



# haematologica

the hematology journal

Early Release Paper

## Patterns of survival and causes of death following a diagnosis of monoclonal gammopathy of undetermined significance (MGUS): a population-based study

by Sigurdur Y Kristinsson, Magnus Björkholm, Therese M-L Andersson, Sandra Eloranta, Paul W Dickman, Lynn R Goldin, Cecilie Blimark, Ulf-Henrik Mellqvist, Anders Wahlin, Ingemar Turesson, and Ola Landgren

*Haematologica* 2009 [Epub ahead of print]

doi:10.3324/haematol.2009.010066

### *Publisher's Disclaimer.*

*E-publishing ahead of print is increasingly important for the rapid dissemination of science. Haematologica is, therefore, E-publishing PDF files of an early version of manuscripts that have completed a regular peer review and have been accepted for publication. E-publishing of this PDF file has been approved by the authors. This paper will now undergo editing, proof correction and final approval by the authors. Please note that during this production process changes may be made, and errors may be identified and corrected. The final version of the manuscript will appear both in the print and the online journal. All legal disclaimers that apply to the journal also pertain to this production process.*

Haematologica (pISSN: 0390-6078, eISSN: 1592-8721, NLM ID: 0417435, [www.haematologica.org](http://www.haematologica.org)) publishes peer-reviewed papers across all areas of experimental and clinical hematology. The journal is owned by the Ferrata Storti Foundation, a non-profit organization, and serves the scientific community with strict adherence to the principles of open access publishing ([www.doaj.org](http://www.doaj.org)). In addition, the journal makes every paper published immediately available in PubMed Central (PMC), the US National Institutes of Health (NIH) free digital archive of biomedical and life sciences journal literature. Haematologica is the official organ of the European Hematology Association ([www.ehaweb.org](http://www.ehaweb.org)).

Support Haematologica and Open Access Publishing by becoming a member of the European Hematology Association (EHA) and enjoying the benefits of this membership, which include free participation in the online CME program

# Patterns of survival and causes of death following a diagnosis of monoclonal gammopathy of undetermined significance (MGUS): a population-based study

Sigurdur Y Kristinsson,<sup>1</sup> Magnus Björkholm,<sup>1</sup> Therese M-L Andersson,<sup>2</sup> Sandra Eloranta,<sup>2</sup> Paul W Dickman,<sup>2</sup> Lynn R Goldin,<sup>3</sup> Cecilie Blimark,<sup>4</sup> Ulf-Henrik Mellqvist,<sup>4</sup> Anders Wahlin,<sup>5</sup> Ingemar Turesson,<sup>6</sup> and Ola Landgren<sup>1,3</sup>

<sup>1</sup>Department of Medicine, Division of Hematology, Karolinska University Hospital Solna and Karolinska Institutet, Stockholm, Sweden; <sup>2</sup>Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; <sup>3</sup>National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA; <sup>4</sup>Department of Medicine, Section of Hematology and Coagulation, Sahlgrenska University Hospital, Gothenburg, Sweden, and <sup>5</sup>Cancer Centre, Section of Hematology, Umea University Hospital, Umea, Sweden, and <sup>6</sup>Department of Medicine, Section of Hematology, Malmö University Hospital, Malmö, Sweden

## ABSTRACT

### Background

There are limited data on survival patterns among patients with monoclonal gammopathy of undetermined significance (MGUS).

### Design and Methods

We included, from hematology outpatient units in Sweden, 4,259 MGUS patients and compared survival to the general population by computing relative survival ratios (RSRs). We also compared causes of death with 16,151 matched controls.

### Results

One-, 5-, 10-, and 15-year RSRs were 0.98 (95% CI 0.97-0.99), 0.93 (0.91-0.95), 0.82 (0.79-0.84), and 0.70 (0.64-0.76), respectively. Younger age at MGUS diagnosis was associated with a significantly lower excess mortality compared to older ( $p < 0.001$ ). The excess mortality among MGUS patients increased with longer follow-up ( $p < 0.0001$ ). IgM (versus IgG/A) MGUS was associated with a superior survival ( $p = 0.038$ ). MGUS patients had an increased risk of dying from multiple myeloma (hazards ratio (HR)=553; 95% CI 77-3946), Waldenström's macroglobulinemia (HR= $\infty$ ), other lymphoproliferative malignancies (6.5; 2.8-15.1), other hematological malignancies (22.9; 8.9-58.7), amyloidosis (HR= $\infty$ ), bacterial infections (3.4; 1.7-6.7), ischemic heart (1.3; 1.1-1.4), other heart (1.5; 1.2-1.8), other hematological conditions (6.9; 2.7-18), liver (2.1; 1.1-4.2), and renal diseases (3.2; 2.0-4.9).

### Conclusions

Our findings of a decreased life expectancy in MGUS patients, most pronounced in the elderly, explained by both malignant transformation and non-malignant causes are of importance in the understanding and clinical management of MGUS. The underlying mechanisms may be causally related to the MGUS, but may also be explained by underlying disease that led to the detection of MGUS. Our results are of importance since they give a true estimation of survival in MGUS patients diagnosed in clinical practice.

Key words: monoclonal gammopathy of undetermined significance, multiple myeloma, prognosis, survival, sex, older age, cause of death, population-based.

Citation: Kristinsson SY, Björkholm M, Andersson TM-L, Eloranta S, Dickman PW, Goldin LR, Blimark C, Mellqvist U-H, Wahlin A, Turesson I, and Landgren O. Patterns of survival and causes of death following a diagnosis of monoclonal gammopathy of undetermined significance (MGUS): a population-based study. *Haematologica* 2009; 94:xxx  
doi:10.3324/haematol.2009.010066

©2009 Ferrata Storti Foundation. This is an open-access paper.

Funding: this research was supported by the Intramural Research Program of the NIH and the National Cancer Institute; and by grants from the Swedish Cancer Society, Stockholm County Council, and the Karolinska Institutet Foundations.

Acknowledgments: the authors thank Ms. Shiva Ayobi, The National Board of Health and Welfare, Stockholm, Sweden; Ms. Susanne Dahllöf, Statistics Sweden, Örebro, Sweden; and Ms. Charlotta Ekstrand, Ms. Molly Collin and Ms. Lisa Camner, Karolinska Institutet, Stockholm, Sweden, for invaluable ascertainment of MGUS data. The authors have no conflict of interest to declare.

Manuscript received April 13, 2009; revised version arrived May 18, 2009; manuscript accepted June 16, 2009.

Correspondence: Sigurdur Yngvi Kristinsson, M.D., Ph.D., Department of Medicine, Division of Hematology, Karolinska University Hospital Solna, SE-171 76 Stockholm, Sweden. E-mail: sigurdur.kristinsson@karolinska.se

## Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is one of the most common premalignant conditions in western countries with a prevalence of 3.2 percent in the Caucasian general population 50 years of age or older.<sup>1</sup> It is characterized by the presence of a monoclonal immunoglobulin (Ig) (M-protein) in individuals lacking evidence of multiple myeloma (MM) or other lymphoproliferative malignancies such as Waldenström's macroglobulinemia (WM), primary amyloidosis, chronic lymphocytic leukemia (CLL), or B-cell lymphoma.<sup>2,3</sup> A recent study based on 77,469 healthy adults enrolled in a U.S. nationwide population-based prospective cancer screening trial identified 71 individuals who developed MM during the course of the study. Using serially-collected pre-diagnostic serum samples obtained up to almost 10 years prior to MM diagnosis, all MM cases were found to be preceded by MGUS.<sup>4</sup> This finding establishes a key role for MGUS in the pathway to MM. Indeed, long-term follow-up of MGUS patients reveals an average one percent annual risk of developing lymphoproliferative malignancies.<sup>5,6</sup> Additional data suggests that MGUS patients with an abnormal serum  $\kappa$ - $\lambda$  free light chain-ratio, non-IgG MGUS and a high serum M-protein level (>1.5 g/dL) have a 58% absolute risk of developing MM at 20 years of follow-up, while, in sharp contrast, MGUS patients with none of these risk factors have only a 5% absolute risk of MM progression.<sup>7</sup> These observations show that the risk of MM progression among MGUS patients is highly heterogeneous, and, in fact, the vast majority of MGUS patients will never develop a lymphoproliferative malignancy.<sup>7</sup>

Although there have been several investigations focusing on the risk for developing lymphoproliferative tumors following a diagnosis of MGUS,<sup>5-11</sup> there is only limited available data on survival patterns among MGUS patients.<sup>5,6,10-12</sup> Data from the Mayo Clinic show that the median survival of MGUS patients was about 45% shorter at 15 years of follow-up than that of a comparable US population.<sup>5</sup> In a prior study from Denmark, 1,324 MGUS patients were found to have a 2-fold higher mortality compared to the general population.<sup>12</sup> Similarly, a single center study from the Netherlands including 1,464 MGUS patients reported inferior survival than a matched cohort.<sup>11</sup>

These and other smaller studies have reported the dominant causes of death among MGUS patients to be hematological malignancies, solid tumors, cardiovascular diseases, and infections.<sup>10,12,13</sup> However, to our knowledge, no population-based large study has been conducted to determine excess mortality patterns and simultaneously assess causes of death in MGUS patients compared to controls. Using population-based and hospital-based registries from Sweden, we identified a nationwide cohort of 4,259 MGUS patients diagnosed in 1986-2005. Aims of our study were to assess pattern of MGUS survival compared to the general population, and to classify causes of death in MGUS patients compared to 16,151 matched controls.

## Design and Methods

### MGUS patients and controls

Because MGUS is by definition an asymptomatic condition, it is usually diagnosed during a medical work-up for another cause. Consequently, in the general population, MGUS patients are identified within a broad range of medical specialties. In Sweden, a clinician who detects a patient with an M-protein will typically consult with a hematology specialist at a hospital-based center, and if needed, refer the patient for further work-up, especially to rule out an underlying malignancy.

MGUS is defined by the presence of a monoclonal immunoglobulin of less than 3 grams per deciliter in serum; fewer than 10% plasma cells in the bone marrow; no evidence of other lymphoproliferative disorders; and the absence of clinical manifestations related to the monoclonal gammopathy.<sup>2</sup> These criteria are essentially the same as have been used at Swedish hospitals during the study period.

We established a nationwide MGUS cohort (as described in detail elsewhere)<sup>14</sup> by retrieving information on all incident patients through a national network, which included all in- and outpatient units from major hospital-based hematology/oncology centers in Sweden. For all MGUS patients, we obtained information on sex, date of birth, date of diagnosis, and region/unit where the diagnosis was made. When available, we also collected information on MGUS subtype and concentration of the M-protein at diagnosis. In the present study, we included all MGUS patients diagnosed in outpatient units between 1986 and 2005. MGUS patients who were diagnosed with a previous hematological malignancy or a lymphoproliferative malignancy within 6 months following MGUS diagnosis were excluded from the MGUS cohort. Follow-up commenced 6 months following diagnosis so patients who died within 6 months following MGUS diagnosis were excluded in this study.

For each MGUS patient, four population-based controls (matched by sex, year of birth, and region) were chosen randomly from the Swedish Population database (cause of death analyses). All controls had to be alive at the time of MGUS diagnosis of the corresponding case and with no previous hematological malignancy at the date of the corresponding case's diagnosis.

Using the nationwide Cause of Death Registry, we obtained information on date and cause of death for all subjects (MGUS patients and controls) who had died up to December 31, 2006. We grouped causes of death into categories based on the International Classification of Diseases (ICD) classification versions 9 and 10.

Approval was obtained from the Karolinska Institutional Review Board (IRB) for this study. Informed consent was waived because we had no contact with study subjects. An exemption from IRB review was obtained from the National Institutes of Health Office of Human Subjects Research because we used existing data without personal identifiers.

### Statistical analysis

Relative survival ratios (RSRs) were computed as measures of MGUS survival.<sup>15,16</sup> RSRs provide a measure of total excess mortality associated with a diagnosis of MGUS. One-, 5-, 10-, and 15-year RSRs can be interpreted as the proportion of patients who survived their MGUS at 1, 5, 10, and 15 years, respectively. RSR is defined as the observed survival in the patient group (where all deaths are considered events) divided by the expected survival of a comparable group from the general population, which is assumed to be free of the condition in question. Expected survival was estimated using the Ederer II method<sup>17</sup> from Swedish population life-tables stratified by age, sex, and calendar time.

One-, 5-, 10-, and 15-year RSRs were calculated for two calendar periods: 1986-1995 and 1996-2005, and five age categories (<50, 50-59, 60-69, 70-79, and >80 years). We constructed regression models with the goal of estimating the effect of the target factors previously defined in this article, while controlling for potential confounding factors. Poisson regression was used to model excess mortality.<sup>18</sup> The estimates from this model are interpreted as excess mortality ratios; an excess mortality ratio of 1.5, for example, for males/females indicates that males experience 50% higher excess mortality than females.

We used Cox's proportional hazards regression models to estimate mortality rate ratio for each cause of death comparing MGUS patients to controls. A separate model was estimated for each cause of death. All calculations were performed using Stata version 10 (StataCorp 2007 Stata Statistical Software: Collage Station, TX, USA).

### Results

A total of 4,259 MGUS patients (diagnosed 1986-2005) and 16,151 population-based controls were included in the study. Demographic and clinical characteristics of MGUS patients and controls are shown in Table 1. The median age at MGUS diagnosis was 70 years (range 22-97 years). Among the MGUS patients, there were 1,822 (42.8%), 493 (11.6%), 523 (12.3%), and 2 (0.02%) diagnosed with MGUS subtypes IgG, IgA, IgM, and IgD, respectively. Information on MGUS subtype was missing for 1,419 (33.3%). Data on M-protein concentrations was available for 2,436 (57.2%) patients; the median concentration was 0.8 g/dL (interquartile range: 0.5-1.5 g/dL). The median M-protein concentration was the same in the two calendar periods 1986-1995 and 1996-2005.

### Patterns of survival

The median follow-up time was 5.6 years and 1,565 (37%) deaths were observed among the MGUS patients. When we estimated the cumulative RSRs for the entire MGUS cohort, the 1-year, 5-year, 10-year, and 15-year RSRs was 0.98 (95% CI 0.97-0.99), 0.93 (0.91-0.95), 0.82 (0.79-0.84), and 0.70 (0.64-0.76), respectively (Figure 1 and Table 2). When we evaluated survival patterns by age, we found the youngest age category (<50

**Table 1. Characteristics of MGUS patients and matched controls.**

	MGUS patients	Controls
Total No. of cases (%)	4,259 (100)	16,151 (100)
Age group, n (%)		
Less than 50	396 (9.3)	1,581 (9.8)
50-59	668 (15.7)	2,653 (16.4)
60-69	1,005 (23.6)	3,938 (24.4)
70-79	1,372 (32.2)	5,139 (31.8)
80 and above	818 (19.2)	2,840 (17.6)
Median age at diagnosis, years	70	69
Males	2,129 (50.0)	8,008 (49.6)
Females	2,130 (50.0)	8,143 (50.4)
MGUS subtype, n (%)		
IgG	1,822 (42.8)	N.A.
IgA	493 (11.6)	N.A.
IgM	523 (12.3)	N.A.
IgD	2 (0.04)	N.A.
missing	1,419 (33.3)	N.A.
M-protein concentration, n (%)		
<1.0 g/dL	1,301 (30.5)	N.A.
>1.0 g/dL	1,135 (26.7)	N.A.
missing	1,823 (42.8)	N.A.
Calendar period		
1986-1995	1,807 (42.4)	6,823 (42.2)
1996-2005	2,452 (57.6)	9,328 (57.8)

N.A.: not applicable.

years) to have 1-year, 5-year, 10-year, and 15-year RSRs of 0.99 (95% CI 0.97-1.00), 0.98 (95% CI 0.96-1.00), 0.93 (95% CI 0.89-0.96), and 0.90 (95% CI 0.81-0.95), respectively (Figure 2 and Table 2). For the oldest age category (>80 years), the 1-year, 5-year, 10-year, and 15-year RSRs was 0.97 (95% CI 0.94-0.99), 0.82 (95% CI 0.75-0.89), 0.60 (95% CI 0.44-0.77), and 0.74 (95% CI 0.11-2.41), respectively. When we conducted internal comparison analyses (Table 3), a younger age at MGUS diagnosis was associated with a significantly lower excess mortality ( $p<0.001$ ). The excess mortality among MGUS patients increased with a longer follow-up ( $p<0.001$ ). We also found IgM (versus IgG/A) MGUS to be associated with a superior survival ( $p=0.038$ ). However, we did not find any difference in survival in relation to M-protein concentration (above/below 1.0 g/dL or above/below 1.5 g/L). Also, within each MGUS subtype (IgG, IgA, and IgM), there was no difference in survival in relation to M-protein concentration at diagnosis (Table 3). Finally, when we evaluated survival patterns by sex, we found females to have a lower excess mortality than males (Table 3).

### Causes of death

As shown in Table 4, compared to controls, MGUS patients had an increased risk of dying from MM (hazards ratio (HR)=553; 95% CI 77-3946), WM (18 cases and 0 controls, HR=infinity), other lymphoproliferative malignancies (HR=6.5; 95% CI 2.8-15.1) and other

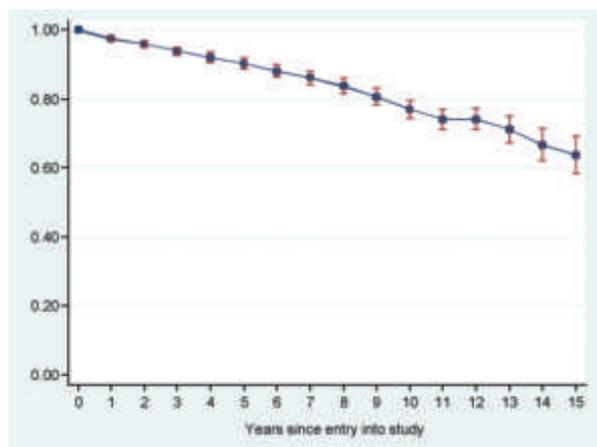


Figure 1. Relative survival ratios for MGUS patients

hematological malignancies (most commonly, acute myeloid leukemia) (RR=22.9; 95% CI 8.9-58.7). However, there was no increased risk of dying from solid tumors (HR=0.9; 95% CI 0.8-1.1). Furthermore, compared to controls, we found MGUS patients to have an increased risk of dying due to amyloidosis (24 cases and 0 controls, HR=infinity), bacterial infections (HR=3.4; 95% CI 1.7-6.7), ischemic heart disease (HR=1.3; 95% CI 1.1-1.4), other heart disorders (mainly congestive heart failure, heart valve diseases, cardiomyopathy, and arrhythmias) (HR=1.5; 95% CI 1.2-1.8), liver diseases (typically, liver failure and cirrhosis) (HR=2.1; 95% CI 1.1-4.2), other hematological disorders (most frequently hemolytic anemia and aplastic anemia) (HR=6.9; 95% CI 2.7-18), and renal diseases (mainly renal failure and glomerular diseases) (HR=3.2; 95% CI 2.0-4.9) (Table 4).

When comparing causes of death stratified by age at diagnosis (below vs. above 60 years), the risk estimates followed a similar pattern as the results from the main analyses. However, we found a higher proportion of hematological malignancies, amyloidosis, and liver disorders in younger MGUS patients compared to older MGUS patients. Also, we found a higher proportion of heart disease and vascular disorders in older (versus younger) MGUS patients (*data not shown*). For example hematological malignancy was the underlying cause of death in 35%, 34%, 22%, 16%, and 11% in age categories <50, 50-59, 60-69, 70-79, and >79 years, respectively, whereas heart disease was the underlying cause of death in 10%, 13%, 20%, 32%, and 35% in the corresponding age categories. The main causes of death according to MGUS subtype were essentially the same,

except that MGUS patients who subsequently died due to WM were predominantly IgM MGUS and those who died from MM were typically IgG/IgA MGUS. Causes of death were similar between the two calendar periods, 1986-1995 and 1996-2005 (*data not shown*).

## Discussion

In this large nationwide study including more than 4,000 MGUS patients diagnosed in a clinical context at outpatient units in Sweden between 1986 and 2005, we show that individuals with MGUS have a poorer survival than the general population. In accordance with the literature,<sup>5,6</sup> major causes of the observed excess mortality include MM, WM, and other lymphoproliferative diseases including amyloidosis. In addition, we found MGUS patients to have an increased risk of dying due to myeloid malignancies, bacterial infections, heart diseases, liver disorders, and renal diseases. Explanations for our findings probably include a combination of pathogenetic mechanisms related to MGUS as well as factors related to the underlying disease which led to medical work-up and detection of MGUS.

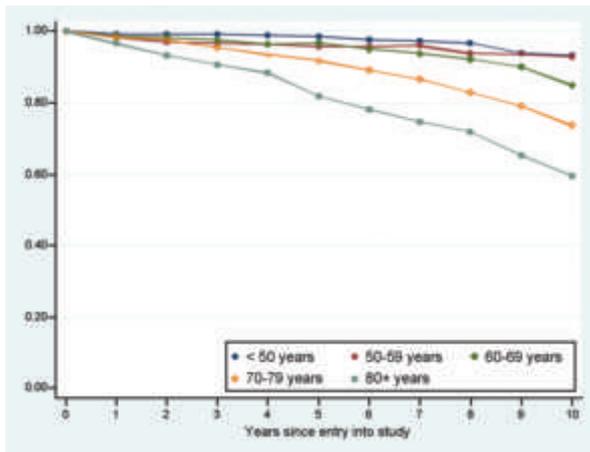
We found MGUS patients to have RSRs of 82% and 70% respectively at 10 and 15 years following diagnosis. Prior studies have also shown a lower life expectancy in MGUS patients;<sup>5,6,10-12,19,20</sup> however, in none of these have cause of death patterns among MGUS patients been compared to matched controls. Our finding of an increasing excess mortality rate with time from diagnosis, is novel and in contrast to a study from Denmark.<sup>12</sup> The discrepancy between these studies may involve selection mechanisms. Also, we found the excess mortality associated with having MGUS to be four times higher after 8-10 years of follow-up compared to 2-4 years.

Based on studies with long-term follow-up the main causes of deaths in MGUS patients were malignant diseases, cardiovascular, cerebrovascular diseases and infections.<sup>10,12,13</sup> In our study, compared to controls, we confirmed an increased risk of dying from lymphoproliferative disorders,<sup>5,6</sup> and in addition we found an excess risk of death in myeloid (mainly acute myeloid leukemia) malignancies and a wide variety of non-malignant disorders.

Importantly, we found excess mortality patterns among MGUS patients to be highly dependent on age at diagnosis, as has been observed in a Dutch<sup>11</sup> but not the Danish study.<sup>12</sup> In our study, at 5 years of follow-up, younger MGUS patients had a RSR of 98%, however older (>80 years) MGUS patients, had a 5-year RSR of

Table 2. One-, 5-, 10- and 15-year relative survival ratios (RSR) in 4,259 MGUS patients, stratified by age at diagnosis.

	<50 years	50-59 years	60-69 years	70-79 years	>80 years	All patients
1-year RSR (95% CI)	0.99 (0.97-1.00)	0.98 (0.97-0.99)	0.99 (0.97-1.00)	0.98 (0.97-0.99)	0.97 (0.94-0.99)	0.98 (0.97-0.99)
5-year RSR (95% CI)	0.98 (0.96-1.00)	0.96 (0.93-0.98)	0.97 (0.94-0.99)	0.92 (0.89-0.95)	0.82 (0.75-0.89)	0.93 (0.91-0.95)
10-year RSR (95% CI)	0.93 (0.89-0.96)	0.93 (0.89-0.96)	0.85 (0.80-0.89)	0.74 (0.68-0.80)	0.60 (0.44-0.77)	0.82 (0.79-0.84)
15-year RSR (95% CI)	0.90 (0.81-0.95)	0.77 (0.65-0.86)	0.74 (0.63-0.84)	0.59 (0.42-0.78)	0.74 (0.11-2.41)	0.70 (0.64-0.76)



**Figure 2.** Relative survival ratios for MGUS patients, stratified by age.

82%. The main causes of death in younger patients were lymphoproliferative malignancies, amyloidosis, and liver disorders, whereas cardiovascular diseases dominated in elderly MGUS patients. The observed

**Table 3.** Excess mortality ratios and 95% CIs during the first 10 years after MGUS diagnosis, by age at diagnosis, time since diagnosis, MGUS subtype, concentration of M-protein at diagnosis, and sex.

Variable	Excess mortality ratio*	p value	95% CI
<b>Age at MGUS diagnosis</b>			
< 50 years	0.40	0.003	0.22-0.73
50-59 years	0.57	0.026	0.35-0.94
60-69 years	1.00 (reference)		
70-79 years	1.87	0.001	1.31-2.67
> 79 years	3.23	<0.001	2.05-5.08
<b>Time since diagnosis</b>			
0.5-2 years	1.14	0.562	0.74-1.75
2-4 years	1.00 (reference)		
4-6 years	1.31	0.256	0.82-2.09
6-8 years	1.88	0.010	1.17-3.03
8-10 years	3.93	<0.001	2.52-6.14
<b>MGUS subtype**</b>			
IgG	1.00 (reference)		
IgA	1.09	0.717	0.69-1.71
IgM	0.24	0.038	0.06-0.93
IgG / IgA	1.00 (reference)		
IgM	0.23	0.035	0.06-0.90
<b>M-protein concentration***</b>			
<1.0 g/dL	1.00 (reference)		
>1.0 g/dL	0.95	0.835	0.60-1.52
<b>Sex</b>			
Male	1.00 (reference)		
Female	0.67	0.004	0.50-0.88

\*Adjusted for calendar period at diagnosis and all other variables in the table; \*\*Analyses based only on patients with a known MGUS subtype; \*\*\* Analyses based only on patients with a known concentration of M-protein. MGUS: monoclonal gammopathy of undetermined significance; CI: confidence interval.

**Table 4.** Causes of death among MGUS patients and controls and hazard ratios and 95% CIs as measures of excess risk of dying among MGUS patients versus controls.

Cause of death	MGUS patients	Controls	Hazard Ratio	95% CI
All causes	1,565	4,405	1.5	1.4-1.6
Any cancer	469	954	2.0	1.8-2.2
Any hematological malignancy	259	21	54.2	31.6-93.0
Multiple myeloma	185	1	553	77-3946
Waldenström's macroglobulinemia	18	0	∞	N.A.
Other lymphoproliferative malignancies	20	12	6.5	2.8-15.1
Myeloid malignancy	36	8	22.9	8.9-58.7
Any solid tumor	210	933	0.9	0.8-1.1
Amyloidosis	24	0	∞	N.A.
Infections	79	236	1.4	1.0-1.8
Bacterial	19	24	3.4	1.7-6.7
Pneumonia	46	158	1.1	0.8-1.6
Tuberculosis	0	2	0	NA
Other	14	52	1.2	0.6-2.2
Heart disease	460	1,441	1.3	1.2-1.5
Ischemic heart disease	319	1,053	1.3	1.1-1.4
Other heart disease	141	388	1.5	1.2-1.8
Vascular	192	644	1.2	1.0-1.4
Pulmonary embolism/ deep vein thrombosis	15	49	1.3	0.7-2.5
Cerebrovascular	125	444	1.1	0.9-1.4
Peripheral vascular	52	151	1.3	0.9-1.9
Gastrointestinal disease	57	154	1.6	1.1-2.2
Bowel diseases	35	108	1.4	0.9-2.1
Liver diseases	14	26	2.1	1.1-4.2
Biliary/Pancreatic disorders	8	20	1.9	0.7-4.6
Pulmonary diseases	53	191	1.0	0.7-1.4
Musculoskeletal diseases	13	26	1.2	0.6-2.5
Endocrine/metabolic disorders	30	98	1.3	0.9-2.1
Diabetes mellitus	23	85	1.2	0.7-1.9
Other	7	13	2.2	0.8-5.7
Other hematological disorders	16	9	6.9	2.7-18.0
Psychiatric illnesses	33	216	0.6	0.4-0.9
Neurological disease	28	102	1.3	0.8-2.0
Renal diseases	45	62	3.2	2.0-4.9

N.A.: not applicable.

age-related difference in survival patterns and causes of death, may have implications on the management of MGUS, and support a risk adapted strategy for follow-up and intervention in MGUS patients.

To our knowledge, we are the first to report that IgM MGUS patients had a superior survival compared to MGUS of IgG and IgA subtype. However, Schaar *et al.* did not observe any difference in survival by MGUS subtype.<sup>11</sup> IgM MGUS was reported to have a higher risk of malignant transformation compared to IgG

MGUS.<sup>5</sup> In our study, we found similar cause of death patterns by MGUS subtype, except that MGUS patients who subsequently died due to WM were predominantly IgM MGUS and those who died from MM were typically IgG/IgA MGUS. High M-protein concentration at diagnosis has been reported to predict a poorer outcome in MM and MGUS.<sup>5,6,9</sup> We did not observe such an association between M-protein concentration at diagnosis and survival, in accordance with another MGUS study.<sup>11</sup>

Our study has several strengths, including its large size as well as the application of high-quality data from Sweden in a population with access to standardized universal medical health care during the entire study period. In our study, we used a register-based cohort design, which ensured a population-based setting and generalization of our findings. As reported previously,<sup>21</sup> the MGUS diagnoses in the study were established at hematology/oncology units, typically including a bone marrow examination. In addition, ascertainment and diagnostic accuracy for lymphoproliferative disorders is very high in Sweden.<sup>22</sup>

Limitations include lack of information on potential confounders (although the matched design and analyses ensured adjustment for sex, age, and geography), and lack of detailed clinical data including co-morbidity. Because we did not screen for MGUS, we did not identify all MGUS cases in Sweden during the study period. Also since our MGUS cases were defined in a clinical setting, they might have higher M-protein concentrations than cases identified in a screening study. As already pointed out, the observed excess mortality among MGUS patients may, at least to a certain degree, reflect various underlying medical illnesses that contributed to the medical work-up eventually leading to the detection of MGUS. To better define the role of pathogenetic mechanisms that are specific for MGUS and their influence on mortality, we are planning an MGUS screening-based mortality study. We believe these two studies will provide different insights and shed light at the clinical and scientific perspective, respectively. To minimize such influences, MGUS patients with a diagnosis of a lymphoproliferative malignancy and/or who died within 6 months following MGUS diagnosis were excluded from our analyses. Furthermore, we did not include patients diagnosed during an inpatient visit. There may be inaccuracies in the specified causes of death, which are based on death certificates. However, because we compared causes of death between cases and matched controls using data obtained from the same registries, the ascertainment should be non-differential and the relative risks should not be biased. An important aspect to keep in mind when interpreting our results is that we included MGUS patients diagnosed in an outpatient setting in standard clinical practice. Consequently, our findings are relevant

to clinicians managing MGUS patients, since MGUS is associated with an excess mortality, not only restricted to MM and other lymphoproliferative disorders, but also other non-malignant diseases. It cannot be ruled out that the observed increased risk of dying due to bacterial infections, renal, and heart diseases, at least in some cases, might be reflections of early MM, amyloidosis or another lymphoproliferative malignancy. This emphasizes the importance for clinicians to suspect a potential transformation to MM or another lymphoproliferative disorder, when encountering new clinical signs or symptoms in a patient with MGUS.

In summary, we found that individuals diagnosed with MGUS in a clinical setting had a significantly reduced life expectancy. The rate of transformation of MGUS to MM or other lymphoproliferative diseases is one percent per year,<sup>5,6</sup> however the majority of MGUS patients are diagnosed as a result of a clinical investigation for different medical reasons, and were found to die from other causes. The observed excess mortality was particularly pronounced among elderly MGUS patients. Besides the well-known increased risk of dying from MM and other lymphoproliferative diseases, we found excess risk of dying due to bacterial infections, heart-, liver-, and renal diseases. Our findings show that a diagnosis of MGUS is of significance, not only with regard to the increased risk for malignant transformation but also with regard to an excess mortality of other causes. The observed cause of death patterns varied by age at MGUS diagnosis, and may have clinical implications. Future studies are needed to provide new insights on the pathogenesis of MGUS and better predictors for development of lymphoproliferative malignancies and other morbidities. Such knowledge will hopefully lead to early actions to prevent or delay MGUS progression and complications.

## Authorship and Disclosures

SYK, MB, IT, and OL, designed the study; SYK, MB, IT, and OL obtained data and initiated this work; TMLA, SE, and PWD performed all statistical analyses. All the authors were involved in analyses and the interpretation of the results; SYK and OL wrote the report. All authors read, gave comments, and approved the final version of the manuscript. All the authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

The authors reported no potential conflicts of interest.

## References

1. Kyle RA, Therneau TM, Rajkumar SV, Larson DR, Plevak MF, Offord JR, et al. Prevalence of monoclonal gammopathy of undetermined significance. *N Engl J Med* 2006; 354:1362-9.
2. Anonymous. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *Br J Haematol* 2003; 121:749-57.
3. Kyle RA. Monoclonal gammopathy of undetermined significance. Natural history in 241 cases. *Am J*

- Med 1978;64:814-26.
4. Landgren O, Kyle RA, Pfeiffer RM, Katzmann JA, Caporaso NE, Hayes RB, et al. Monoclonal gammopathy of undetermined significance (MGUS) preceding multiple myeloma: a prospective study. *Blood* 2009; 113:5412-7.
  5. Kyle RA, Therneau TM, Rajkumar SV, Offord JR, Larson DR, Plevak MF, et al. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. *N Engl J Med* 2002;346:564-9.
  6. Kyle RA, Therneau TM, Rajkumar SV, Offord JR, Larson DR, Plevak MF, et al. Long-term follow-up of IgM monoclonal gammopathy of undetermined significance. *Blood* 2003;102:3759-64.
  7. Rajkumar SV, Kyle RA, Therneau TM, Melton LJ 3rd, Bradwell AR, Clark RJ, et al. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. *Blood* 2005;106:812-7.
  8. Kyle RA, Rajkumar SV, Therneau TM, Larson DR, Plevak MF, Melton LJ 3rd. Prognostic factors and predictors of outcome of immunoglobulin M monoclonal gammopathy of undetermined significance. *Clin Lymphoma* 2005;5:257-60.
  9. Kyle RA, Remstein ED, Therneau TM, Dispenzieri A, Kurtin PJ, Hodnefield JM, et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. *N Engl J Med* 2007;356:2582-90.
  10. Kyle RA, Therneau TM, Rajkumar SV, Larson DR, Plevak MF, Melton LJ 3rd. Long-term follow-up of 241 patients with monoclonal gammopathy of undetermined significance: the original Mayo Clinic series 25 years later. *Mayo Clin Proc* 2004;79:859-66.
  11. Schaar CG, le Cessie S, Snijder S, et al. Long-term follow-up of a population based cohort with monoclonal proteinemia. *Br J Haematol* 2008.
  12. Gregersen H, Ibsen J, Mellemkjoer L, Dahlerup J, Olsen J, Sorensen HT. Mortality and causes of death in patients with monoclonal gammopathy of undetermined significance. *Br J Haematol* 2001;112:353-7.
  13. Pasqualetti P, Festuccia V, Collacciani A, Casale R. The natural history of monoclonal gammopathy of undetermined significance. A 5- to 20-year follow-up of 263 cases. *Acta Haematol* 1997;97:174-9.
  14. Kristinsson SY, Bjorkholm M, Goldin LR, McMaster ML, Turesson I, Landgren O. Risk of lymphoproliferative disorders among first-degree relatives of lymphoplasmacytic lymphoma/Waldenstrom macroglobulinemia patients: a population-based study in Sweden. *Blood* 2008; 112:3052-6.
  15. Dickman PW, Adami HO. Interpreting trends in cancer patient survival. *J Intern Med* 2006;260:103-17.
  16. Henson DE, Ries LA. The relative survival rate. *Cancer* 1995; 76:1687-8.
  17. Hakulinen T. Cancer survival corrected for heterogeneity in patient withdrawal. *Biometrics* 1982; 38:933-42.
  18. Dickman PW, Sloggett A, Hills M, Hakulinen T. Regression models for relative survival. *Stat Med* 2004; 23:51-64.
  19. Blade J, Lopez-Guillermo A, Rozman C, Cervantes F, Salgado C, Aguilar JL, et al. Malignant transformation and life expectancy in monoclonal gammopathy of undetermined significance. *Br J Haematol* 1992;81:391-4.
  20. van de Poel MH, Coebergh JW, Hillen HF. Malignant transformation of monoclonal gammopathy of undetermined significance among out-patients of a community hospital in southeastern Netherlands. *Br J Haematol* 1995;91:121-5.
  21. Landgren O, Kristinsson SY, Goldin LR, et al. Risk of plasma-cell and lymphoproliferative disorders among 14,621 first-degree relatives of 4,458 patients with monoclonal gammopathy of undetermined significance (MGUS) in Sweden. *Blood* 2009;[e-published].
  22. Turesson I, Linet MS, Bjorkholm M, Kristinsson SY, Goldin LR, Caporaso NE, et al. Ascertainment and diagnostic accuracy for hematopoietic lymphoproliferative malignancies in Sweden 1964-2003. *Int J Cancer* 2007;121:2260-6.