Risk of progression of monoclonal gammopathy of undetermined significance into lymphoplasmacytic malignancies: determining demographic differences in the USA

Virtually all lymphoplasmacytic malignancies (LPM) defined by the presence of a monoclonal protein are preceded by monoclonal gammopathy of undetermined significance (MGUS).[1] Two large population-based landmark studies have determined the progression rates of the two types of MGUS, those with both immunoglobulin heavy and light chains and those with light chain only, to be 1.0 and 0.3/100 person-years, respectively.[2,3] These studies included patients ≥50 years residing in southeastern Minnesota who were part of epidemiological surveys in which serological screening for monoclonal protein was performed. Several questions pertaining to the progression of MGUS into LPM remain unanswered. It is unclear whether progression rates are similar between patients whose disease was detected during screening as part of a research study and those clinically diagnosed during the evaluation of signs or symptoms suspicious of LPM. In the Minnesota studies, most (78%) of the MGUS patients were diagnosed via population screening using stored sera (henceforth screen detected) and only 22% were discovered through routine clinical care (henceforth clinically diagnosed).[4] However, in practice, almost all MGUS are clinically diagnosed and not detected by screening. Patients with clinically diagnosed MGUS are expected to be symptomatic and have more comorbidities. It is possible that clinically diagnosed MGUS may have a different natural history compared to screen-detected MGUS. Recent studies have shown differences in prevalence rates according to demographic subgroups and depending on how MGUS is diagnosed.[5,6] Whether a similar disparity also exists in progression rates among demographic subgroups, e.g., by sex, age, and race, remains unclear. Prior studies with demographic considerations had relatively small MGUS sample sizes with limited numbers of transformations to LPM (*Online Supplementary Table S1*).[7-11] We conducted a retrospective claims data analysis using the OptumLabs™ Data Warehouse to address the outstanding issues.

OptumLabs™ is a commercial data infrastructure service, and care organization that is part of UnitedHealth Group. It has a database of de-identified information on more than 150 million privately insured and Medicare Advantage enrollees throughout the USA.[12] Our study was exempt from institutional review board approval due to the pre-existing and de-identified nature of the dataset. Using previously reported claims criteria, we identified 63,829 adult enrollees (age ≥18 years) from 2006-2013 with an incident diagnosis of MGUS, defined as ≥1 inpatient or outpatient claims with an International Classification of Diseases, Ninth Revision (ICD-9) code of 273.1.[13,14] We considered the date of the first MGUS claim to be the incident date. We excluded the following patients: (i) those having a <1 year period of lookback for ascertainment of prior diagnoses (n=37,710); and (ii) those who had a prior diagnosis of LPM any time before (n=5,471) or ≤3 months after the diagnosis of incident MGUS (n=2,685). This latter exclusion criterion was applied to minimize pre-existing, but undiagnosed LPM. For this study, we considered the following as LPM (≥1 inpatient or >1 outpatient claim): amyloidosis (ICD9: 277.30, 277.39), B-cell non-Hodgkin lymphoma (ICD9: 200.x), chronic lymphocytic leukemia (ICD9: 204.1), hairy cell leukemia (ICD9: 202.4), multiple myeloma (ICD9: 203.x; 238.6), and Waldenström macroglobulinemia (ICD9: 273.3).[13] The rate of progression into LPM (event) was expressed as number/100 person-years of MGUS follow-up. We calculated the overall and subgroup event rates based on demographics and duration of MGUS follow-up. Differences were analyzed using univariable Cox proportional hazards model.

There were 17,963 incident MGUS cases with a total follow-up of 46,276 person-years. The median age at MGUS diagnosis was 63 years (range, 18 to ≥86) and most were women (55.6%). The demographic characteristics of patients and number of events according to the number of years of enrollment are shown in *Online Supplementary Table S2*. A total of 726 LPM occurred: multiple myeloma (70.5%), non-Hodgkin lymphoma (14.1%), Waldenström macroglobulinemia (10.2%), amyloidosis (4.9%), and chronic lymphocytic leukemia (0.3%). The annual and cumulative rates of progression into LPM are shown in Figure 1. The 5-year progression rate was 5.66/100 person-years, equivalent to an annualized average rate of 1.13/100

Table 1. Rates of transformation into lymphoplasmacytic malignancies according to demographic subgroups and duration of follow-up.

Period of follow-up	All	Sex*		Race			Age (years)*		
		Women	Men	Asian	Black	White	<50	50-69	>70
Years 1-5	1.57 (1.46, 1.69)	1.41 (1.27, 1.56)	1.78 (1.60, 1.97)	1.18 (0.65, 2.13)	1.89 (1.57, 2.27)	1.57 (1.43, 1.73)	0.95 (0.75, 1.19)	1.60 (1.45, 1.78)	1.83 (1.62, 2.05)
Year 1	2.12 (1.91, 2.35)	1.93 (1.67, 2.24)	2.35 (2.03, 2.73)	1.49 (0.62, 3.57)	2.39 (1.82, 3.14)	2.11 (1.84, 2.42)	1.30 (0.93, 1.83)	2.12 (1.83, 2.46)	2.48 (2.10, 2.92)
Year 2	1.56 (1.35, 1.79)	1.52 (1.26, 1.84)	1.61 (1.30, 1.99)	1.95 (0.81, 4.69)	1.86 (1.30, 2.65)	1.55 (1.28, 1.86)	0.81 (0.49, 1.32)	1.68 (1.38, 2.03)	1.74 (1.39, 2.18)
Year 3	1.15 (0.94, 1.40)	0.94 (0.71, 1.26)	1.42 (1.09, 1.86)	Not calculable	1.34 (0.81, 2.22)	1.15 (0.88, 1.49)	0.96 (0.57, 1.61)	1.11 (0.83, 1.47)	1.31 (0.95, 1.8)
Year 4	1.04 (0.80, 1.35)	0.83 (0.56, 1.21)	1.34 (0.94, 1.92)	Not calculable	1.71 (0.97, 3.02)	1.07 (0.76, 1.51)	0.59 (0.26, 1.31)	1.14 (0.80, 1.62)	1.16 (0.74, 1.82)
Year 5	0.82 (0.57, 1.20)	0.67 (0.39, 1.15)	1.06 (0.63, 1.78)	1.69 (0.24, 11.9)	1.17 (0.49, 2.80)	0.84 (0.50, 1.39)	0.58 (0.22, 1.54)	0.84 (0.49, 1.41)	1.00 (0.52, 1.91)

*P<0.05 for within subgroup comparison of event rates.

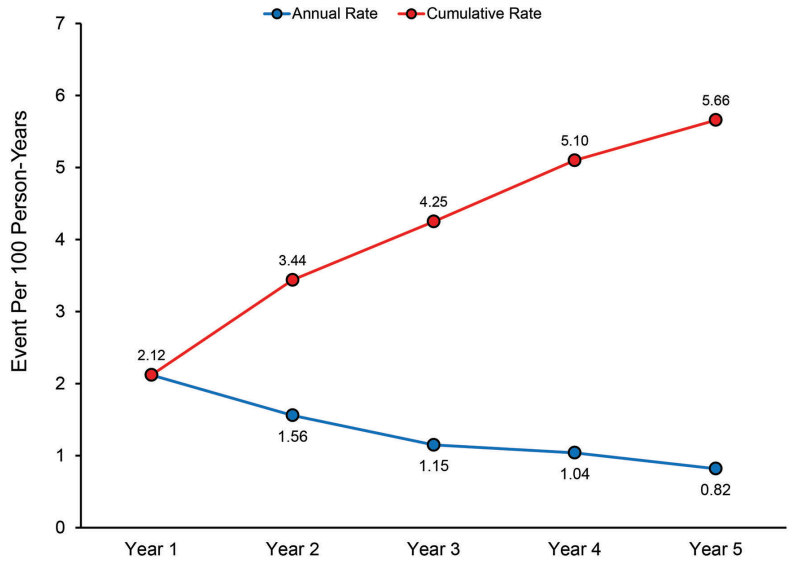

Figure 1. Annual and cumulative rates of transformation of monoclonal gammopathy of undetermined significance into lymphoplasmacytic malignancies.

person-years. The rate was highest during the first year of follow-up (2.12/100 person-years) with a sharp decrease in the second year (26.4% reduction). The rate in the fifth year was 61.3% lower than that in the first year. Compared to their counterparts, the rates of MGUS progression into LPM were higher in men and older patients but similar among races (Table 1). Comparative rates stratified by sex and age combinations are presented in Table 2. For all age groups and regardless of sex, there was almost a consistent pattern of declining rate of progression as follow-up period increased. The highest rate was among males aged ≥70 years during the first year (2.73/100 person-years), while the lowest rate was among females aged <50 years during the fifth year of follow-up (0.22/100 person-years).

We showed that MGUS progression during the initial 5 years occurred at an average rate of 1.13/100 person-years, which is similar to that found in the Minnesota study (1.0/100 person-years).[2] However, unlike the prior study which showed a stable rate of progression over time, our study demonstrated that progression was weighted heavily towards the first 2 years of follow-up, such that over half of the events occurred during this time period. Our results are consistent with previous findings from Icelandic, Dutch, and Swedish epidemiological studies.[8,10,11] Misdiagnosis of LPM as MGUS does, therefore, seem a less likely explanation of this observation. We postulate two other explanatory hypotheses. First, it is possible that the biology of clinically detected MGUS is different from that of screen-detected MGUS. Screen-detected MGUS, and LPM arising from them, may have a more indolent natural history. Second, because patients with clinically diagnosed MGUS generally have more comorbidities than those with screen-detected MGUS, the former are more likely to undergo bone marrow biopsies or imaging studies resulting in earlier diagnosis of LPM. Regardless, our findings reflect what is seen in the real-world situation. Our findings provide a strong rationale to support current MGUS clinical practice guidelines recommending more frequent follow-up visits during the first 2 years after diagnosis.

We found that the rate of transformation of MGUS into LPM was higher in males and in older patients. Males had a higher rate of transformation than females at any age group. This was at variance with a Dutch study in which no sex difference was found and a Danish study that showed, in contrast, a higher risk among females.[7,10] Based on our study, the higher rate of MGUS progression may also contribute to the higher incidence of LPM among males. This is in addition to the fact that the incidence of MGUS is already higher among males.[4] In our study, patients ≥70 years old had a nearly two-fold higher risk than those <50 years of age. Prior studies showed conflicting results regarding the impact of age.[7,10,15] These studies may have been constrained by the limited number of MGUS patients who were followed and LPM events that occurred. While the higher incidence of LPM among blacks is generally attributed to their higher prevalence of MGUS,[5] very few studies have investigated the effect of race on MGUS progression rate. We have determined in our study that such a progression did not differ significantly among Asians, blacks, and whites.

Our study has several strengths and some limitations. Unlike the landmark southeastern Minnesota epidemiological studies,[2,3] our study population was comprised predominantly of clinically diagnosed as opposed to screen-detected MGUS patients. To our knowledge, this is the largest MGUS study to date and the most racially diverse. Prior studies were conducted on much smaller scales with relatively fewer events (*Online Supplementary Table S1*). Our study was limited by a relatively short follow-up. The exclusion of patients who developed LPM within 3 months of the diagnosis of MGUS was an arbitrary decision. Since ours was a claims-based study, we did not have either biological information including immunoglobulin isotype and free light chain levels or data on the type of LPM according to immunoglobulin isotype. There was no ICD9 code specific for light chain amyloidosis. We, therefore, had to use general amyloidosis codes (ICD9: 277.30, 277.39), which might also be used for non-light chain amyloidosis. However, since all of our patients had MGUS and light chain amyloidosis comprises the majority of all newly diagnosed amyloidoses, it is very likely that most of our cases of amyloidosis were in fact of the light chain subtype.

In conclusion, our study showed demographic differences in the risk of MGUS progression into LPM. This has potential implications for the future of MGUS follow-up practice. Current practice guidelines generally recommend adjusting the intensity of follow-up according to MGUS risk categories, which are based exclusively on biological markers. Patient-specific clinical factors, such as demographics and comorbidities, are generally not taken into

Table 2. Rates of transformation of monoclonal gammopathy of undertermined significance into lymphoplasmacytic malignancies by sex and age group combinations.

Time period of follow-up	Event rate per 100 person-years (95% CI) Sex*					
	Women			Men		
	<50 years	51-69 years	>70 years	<50 years	51-69 years	>70 years
Years 1-5	0.84 (0.62, 1.14)	1.54 (1.34, 1.77)	1.54 (1.30, 1.83)	1.14 (0.81, 1.62)	1.69 (1.45, 1.96	2.18 (1.85, 2.55)
Year 1	1.18 (0.76, 1.86)	1.98 (1.61, 2.43)	2.26 (1.79, 2.86)	1.50 (0.89, 2.53)	2.30 (1.86, 2.85)	2.73 (2.17, 3.44)
Year 2	0.64 (0.32, 1.27)	1.87 (1.47, 2.39)	1.48 (1.06, 2.06)	1.10 (0.55, 2.21)	1.43 (1.04, 1.95)	2.06 (1.51, 2.80)
Year 3	1.07 (0.58, 1.99)	0.79 (0.50, 1.23)	1.11 (0.70, 1.76)	0.75 (0.28, 2.01)	1.52 (1.05, 2.18)	1.56 (1.01, 2.43)
Year 4	0.46 (0.15, 1.42)	0.98 (0.59, 1.63)	0.84 (0.42, 1.67)	0.82 (0.27, 2.55)	1.34 (0.82, 2.19)	1.63 (0.90, 2.94)
Year 5	0.22 (0.03, 1.59)	1.05 (0.56, 1.95)	0.36 (0.09, 1.45)	1.21 (0.39, 3.77)	0.55 (0.21, 1.47)	1.98 (0.94, 4.14)

*$P<0.05$ for within subgroup comparison of event rates.

account. Because MGUS is a chronic condition of the elderly with a slow rate of malignant transformation, it is likely that a substantial proportion of patients (even in the high-risk group) may succumb to competing causes of death before any LPM develops and, therefore, not benefit from MGUS follow-up. Thus, there is an opportunity to develop a more refined and personalized, risk-based MGUS follow-up strategy that incorporates not only MGUS biological markers but also the patient's demographics, comorbidities, and estimated life expectancy.

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