Fig 1D](#)). Furthermore, the 2-year progression rate in patients with

**TABLE 1.** Baseline Characteristics of Patients With AWM in the DFCl Cohort

Characteristic	Total (N = 439)
Median age, years (range)	61 (26-91)
Sex, male	273 (62.2)
Light chain type	
Kappa	328 (74.7)
Lambda	108 (24.6)
Biclonal	3 (0.7)
Autoimmune	124 (28.3)
Family history of WM	41 (9.3)
Family history of hematologic malignancies	87 (19.8)
MYD88 L265P mutation	68 (82)
Lab data, median (IQR)	
IgM, mg/dL	2,196.0 (1,170.0-3,440.0)
≥ 4,500	44 (10.0)
M-protein, g/dL	1.6 (0.9-.3)
≥ 3	29 (6.6)
Kappa, mg/L	22.4 (12.6-63.1)
Lambda, mg/L	10.2 (6.0-18.0)
Absolute FLC ratio	5.0 (2.5-14.3)
> 8	39 (8.9)
BM involvement (% total cellularity)	40 (20-70)
≥ 70	110 (25.1)
BM Intertrabecular involvement (%)	30 (10-50)
≥ 60	73 (16.6)
β2-microglobulin, mg/dL	2.3 (1.9-2.9)
≥ 4.0	16 (3.6)
Albumin, g/dL	4.1 (3.8-4.3)
< 3.5	28 (6.4)
WBC, K/uL	6.8 (5.5-8.2)
Hemoglobin, g/dL	12.6 (11.6-13.3)
< 11.5	81 (18.5)
Lymphocyte count, K/uL	1,740.0 (1,392.0-2,290.0)
Platelet count, K/uL	267.0 (212.5-334.0)
< 120	9 (2.1)
Creatinine mg/dL	1.0 (0.8-1.1)
Lactate dehydrogenase U/L	136.0 (118.0-184.0)
Erythrocyte sedimentation rate, mm/hr	77.0 (44.0-102.0)

NOTE. Data are No. (% or range) unless otherwise indicated. Some data were not available for all patients at diagnosis.

Abbreviations: AWM, asymptomatic WM; BM, bone marrow; DFCl, Dana-Farber Cancer Institute; FLC, free light chains; IQR, interquartile range; WM, Waldenström macroglobulinemia.

albumin less than 3.5 g/dL was 60.7% (95% CI, 43.5% to 78.3%), but only 27.1% (95% CI, 21.8% to 33.3%) in those with higher albumin levels ( $P < .001$ ; Fig 1E).

The reasons for treatment initiation in the 317 patients who progressed to symptomatic WM were documented. Two thirds (67%) developed anemia associated with increasing IgM levels and constitutional symptoms. Peripheral neuropathy with increasing IgM levels were reported in 19.8% of the patients, whereas 15% developed hyperviscosity symptoms, and only 10.4% had organomegaly (lymphadenopathy and/or splenomegaly).

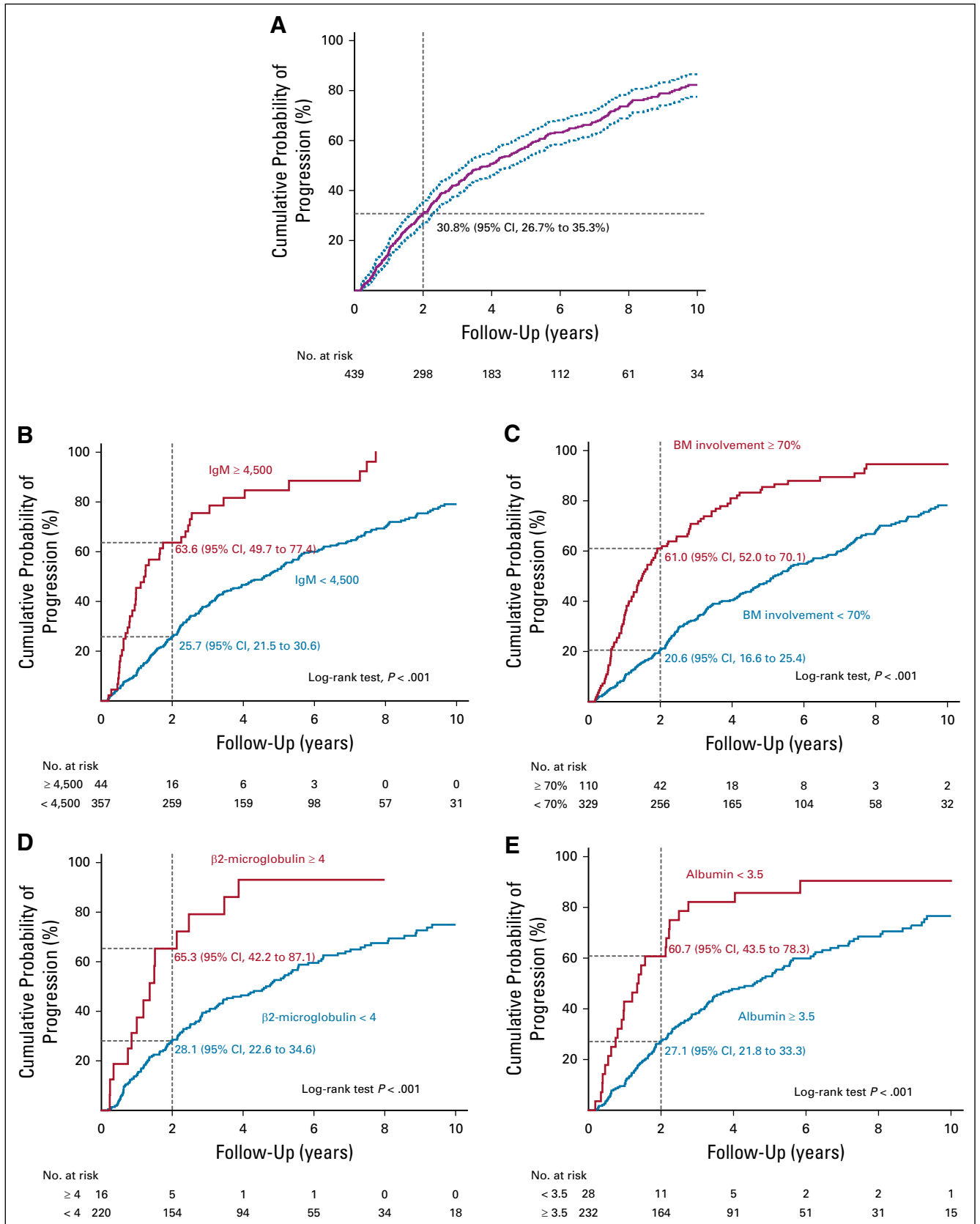
Of note, BM lymphoplasmacytic infiltration of 10% or more was associated with a significant increase in the risk of progression to symptomatic WM (log-rank test,  $P < .001$ ). We also identified a small subgroup of patients ( $n = 24$ ) with BM lymphoplasmacytic infiltration less than 10% and IgM less than 2,000 mg/dL, for which cumulative progression risk was particularly low, with 5- and 10-year progression-free survival of 100.0% and 78.7% (95% CI, 46.2 to 92.8), respectively (Data Supplement).

### Risk Factors of Progression

We selected the previously mentioned cutoffs on the basis of their association with 60% or greater probability of progression to symptomatic WM within 2 years of diagnosis (Data Supplement). In the univariable analysis, the risk of progression to WM was significantly higher for patients with IgM 4,500 mg/dL or greater (hazard ratio [HR], 3.04), BM involvement percentage 70% or greater (HR, 2.78), β2-microglobulin 4.0 mg/dL or greater (HR, 3.01), and albumin less than 3.5 g/dL (HR, 2.79). In the multivariable model, IgM 4,500 mg/dL or greater (HR, 4.65; 95% CI, 2.52 to 8.58;  $P < .001$ ), BM involvement percentage 70% or greater (HR, 2.56; 95% CI, 1.69 to 3.87;  $P < .001$ ), β2-microglobulin 4.0 mg/dL or greater (HR, 2.31; 95% CI, 1.19 to 4.49;  $P = .014$ ), and albumin less than 3.5 g/dL (HR, 2.78; 95% CI, 1.52 to 5.09;  $P = .001$ ) were independent predictors of disease progression. The multivariable regression analysis results are listed in Table 2.

### Risk Stratification by a Proportional Hazards Model

The four factors that were significant in the multivariable analysis (BM infiltration, serum IgM, β2-microglobulin, and albumin) were then included as continuous variables in a proportional hazards model to predict TTP. The model was able to separate patients whose risk scores were below the first quartile (low risk) from those whose risk scores were in the interquartile range (intermediate risk) and those whose risk scores were above the third quartile (high risk). Effectively, this model divided the cohort into three distinct groups: (1) a high-risk group with a median TTP of 1.8 years (95% CI, 1.02 to 2.2 years), (2) an intermediate-risk group with a median TTP of 4.8 years (95% CI, 2.2 to 6.2 years), and (3) a low-risk group with a median TTP of 9.3 years (95% CI, > 5.5 years; Fig 2A). The model also successfully identified three risk groups with clear curve separation and similar medians and CIs when we divided the cohort into two groups on the basis of the diagnosis date (Data Supplement).



**FIG 1.** Cumulative probability of progression among patients. The Kaplan-Meier method was used for estimation of cumulative incidence of progression (A) among patients with asymptomatic Waldenström macroglobulinemia and stratified by (B) immunoglobulin M (IgM) levels, (C) bone marrow (BM) involvement, (D)  $\beta$ 2-microglobulin, and (E) albumin.

**TABLE 2.** Risk Factors for Disease Progression in Patients With AWM in DFCI Cohort

Predictive Variables	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age, years	1.00 (0.99 to 1.01)	.643		
Sex, male	1.01 (0.81 to 1.27)	.920		
Light chain type				
Kappa $\nu$ lambda	1.08 (0.84 to 1.40)	.549		
Autoimmune diseases	0.84 (0.66 to 1.07)	.150		
Family history of WM	1.09 (0.76 to 1.57)	.652		
Family history of blood cancer	1.17 (0.89 to 1.54)	.260		
Laboratory data				
IgM $\geq$ 4,500	3.04 (2.16 to 4.29)	< .001	4.65 (2.52 to 8.58)	< .001
BM involvement percentage $\geq$ 70	2.78 (2.18 to 3.56)	< .001	2.56 (1.69 to 3.87)	< .001
WBC < 4,000	0.76 (0.34 to 1.72)	.512		
Hemoglobin < 11.5	2.66 (2.02 to 3.50)	< .001		
Lymphocyte count < 1,500	0.90 (0.61 to 1.32)	.579		
$\beta$ 2-microglobulin $\geq$ 4.0 mg/dL	3.01 (1.72 to 5.26)	< .001	2.31 (1.19 to 4.49)	.014
Albumin < 3.5	2.79 (1.83 to 4.25)	< .001	2.78 (1.52 to 5.09)	.001

NOTE. Only variables available for  $\geq$  80% of patients were included in the multivariable model.

Abbreviations: AWM, asymptomatic WM; BM, bone marrow; DFCI, Dana-Farber Cancer Institute; HR, hazard ratio; IgM, immunoglobulin M; WM, Waldenström macroglobulinemia.

Because of competing risks of death in our cohort with a median age of 61 years, disease-specific survival was calculated, censoring patients whose death was deemed unrelated to WM or its complications. We observed that high-risk AWM patients had significantly lower disease-specific survival compared to intermediate and low-risk groups (log-rank test,  $P = .029$ ; Data Supplement).

#### External Validation of Predictive Model

With a median follow-up of 9.4 years, the first cohort, from Mayo Clinic, Rochester, MN, comprised 48 patients with a median TTP of 4.6 years and a progression rate of 77%. The model successfully divided the cohort into three groups with a median TTP of 2.4 years (95% CI, 1.4 to 4.9 years), 5.7 years (95% CI, 3.4 to 9.3 years), and 10.2 years (95% CI, > 5.58 years) for the high-, intermediate- and low-risk groups, respectively (Fig 2B). Similarly, with a median follow-up of 7.2 years, the second cohort, from Greece, which comprised 47 patients with a 34% progression rate, the model successfully divided the patients into three groups, with a median TTP of 2.92 years (95% CI, > 1.3 years), 7.25 years (95% CI, > 5.6 years), and not reached (95% CI, > 5.35 years) for the high-, intermediate-, and low-risk groups, respectively (Fig 2C).

#### Web Page Development

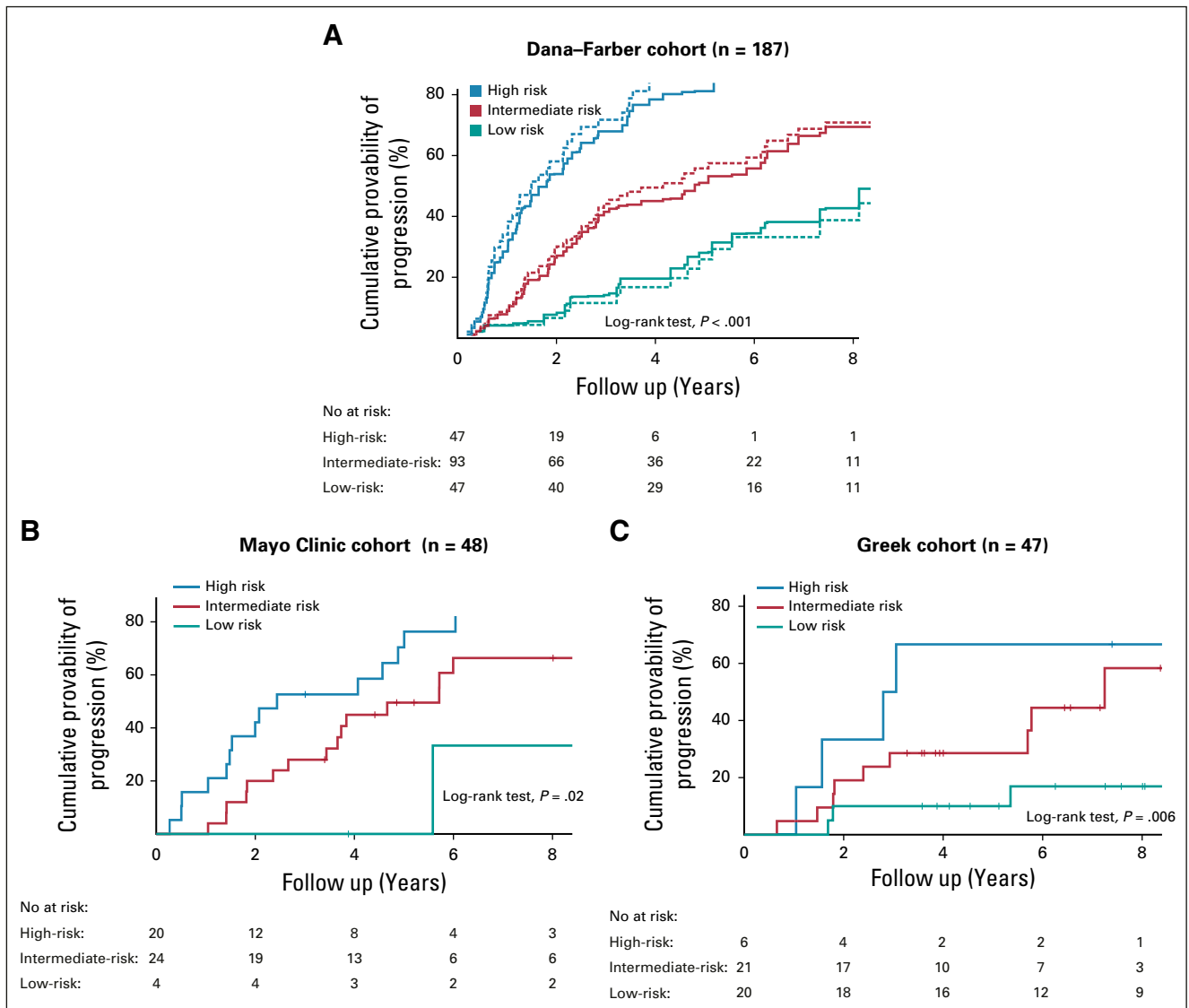
For clinical applicability, we designed a Web page application that allows clinicians to input patient laboratory values for the designated variables and obtain a risk score that places the patient in one of three risk groups: low, intermediate, or high (Data Supplement).

#### MYD88 Mutation Status Is an Independent Risk Factor of Progression

We combined available data on *MYD88* mutation status from the Dana-Farber Cancer Institute cohort and the Greek cohort. In total, 106 patients from both cohorts had been genotyped; 89 patients (84%) carried *MYD88* L265P and 17 (16%) were wild type (WT). The median TTP was 4.9 years (95% CI, 3.1 to 6.2 years) versus 1.8 years (95% CI, > 1.5 years) in patients with *MYD88* L265P and *MYD88* WT, respectively (log-rank test,  $P < .001$ ; Fig 3). Wild type *MYD88* was a significant independent risk factor for progression in multivariable analysis (HR, 2.7; 95% CI, 1.5 to 5;  $P < .001$ ).

#### DISCUSSION

Because of its rarity, AWM has not been extensively studied, and only a few studies have been conducted in small cohorts.<sup>13,19,20</sup> In fact, there are two sets of diagnostic criteria for AWM.<sup>2,13</sup> The one proposed by Mayo Clinic requires 10% or greater BM lymphoplasmacytic cells for an SWM diagnosis and recommends a diagnosis of IgM MGUS for patients with less than 10% lymphoplasmacytic cells,<sup>13,15</sup> whereas the recommendations of the Second International Workshop on Waldenström Macroglobulinemia panel defined AWM as the presence of any percentage of BM infiltration in the absence of WM symptoms, reserving the diagnosis of IgM MGUS for patients in whom there is no immunophenotypic evidence of WM.<sup>2,15-17</sup> Until now, there has been no clear answer regarding which



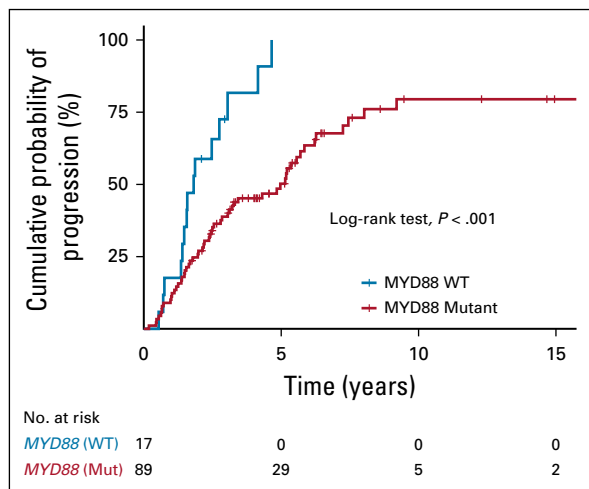
**FIG 2.** Cumulative probability of disease progression among patients with different risk scores according to the proportional hazards model and model performance in external validation cohorts. (A) The model was built using four variables: BM involvement, immunoglobulin M (IgM) levels,  $\beta 2$ -microglobulin, and albumin. It divided the cohort into three risk groups, corresponding to low-, intermediate-, and high-risk AWM with a median time to progression (TTP) of 9.3, 4.8, and 1.8 years, respectively. Dashed and solid lines represent the results of training set and cross-validation, respectively. (B) Mayo Clinic, Rochester, MN, cohort: median TTP of 10.2, 5.7, and 2.4 years, for the low-, intermediate-, and high-risk groups, respectively. (C) National and Kapodistrian University, Athens, Greece, cohort: median TTP of not reached, 7.3, and 2.9 years, for the low-, intermediate-, and high-risk groups, respectively. BM, bone marrow; AWM, Asymptomatic Waldenström macroglobulinemia.

threshold is more appropriate. In our cohort, a BM lymphoplasmacytic infiltration of 10% or more was associated with a significantly increased risk of progression to WM. At the same time, we identified a small subgroup of patients with less than 10% infiltration and IgM less than 2,000 mg/dL, whose progression rate over time was similar to what is reported by studies on patients with IgM MGUS.<sup>14</sup>

However, it remains to be seen whether there is such a high-risk subgroup of patients with AWM for which progression is imminent enough to necessitate treatment. Progression risk in AWM has been previously studied by few

groups. In 2003, Alexanian et al<sup>19</sup> reported on a small cohort of 31 patients with AWM at MD Anderson Cancer Center. In that cohort, 19 of the 31 patients had BM infiltration less than 10%, and the median TTP was 6.9 years. Prognostic factors for early progression were hemoglobin less than 11.5 g/dL,  $\beta 2$ -microglobulin 3.0 mg/L or greater, and IgM monoclonal protein greater than 3.0 g/dL. In 2005, Baldini et al<sup>20</sup> reported results from a European cohort of 201 patients with SWM. With a median follow-up of only 5 years, approximately 22% of the patients progressed to overt disease. Independent risk factors of progression





**FIG 3.** MYD88 mutation status is an independent risk factor for progression to symptomatic Waldenström macroglobulinemia. The Kaplan-Meier method was used to compare progression-free survival between patients with *MYD88* L265P and wild-type (WT) disease.

included increasing serum M-spike, decreasing hemoglobin, and male sex. In 2012, Kyle et al<sup>13</sup> reported their results from a prospective cohort of 46 patients with SWM at Mayo Clinic, wherein approximately 71% of the patients had progressed to overt disease after a median follow-up of 15.4 years. In their study, independent risk factors for progression included BM lymphoplasmacytic infiltration percentage, serum M-spike, hemoglobin, and reduced serum IgA levels.

In this cohort of 439 patients with AWM, approximately 72% of the patients progressed to overt disease. In that respect, our cohort was more similar to that reported by Kyle et al.<sup>13</sup> Independent risk factors of progression included BM lymphoplasmacytic infiltration 70% or greater, serum IgM 4,500 mg/dL or greater,  $\beta$ 2-microglobulin 4 mg/dL or greater, and albumin less than 3.5 g/dL. These cutoffs were associated with a greater than 60% probability of disease progression within 2 years. Serum IgM was preferred as a biomarker over serum M-spike because of its ease of measurement and broad applicability. Hemoglobin was purposefully avoided as a predictor, given that its levels are already used as a threshold for treatment initiation in patients with AWM.

To predict progression to symptomatic WM, we proceeded to build a proportional hazards model using the four risk factors that were significant in the multivariable analysis. Given that these factors were continuous variables, we avoided dichotomizing them on the basis of artificial cutoffs and instead included them in the model as such. Because of that, our model was more flexible and comprehensive in stratifying patients with AWM. The model effectively divided the cohort into three risk groups—low, intermediate, and high-risk AWM—with a median TTP of 9.3, 4.8, and

1.8 years, respectively. The clear separation of risk group curves, as well as their corresponding TTP medians spanning a wide time interval, indicates that this model is representative of the whole spectrum of the asymptomatic disease state and can thus be used for comprehensive stratification of patients with AWM. Moreover, high-risk patients were shown to have significantly lower disease-specific survival, indicating a worse prognosis and suggesting that a potential intervention in this risk group might be warranted. To address generalizability concerns, we proceeded to validate our predictive model using two external cohorts from Mayo Clinic, Rochester, MN, and from the National and Kapodistrian University of Athens, Greece. The former was more enriched in high-disease-burden patients (77% progression rate), whereas the latter comprised more low-burden patients, with a progression rate of 34%. Our model had good discrimination properties in both cohorts, where it was able to identify three distinct risk groups with median times to progression that were similar to the ones in our cohort. These results serve to underline the robustness of our model, which was impervious to differences among cohorts spanning different centers and countries.

To simplify the application of the model, which we consider a key characteristic for clinical applicability, we made it available as an interactive Web application ([www.awmrisk.com](http://www.awmrisk.com)), where oncologists can enter an individual patient's values and obtain information regarding their risk group and estimated risk of progression to symptomatic WM at any given timepoint.

As its most significant contribution, our model has managed to identify in all three cohorts a high-risk group of patients with AWM with an increased probability of progression within a short period of time from diagnosis. Such patients should be followed more closely or perhaps considered for early intervention in a clinical trial setting.

A previous study on patients with SWM ( $n = 66$ ) showed that median TTP was 2.8 versus 1.9 years in patients with *MYD88* L265P and *MYD88* WT disease, respectively ( $P = .21$ ).<sup>21</sup> To investigate the role of *MYD88* mutation status in disease progression in our study, we increased the number of patients with available *MYD88* data by combining our cohort with the Greek cohort. In the combined data set ( $n = 106$ ), patients with *MYD88* WT disease had a significantly shorter TTP, and patients who carried *MYD88* L265P mutation were 6.7 times less likely to progress to symptomatic WM, compared with patients with WT. Of note, all patients with WT disease in our data set progressed within 5 years from diagnosis. These results are in line with previous studies showing that *MYD88* WT represents a more aggressive disease with a higher risk of transformation, resistance to therapy, and worse survival.<sup>22,23</sup>

Drawing on this large study on AWM, and with two external validation cohorts spanning the United States and Europe, we are uniquely positioned to address AWM diagnosis and stratification and lay the foundation for a broader consensus in the future. Our progression risk-based classification could help physicians improve the management of

patients with AWM by distinguishing those who need closer follow-up or early intervention from those who do not and facilitate the design and implementation of clinical trials at the AWM stage, in the hopes of preventing disease progression with end-organ damage and improving patient outcomes.

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## EQUAL CONTRIBUTION

M.B., R.S.-P., P.K., and C.-J.L. contributed equally to this work as first authors.

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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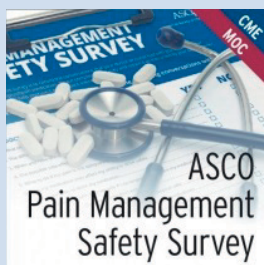
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**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST****Progression Risk Stratification of Asymptomatic Waldenström Macroglobulinemia**

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