

Disease associations with monoclonal gammopathy of undetermined significance can only be evaluated using screened cohorts: results from the population-based iStopMM study

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Abstract

Monoclonal gammopathy of undetermined significance (MGUS) is an asymptomatic precursor condition that precedes multiple myeloma and related disorders but has also been associated with other medical conditions. Since systematic screening is not recommended, MGUS is typically diagnosed due to underlying diseases and most cases are not diagnosed. Most previous studies on MGUS disease associations have been based on clinical cohorts, possibly resulting in selection bias. Here we estimate this selection bias by comparing clinically diagnosed and screened individuals with MGUS with regards to demographics, laboratory features, and comorbidities. A total of 75,422 participants in the Iceland Screens, Treats, or Prevents Multiple Myeloma (iStopMM) study were screened for MGUS by serum protein electrophoresis, immunofixation and free light chain assay (*clinicaltrials.gov. Identifier: NCT03327597*). We identified 3,352 individuals with MGUS, whereof 240 had previously been clinically diagnosed (clinical MGUS), and crosslinked our data with large, nationwide registries for information on comorbidities. Those with clinical MGUS were more likely to have at least one comorbidity (odds ratio=2.24; 95% confidence interval: 1.30–4.19), and on average had more comorbidities than the screened MGUS group (3.23 vs. 2.36, mean difference 0.68; 95% confidence interval: 0.46–0.90). They were also more likely to have rheumatological disease, neurological disease, chronic kidney disease, liver disease, heart failure, or endocrine disorders. These findings indicate that individuals with clinical MGUS have more comorbidities than the general MGUS population and that previous studies have been affected by significant selection bias. Our findings highlight the importance of screening data when studying biological and epidemiological implications of MGUS.

Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is an asymptomatic precursor condition that consistently precedes multiple myeloma and related disorders. It is present in approximately 4.5% of the general population over the age of 50 years.^{1–6} MGUS is asymptomatic and is, therefore, typically diagnosed incidentally during clinical workup for various medical conditions, while most patients remain undiagnosed.¹ Although asymptomatic, MGUS has been associated with over 100

medical disorders, that are either assumed to cause or result from MGUS. These include thrombosis,⁷ infections,⁸ autoimmune diseases,^{9,10} fractures,^{11,12} neuropathies,¹³ as well as excess mortality.¹⁴ In some cases, there exists histopathologic evidence of a causative relationship between MGUS and disease, usually with the identification of the monoclonal immunoglobulin in the affected tissue (for example glomerulus or skin lesion).¹⁵ However, the majority of previously reported disease associations with MGUS have been found in retrospective epidemiological studies. Since systematic screening for MGUS is currently not rec-

ommended, most prior studies have been based on clinical cohorts of individuals diagnosed with MGUS as part of routine workup for other clinical signs or symptoms. Therefore, the diagnosis of MGUS is usually made due to the diagnosis of another disease, including autoimmune disorders or kidney diseases. This leads to a potential bias in the selection of individuals with more medical conditions into previously studied MGUS cohorts and, therefore, overestimation of the associations between MGUS and disease. This is supported by the only prior screening study on disease associations with MGUS, where in a screened cohort in Olmsted County, Minnesota, (n=17,398) only 14 of 75 previously reported associations were confirmed.¹⁶ However, the study included numerous distinct and specific diagnostic codes with unclear clinical correlation and thus, the observed number of cases with underlying conditions were small. This decreased statistical power and necessitated the adjustments for multiple comparisons, limiting the possibility of detecting true subtle associations.¹⁷

The Iceland Screens, Treats, or Prevents Multiple Myeloma (iStopMM) study is a large Icelandic screening study for MGUS.¹⁸ It included both individuals with incidentally diagnosed (clinical) MGUS and people diagnosed through screening, providing a unique opportunity to explore the differences between clinical and screened MGUS with regards to selection bias in clinical cohorts. The aim of this study was to systematically estimate possible selection bias in studies on MGUS by comparing the association of demographic, clinical, and laboratory factors with clinical MGUS with their association with MGUS diagnosed by systematic screening.

Methods

iStopMM study

The iStopMM study is a population-based, nationwide screening study and randomized controlled trial of follow-up strategies that aims to evaluate the benefits and potential harms of screening for MGUS (*clinicaltrials.gov. Identifier: NCT03327597*). The study has previously been described in detail.¹⁸ Briefly, 80,759 individuals, more than half of the Icelandic population aged ≥ 40 years in 2016, provided informed consent and 75,422 (>93%) of them were subsequently screened for MGUS using serum protein electrophoresis (SPEP), immunofixation and free light chain (FLC) assay. Those who had abnormal screening results, in absence of a more advanced disease, were randomized into one of three study arms, where arm 1 continued as they had never undergone screening while arm 2 and 3 followed different follow-up strategies.¹⁸ The study protocol and all information material from the iStopMM study has been approved by the Icelandic National

Bioethics Committee and the Icelandic Data Protection Authority. Access to national healthcare registries has been approved by the Icelandic Directorate of Health and the Icelandic Cancer Society.

Study cohort and data

Participants who had an M-protein on SPEP or an abnormal FLC ratio and were randomized into one of our three study arms were eligible for this study. Participants who had M-protein levels ≥ 3.0 g/dL or an FLC ratio ≥ 100 or ≤ 0.01 were excluded as they, by definition, have smoldering myeloma or multiple myeloma.¹⁹ Data from the Icelandic Cancer Registry and laboratory records from Landspítali - the National University Hospital of Iceland (NUHI) and Læknasetrið, the only laboratories performing SPEP in Iceland, were crosslinked to the study cohort. Those who had M-protein previously identified in the clinical setting, were defined as clinical MGUS. M-protein concentration, MGUS isotype, and FLC ratio were acquired from the study screening samples. Finally, comorbidity data was acquired from two national registries: the Hospital Discharge Register and Register of Primary Health Care Contacts, where the accuracy of chronic disease diagnoses has been found to be >95%.²⁰ International Classification of Diseases, 10th Revision (ICD-10) codes from the registries were grouped together into relevant disease categories (*Online Supplementary Table S1*) and their prevalence compared between clinical and screened MGUS.²¹

Statistical analyses

All statistical analyses compared clinical MGUS to screened MGUS. Demographic features (age, sex, and residence) were evaluated by *t* test and χ^2 test for continuous and binary variables, respectively. When comparing laboratory features, linear regression was used to assess continuous variables (M-protein concentration, number of risk factors for progression), and logistic regression to assess binary variables (M-protein isotype, abnormal serum FLC ratio [<0.26 or >1.65]). Participants' combined number of comorbidities was compared between the two groups by linear regression. Logistic regression was then used to compare the prevalence of each comorbidity category between the groups. All analyses were adjusted for age and sex, except for those regarding demographic differences. A *P* value of <0.05 was considered indicative of statistical significance. R Statistical Software (version 3.6.2; R Core Team 2021) was used for all statistical analyses.²²

Results

A total of 75,422 individuals were screened for MGUS in the iStopMM study, of whom 3,352 were diagnosed with

MGUS based on M-proteins detected by SPEP. Of these individuals, 240 had previously been diagnosed with clinical MGUS (7.2%) (Table 1).

Demographic features

The median age of individuals with clinical MGUS was significantly higher than in the screened MGUS group (73.5 vs. 69 years, respectively; $P<0.001$). The clinical MGUS group was also more likely to reside in Iceland's capital area compared with those with screened MGUS (68.3% vs. 60.6%; $P=0.02$). No differences in sex distribution were detected between the two groups (Table 1).

Laboratory findings

The clinical MGUS group had a 0.17 g/dL higher mean M-protein concentration than those with screened MGUS (0.51 clinical vs. 0.34 g/dL screened, mean difference 0.17 g/dL, 95% confidence interval [CI]: 0.13-0.22; $P<0.001$), after adjusting for age and sex (Table 1). There were no statistically significant differences in the prevalence of each risk factor for progression from MGUS to MM or related lymphoproliferative disease, as defined by the International Myeloma Working Group (M-protein isotype [non-IgG MGUS], M-protein concentration ≥ 1.5 g/dL, and an abnormal FLC ratio [<0.26 or >1.65]), nor in the mean number of risk factors for progression (0.80 clinical vs. 0.74 screened) (Table 1).²³

Comorbidities

Individuals with clinical MGUS were significantly more likely to have at least one comorbidity compared with those with MGUS diagnosed by screening (n=227 [94.6%]

clinical vs. n=2,704 [86.9%] screened; odds ratio [OR] =2.24; 95% CI: 1.30-4.19; $P<0.01$), and had a 37% higher mean number of comorbidities (3.23 clinical vs. 2.36 screened, mean difference 0.68; 95% CI: 0.46-0.90; $P<0.001$), in models adjusting for age and sex. Furthermore, those with clinical MGUS were more likely to have rheumatological disease (OR=2.98; 95% CI: 2.08-4.20; $P<0.001$), neurological disease (OR=2.77; 95% CI: 1.84-4.06; $P<0.001$), chronic kidney disease (OR=2.55; 95% CI 1.65-3.85; $P<0.001$), liver disease (OR=2.39; 95% CI: 1.21-4.35; $P<0.01$), heart failure (OR=2.37; 95% CI: 1.57-3.50; $P<0.001$), and endocrine disorder (OR=1.61; 95% CI: 1.14-2.24; $P<0.01$), after adjusting for age and sex. No significant differences in the prevalence of other disease categories were detected (Table 2; Figure 1).

Discussion

In this large population-based nationwide screening study with over 75,000 participants and detailed nationwide information on comorbidities, we analyzed the differences between individuals with clinically diagnosed and screened MGUS. We found that individuals with a clinical diagnosis of MGUS had a 37% higher number of comorbidities compared with those found to have MGUS as part of our screening study and were two- to three-fold more likely to have been diagnosed with certain medical conditions. Our study shows that individuals diagnosed with MGUS during work-up for other medical conditions have more comorbidities than individuals diagnosed through systematic screening. This shows that studies comparing

Table 1. Demographic and laboratory features of clinical monoclonal gammopathy of undetermined significance (MGUS) and screened MGUS.

| | Clinical MGUS N=240 | Screened MGUS N=3,112 | P |
|--|------------------------|--------------------------|-------------------------------------|
| Median age in years (range) ^a | 73.5 (42-96) | 69 (41-100) | *** |
| Male sex, N (%) ^b | 122 (50.8) | 1,671 (53.7) | |
| Residence in capital area, N (%) ^b | 164 (68.3) | 1,886 (60.6) | * |
| | | | OR (95% CI) |
| Non-IgG MGUS, N (%) ^c | 75 (31.2) | 1,044 (33.5) | 0.87 (0.65-1.15) |
| Pathological FLC ratio, N (%) ^c | 86 (35.8) | 908 (29.2) | 1.29 (0.98-1.70) |
| M-protein ≥ 1.5 g/dL, N (%) ^c | 8 (3.3) | 45 (1.4) | 1.92 (0.83-3.92) |
| | | | Δ (95% CI) |
| Mean number of risk factors of progression (SD) ^d | 0.80 (0.78) | 0.74 (0.73) | 0.04 (-0.06-0.14) |
| Mean M-protein concentration, g/dL (SD) ^d | 0.51 (0.44) | 0.34 (0.33) | 0.17 (0.13-0.22) *** |

An odds ratio (OR) >1.00 and $\Delta >0.00$ indicates increased risk for the clinical monoclonal gammopathy of undetermined significance (MGUS) group. A P value of <0.05 was considered indicative of statistical significance. An FLC ratio <0.26 or >1.65 was considered pathological. ^aAssessed by t test. ^bAssessed by χ^2 test. ^cAssessed by logistic regression, adjusted for age and sex. ^dAssessed by linear regression, adjusted for age and sex. *Indicates $P<0.05$, ** $P<0.01$, *** $P<0.001$. CI: confidence interval; Ig: immunoglobulin; FLC: free light chain; M: monoclonal; SD: standard deviation.

Table 2. Prevalence of comorbidities in clinical monoclonal gammopathy of undetermined significance (MGUS) and screened MGUS.

| | Clinical MGUS N=240 | Screened MGUS N=3,112 | Δ (95% CI) | P |
|--|------------------------|--------------------------|-------------------|-----|
| | Mean N (SD) | Mean N (SD) | | |
| Comorbidities ^a | 3.23 (2.05) | 2.36 (1.78) | 0.68 (0.46-0.90) | *** |
| | N (%) | N (%) | OR (95% CI) | P |
| Any comorbidity ^b | 227 (94.6) | 2,704 (86.9) | 2.24 (1.30-4.19) | ** |
| Rheumatological disease ^b | 47 (19.6) | 225 (7.2) | 2.98 (2.08-4.20) | *** |
| Neurological disease ^b | 35 (14.6) | 169 (5.4) | 2.77 (1.84-4.06) | *** |
| Chronic kidney disease ^b | 31 (12.9) | 154 (4.9) | 2.55 (1.65-3.85) | *** |
| Liver disease ^b | 12 (5.0) | 66 (2.1) | 2.39 (1.21-4.35) | ** |
| Heart failure ^b | 37 (15.4) | 198 (6.4) | 2.37 (1.57-3.50) | *** |
| Dementia ^b | 8 (3.3) | 40 (1.3) | 2.16 (0.91-4.55) | |
| Endocrine disease ^b | 52 (21.7) | 426 (13.7) | 1.61 (1.14-2.24) | ** |
| Arrhythmia ^b | 59 (24.6) | 535 (17.2) | 1.38 (0.99-1.90) | |
| Hypertension ^b | 163 (67.9) | 1,784 (57.3) | 1.34 (1.00-1.82) | |
| Chronic lung disease ^b | 69 (28.8) | 705 (22.7) | 1.31 (0.97-1.75) | |
| Diabetes ^b | 32 (13.3) | 329 (10.6) | 1.24 (0.83-1.81) | |
| Pancreatic disease ^b | 1 (0.4) | 9 (0.3) | 1.22 (0.07-6.60) | |
| Cerebrovascular disease ^b | 22 (9.2) | 223 (7.2) | 1.12 (0.68-1.75) | |
| Cancer ^b | 47 (19.6) | 503 (16.2) | 1.11 (0.78-1.54) | |
| Peripheral vascular disease ^b | 17 (7.1) | 179 (5.8) | 1.10 (0.63-1.81) | |
| Ischemic heart disease ^b | 56 (23.3) | 624 (20.1) | 1.06 (0.76-1.47) | |
| Psychological disease ^b | 85 (35.4) | 1,122 (36.1) | 0.99 (0.75-1.31) | |
| Inflammatory bowel disease ^b | 2 (0.8) | 40 (1.3) | 0.66 (0.11-2.19) | |

An odds ratio (OR) >1.00 and Δ >0.00 indicates increased risk for the clinical monoclonal gammopathy of undetermined significance (MGUS) group. A P value of <0.05 was considered indicative of statistical significance. ^aAssessed by linear regression, adjusted for age and sex. ^bAssessed by logistic regression, adjusted for age and sex. *P<0.05, **P<0.01, ***P<0.001. CI: confidence interval

disease associations with MGUS require data from screened populations to limit selection bias.

Individuals with clinical MGUS were on average 4.5 years older and had 0.17 g/dL higher M-protein concentration than those with screened MGUS. Since, by definition, those with clinical MGUS had had MGUS for a longer time, and because M-protein generally increases over time, these results were expected.²⁴ Both groups had a relatively low mean M-protein concentration (0.51 g/dL clinical vs. 0.34 g/dL screened), a difference that, while statistically significant, is unlikely to be clinically important. Furthermore, no statistically significant differences in the prevalence of individual risk factors of MGUS progression, or in the cumulated number of risk factors, were detected in our study. According to previous studies, the risk of MGUS progression to malignancy is low at 0.5-1.5% per year.^{2,6,24,25} The findings of this study indicate that previous estimates of MGUS progression have not been affected by selection bias and that clinically diagnosed

MGUS is similar to MGUS diagnosed by screening.

The clinical MGUS group had statistically a significantly higher number of comorbidities compared to the screened MGUS group and was more likely to have at least one comorbidity, suggesting higher disease burden in general in clinically diagnosed individuals compared with the total MGUS population. This has previously been hypothesized but evidence has lacked until now.¹⁶ This important finding suggests selection bias in clinical cohorts of MGUS. In particular, chronic kidney disease, endocrine disorders, neurological disease, liver disease and rheumatological disease were more prevalent among those with clinically diagnosed MGUS. This is clinically important since various disorders of these disease categories have previously been associated with MGUS, including glomerulonephritis,^{26,27} immune deposition kidney diseases,²⁸ hyperparathyroidism,²⁹ peripheral neuropathies,¹³ hepatitis C,^{30,31} and rheumatoid arthritis.⁹ Due to these previously reported associations with MGUS, and often indistinct clinical signs

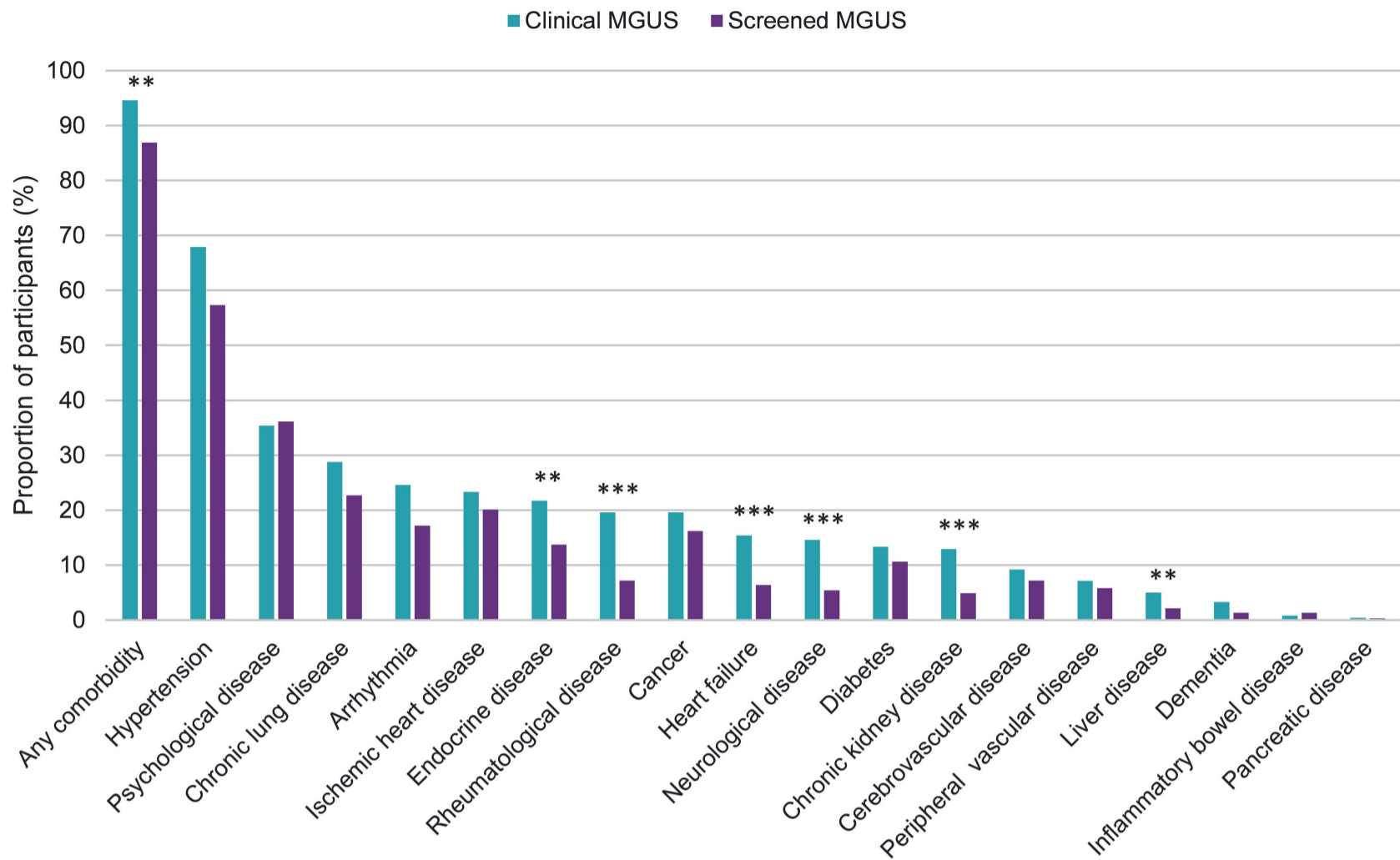


Figure 1. Comorbidity prevalence of the study cohort. A P value of <0.05 was considered indicative of statistical significance. Assessed by logistic regression models. All analyses were adjusted for age and sex. * $P<0.05$, ** $P<0.01$, *** $P<0.001$. MGUS: monoclonal gammopathy of undetermined significance.

and symptoms, affected individuals are more likely to undergo serum protein blood testing (e.g., SPEP, immunofixation, and FLC assays) during clinical workup, leading to the diagnosis of MGUS. For some of these conditions, SPEP is even advised during workup, according to clinical guidelines.^{32,33} This might also explain the higher prevalence of heart failure in the clinical MGUS group, as individuals suspected of amyloidosis causing their symptoms usually undergo SPEP and FLC assays.³⁴ These differences suggest that at least some of the previously reported disease associations with MGUS have been overestimated as the evidence was based on clinical MGUS cohorts. Further studies to estimate true associations between MGUS and other diseases are needed on screened populations. Furthermore, multifaceted data, including information on laboratory markers and medications, in addition to careful, complex data analyses suiting each association, are essential to estimate causal relationships.

Our study has several strengths. It is based on the largest screening study on MGUS to date, and it is the first one that is both population-based and nationwide. The high participation rate in the iStopMM study (54.3% of the Icelandic population ≥ 40 years of age) makes the study cohort highly representative of the general population. Extensive information was gathered on all participants, including M-protein concentration, M-protein isotype, and

FLC ratios, which was used to confirm all MGUS diagnoses. By crosslinking our data to large national registries, where disease diagnoses are recorded prospectively with very high completeness and accuracy, we also gathered high-quality information on participants' comorbidities, including cancer diagnoses. In addition, data was collected prospectively and in the same manner for all participants regardless of exposure status.

Our study also has some important limitations. Relatively few individuals had some of the comorbidities assessed, which may have affected the statistical power to ascertain potential association for those diseases. Additionally, since there were multiple statistical tests done in our study, some associations found may have been spurious. However, due to the hypothesis-generating nature of the study, we did not adjust for multiple testing.¹⁷ Finally, the Icelandic population is ethnically and genetically homogenous. Furthermore, the Icelandic health care system is universal, which makes access to full range health care services available for the entire population. However, this should not affect the results of the higher number of comorbidities among those with MGUS diagnosed in the clinical setting compared with those diagnosed through screening, although the prevalence of certain comorbidities may differ between countries and different health care systems.

In summary, we have shown that there is no meaningful difference in the severity of the precursor condition in individuals with a diagnosis of MGUS in the clinical setting compared with those diagnosed with MGUS in our screening study. However, there is a significant difference with regards to the presence of comorbidities. Those with a clinical diagnosis of MGUS have a higher mean number of comorbidities and are more likely to have been diagnosed with certain medical conditions. Our findings emphasize the fact that MGUS cohorts, based on clinically diagnosed populations, are inherently biased towards individuals with more comorbidities, compared to cohorts consisting of screened individuals. Furthermore, our findings support that selection bias has affected the results of many previous studies reporting on MGUS and various medical associations, and that at least some associations may not be biologically true or have been significantly overestimated. Going forward, it is imperative that screened MGUS cohorts are used to evaluate the epidemiological and biological implications of MGUS and that studies based on clinical MGUS cohorts should be interpreted with caution.

Disclosures

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The remaining authors have no conflicts of interest to disclose.

Contributions

AYS, SR, ST, and SYK designed the study. AYS and SR performed the analyses. AYS, SR, ST, TLJ, and SYK were involved in the interpretation of the results. AYS, SR, and SYK wrote the manuscript, with additional input from the other co-authors. All authors approved the submission of the final manuscript.

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Data-sharing statement

The iStopMM study has been approved by the Icelandic National Bioethics Committee. According to Icelandic law on ethics in research, and due to data privacy regulations and per informed consent from participants in this study, we are not allowed to share patient-level data used for this study. We, however, encourage researchers or parties interested in collaborations for non-commercial use to apply to the corresponding author. All requests will be reviewed by the iStopMM team to verify whether data sharing is within the restrictions of the study's ethical approval.

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