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Prevalence of monoclonal gammopathies and clinical outcomes in a high-risk US population screened by mass spectrometry: A prospective cohort study

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Author Contributions

H.E.K., D.J.L., J.B.A., M.B., E.D.L., R.S.P., T.R.R., G.G., C.R.M., and I.M.G., were in charge of the study design. C.C.M., P.K., J.M., I.M.B., R.F., T.R.R., G.G., C.R.M., and I.M.G., oversaw conceptualization. G.G., C.R.M., and I.M.G., were in charge of funding acquisition. H.E.K., C.J.C., H.B., C.M., and C.J.B., were in charge of sample processing. H.E.K., J.B.A., D.S., D.B., M.C.P., and S.H., acquired and analyzed the mass spectrometry data. J.P., M.B., H. L., A.C., M.I.D., J.A., E.D.L., C.R.M., and I.M.G., were in charge of project management, participants recruitment and acquisition of data for the PROMISE study cohort. D.J.L., J.P., S.T.W., and E.K., were in charge of designing clinical data acquisition and validation from the Mass General Brigham Biobank. H.E.K., D.J.L., J.B.A., R.S.P., L.T., G.G., C.R.M., and I.M.G., interpreted the data. D.J.L., J.B.A., R.R., and L.T. were in charge of formal data analysis, statistical modeling and figure visualization. H.E.K., D.J.L., J.B.A., C.R.M., and I.M.G. had access to and verified the raw data and were responsible for the decision to submit the manuscript. H.E.K., D.J.L., J.B.A., C.R.M., and I.M.G. drafted the manuscript. All authors reviewed, edited, and approved the manuscript.

Declaration of Interests

H.E.K., D.J.L., J-B.A., R.R., CJ.C-C., J.P., H.B., C.M., H.L., A.C., M.I.D., J.A., C.J.B., E.D.L., R.S-P., I.M.B., E.K., L.T., T.R.R., declare no conflicts of interest.

D.S., D.B, M.C.P. are current employees of The Binding Site.

M.B. is a consultant for Takeda and has received honoraria from Takeda, Janssen and BMS.

S.H. is a current employee, member of the Board of Directors, and holds patents related to The Binding Site.

C.C.M. is a consultant for Eli Lilly and Epizyme, is an advisory board member for BMS, has served as a consultant and advisory board member for GSK, has received honoraria Janssen, and received honoraria and served as an advisory board member for Karyopharm and Sanofi.

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J.M. is a consultant for Amgen, BMS, GSK, Janssen, Karyopharm, Sanofi and Takeda.

R.F. is a consultant for AbbVie, Amgen, Bayer, BMS/Celgene, GSK, H3 Therapeutics, Janssen, Juno, Karyopharm, Kite, Merck, Novartis, Oncopeptides, OncoTracker, Pfizer, Pharmacyclics, Regeneron, Sanofi, Takeda and is on scientific advisory board of Adaptive Biotechnologies, Caris Life Sciences, OncoMyx and OncoTracker

G.G. receives research funds from IBM and Pharmacyclics and is an inventor on patent applications related to MSMuTect, MSMutSig, MSIDetect, POLYSOLVER, SignatureAnalyzer-GPU and TensorQTL. G.G. is a founder, consultant and holds privately held equity in Scorpion Therapeutics. C.R.M. has serves as a consultant for JBF Legal and received research funding from GRAIL, Inc. I.M.G. has served as a consultant for AbbVie, Adaptive, Aptitude Health, BMS, Cellectar, CurioScience, Genetch, Janssen, Janssen Central American and Caribbean, Karyopharm, Medscape, Oncopeptides, Sanofi, Takeda, The Binding Site, GNS, and GSK. I.M.G.'s spouse, William Savage MD, PhD, is CMO and equity holder of Disc Medicine.

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Abstract

Background—Monoclonal gammopathy of undetermined significance (MGUS) prevalence estimates are currently based on predominantly White study populations screened by serum protein electrophoresis/immunofixation (SPEP/IFX). A 3% MGUS prevalence is reported in the general population of European ancestry aged ≥50 years. MGUS prevalence is two times higher in individuals of African descent or with a family history of multiple myeloma (MM) related conditions. We aimed to evaluate the prevalence and clinical implications of monoclonal gammopathies (MG) in a high-risk population screened by quantitative mass spectrometry.

Methods—We used quantitative matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) and EXENT-iQ software to screen for and quantify MG in serum

from 7,622 individuals who consented to the prospective PROMISE screening study between February 2019 and November 2021 and the Mass General Brigham Biobank (MGBB) between July 2010 and July 2021. 83% of participants were at high risk for developing an MG, based on Black ancestry or a family history of hematologic malignancies. Participants with a plasma cell malignancy diagnosed prior to screening were excluded. Longitudinal clinical data were available for MGBB participants with a median follow-up time from serum sample screening of 4.5 years (IQR, 2.4 to 6.7 years).

Findings—In our study cohort, the median age at time of screening was 56 years (range, 18 to 95). 5,013 (66%) participants were female and 2,439 (32%) self-identified as Black. Using SPEP/IFX, the MGUS prevalence was 6% in high-risk individuals aged ≥50. Using MS, we observed a >40% total MG prevalence in this group. We termed MGs below the current clinical IFX detection level (<0.2g/L) monoclonal gammopathy of indeterminate potential (MGIP), to differentiate them from higher-concentration MGs, termed MS-MGUS, which had a 13% prevalence by MS in high-risk individuals aged ≥50. MGIP was predominantly of IgM isotype, and its prevalence increased with age. MS-MGUS prevalence increased with age and was higher in males and high-risk individuals. The monoclonal proteins at the MGIP level were confirmed by liquid chromatography mass spectrometry testing. Screen-detected MGs correlated with increased all-cause mortality (HR, 1.55; 95% CI, 1.16–2.08, P=0.003). All MGs were associated with an increased likelihood of comorbidities, including myocardial infarction (MGIP-High: OR, 1.60; 95% CI, 1.26–2.02, P=0.00016; MS-MGUS: OR, 1.39; 95% CI, 1.07–1.80, P=0.015).

Interpretation—MS-based screening detected an unprecedented high prevalence of MGs, including age-associated MGIP and more precise estimates of MS-MGUS compared to conventional gel-based methods. Results from our screening study with a novel technology yielded greater absolute prevalence rates with similar relative differences across risk groups compared to conventional methods. The use of MS for the detection and quantification MG including lower-level ones highlighted their potential hidden clinical significance and allowed for novel insight on possible etiologic implications of lower-level MGIP in the development of MGUS. (PROMISE, NCT03689595).

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Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant clonal expansion of plasma cells[1,2]. It is currently defined as the presence of a serum monoclonal protein (M-protein) concentration less than 30 g/L, less than 10% clonal plasma cells in the bone marrow, and the absence of myeloma-defining events. MGUS carries a 1% per year risk of progression to multiple myeloma (MM) and confers susceptibility to other lymphoproliferative disorders, amyloidosis, or light-chain deposition disease[1–3].

The first studies evaluating MGUS prevalence originated in Sweden over 50 years ago, estimating 3.1% among individuals aged >70 years old[4,5]. A large prospective screening study in Olmsted County, Minnesota subsequently estimated a 3% and 5.3% prevalence among individuals aged >50 and >70 years[4]. These studies, however, were in majority White populations and did not consider that MGUS prevalence is two to three times higher in Blacks than Whites[6–8], with more pronounced differences at younger ages[9]. MGUS and MM appear to be two times more prevalent in individuals who have a first-degree relative diagnosed with an MM-related disorder or other lymphoproliferative disease[10–13]. These data suggest that race and family history are important risk factors in MGUS development and help identify at-risk individuals.

All MGUS prevalence studies to date have relied on SPEP, a gel-based electrophoretic assay, supplemented by immunofixation (IFX) to identify M-proteins. These conventional methods, however, have limited sensitivity in detecting lower-level MGs where the M-protein fades into the polyclonal background. The serum free light chain (sFLC) assay led to improvements in the detection of light chain MGUS (LC-MGUS), which has an estimated 0.8% prevalence in the general population[14]. Later, mass spectrometry (MS) emerged as a more sensitive approach to measure M-proteins, enabling detection of low disease burden, including minimal residual disease following therapy[15,16]. Analyses based on stratified quantification of M-proteins for early disease stages of monoclonal gammopathies (MG) have not yet been reported.

Our study evaluated the prevalence and association with clinical endpoints of screen-detected MGs in individuals at higher-than-average risk for MM based on race and family history, using a high-throughput quantitative MS approach.

Methods

We performed a cohort study to evaluate the prevalence of screen-detected MGs by MS, in a population at high risk for MM and their clinical implications. We screened and analyzed serum from participants in two prospectively followed cohorts. Written informed consent was obtained from participants in both study cohorts upon recruitment. This study was conducted upon approval of protocols 18–370 and 2021P001703 by the institutional review boards of Dana-Farber Cancer Institute and the Mass General Brigham, respectively.

Study participants

PROMISE Study—Predicting Progression of Developing Myeloma in a High-Risk Screened Population (PROMISE, NCT03689595) was initiated as the first nationwide screening study for individuals at high risk for MM, including those who self-identify as Black or with a family history of hematological malignancy (HM). Individuals with a prior diagnosis of MGUS, Smoldering Multiple Myeloma (SMM), MM, Waldenström's Macroglobulinemia, or other malignancies requiring active therapy were excluded. A total of 5,037 participants consented to the PROMISE study between February 2019 and November 2021. Of those, 2,211 provided blood samples during that time. No participants who met the study criteria and provided samples were excluded (Appendix P3).

Mass General Brigham Biobank—We identified individuals from the Mass General Brigham Biobank (MGBB, https://biobank.massgeneralbrigham.org/) who met the PROMISE eligibility criteria and had serum available. We also identified a group of low-risk individuals (non-Black, no family history of HM) to serve as negative controls, and a group of non-Black, mostly White individuals with unknown family history. Participants from the MGBB selected for our study were initially recruited between July 2010 and July 2021 and their banked serum was screened retrospectively. All participants with a MM diagnosis before serum draw date were excluded. Access to participant-level data was conditional upon IRB approval (2021P001703). We extracted and identified clinical diagnoses utilizing PheCodes and hierarchical groupings of International Classification of Diseases, Ninth and Tenth Versions (ICD-9/ICD-10) codes. For all screened participants; we extracted vital status, recorded as alive or deceased; last date of encounter filed in the EHR; and diagnoses, including coronary artery disease (CAD), myocardial infarction (MI), ischemic strokes (ISTR), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Crohn's disease, ulcerative colitis (UC), celiac disease, and lymphoid hematologic malignancies (lymphoid HM) (Appendix P4).

Mass Spectrometry testing

Serum (500μL) was tested using the EXENT® system and immunoglobulin isotype assay, which uses matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) MS to quantify M-proteins (Binding Site Group Ltd.) and Optilite® free light assay to quantify IgG, IgA, IgM, and sFLC. EXENT-iQ software was used for quantitative analysis of detected M-proteins. The lower limit of accurate M-protein quantification by MALDI-TOF MS was 0.015 g/L. More sensitive liquid chromatography-mass spectrometry (LC-MS) was performed on a subset of samples to confirm the presence of M-proteins detected at low concentration by MALDI-TOF MS. Raw LC-MS data were analyzed using PeakView® version 2.2.0.11391 (AB SCIEX). LC-MS results were reviewed and interpreted by scientists from the Binding Site Group Ltd., who were blinded to the initial MALDI-TOF MS observations, who confirmed the monoclonality of all observations (Appendix P5–8).

Comparing the performance of MALDI-TOF MS to conventional testing methods

Serial dilution sensitivity testing results provided by the manufacturer showed MALDI-TOF MS detected all conventional gel-based assays' positive calls. The lower limit of detection for capillary zone electrophoresis, when supplemented with IFX in MS-positive samples, was around 0.2 g/L (0.02 g/dL) Further, in a subset of PROMISE study participants that had SPEP/IFX results available at the time of analysis, the vast majority (96.3%) of isotype-matched M-proteins detected by MALDI-TOF MS and SPEP/IFX had an M-protein concentration of >0.2 g/L (>0.02 g/dL) as estimated by MALDI-TOF MS (Appendix P9–12).

Statistical analyses and missing data

All calculations were done using R (version 4.4.1). Quantitative bio-clinical variables were described with median, interquartile range (IQR), and median absolute deviation (MAD), or mean and standard deviation. Significance of average difference between groups was

assessed with Kruskal-Wallis method for multiple group testing, and/or Wilcoxon test for 2 groups. Multiple group testing was followed by Dunn's post hoc tests when the result was significant. Qualitative variables were described using the frequency of their respective modalities. The significance of difference between frequencies between groups was assessed with Pearson's test (or Fisher's exact test if appropriate) and followed by pairwise Fisher's exact test when significant. For survival analysis, time-to-event was calculated from the serum draw date to the event date, i.e., death from any cause for overall survival, date of initial clinical diagnosis for diseases, or date of the most recent encounter for patients reported as alive when extracted from the MGBB. Hazard ratios (HR) were calculated using univariable and multivariable Cox models (with adjusted covariates listed when appropriate). HRs were reported with 95% confidence intervals (CI). Survival curves were calculated using the Kaplan-Meier method and groups were compared using a Log-rank test. P values were corrected for multiple testing with the Benjamini-Hochberg method. Adjusted p values <0.05 were considered significant (Appendix P13).

One aim of the PROMISE study is to identify clinical and genomic risk factors that predispose high-risk individuals to progress from asymptomatic MM precursor stages to overt malignancy, for this the PROMISE study plans to recruit up to 30,000 participants for screening and prospective follow-up. MS results were available for all participants included in our study. When variables with missing data were included in multivariable models, the few participants with missing data points for those variables included in the model were excluded from the analysis.

Funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. H.E.K., D.J.L., J.B.A., R.R., L.T., C.R.M., and I.M.G. had access to the raw data.

Results

We analyzed serum from 7,622 individuals. Of those, 6,305 (2,211 from PROMISE, 4,094 from MGBB) had high-risk features for MM: 2,439 self-identified as Black (henceforth, referred to as *Black* group) and 3,866 reported a family history of HM or MM precursor (*FH* group). 631 individuals were non-Black with no family history (*Control* group), and 686 were non-Black with missing family history (*Unknown* group) (Figure 1). Median age at time of screening was 56 years (IQR: 45.8–64.1, range, 18 to 95). 5,013/7,622 (66%) were female. Demographic data, including race, gender, and date of birth, was self-reported by participants. Table 1 and Appendix P14–15 show demographic distributions by study cohort and risk group.

We identified the lower limit of detection for conventional gel-based methods (SPEP/IFX) by serial dilution sensitivity testing as 0.2g/L, below which MALDI-TOF MS still detected and quantified the M-proteins (Methods and Appendix P9–12). Accordingly, M-proteins quantified by MS at ≥0.2 g/L are hereafter referred to as MGUS detected by mass spectrometry (MS-MGUS). In contrast, we refer to M-proteins detected by MS at <0.2 g/L as monoclonal gammopathy of indeterminate potential (MGIP) to better preserve the clinical associations with MGUS previously described by Kyle et al.[3]. Hereon, MGIP cases

include participants with an MG detected and quantified <0.2g/L and ≥0.015g/L (lowest limit of quantification), while MS-MGUS cases include participants with a MG detected and quantified ≥0.2 g/L. MS negative cases include participants with no MG detected above 0.015g/L. 75 samples from participants with MGIP were tested by LC-MS. M-protein detection and monoclonality were confirmed in 75/75 (100%) (Appendix P6–8).

MG was detected in 36% (2,740/7,622) of our total screened cohort, MS-MGUS was detected in 10% (755/7,622), and MGIP in 26% (1,952/7,622). The most common immunoglobulin isotype detected in MS-MGUS was IgG (62%, 469/755), followed by IgA (13%, 97/755), IgM (13%, 98/755), and biclonal gammopathy (12%, 91/755). The most common isotype in MGIP was IgM (60%, 1,172/1,952), followed by IgA (10%, 190/1,952) and IgG (6%, 117/1,952). The remaining 24% (473/1,952) of MGIP cases had multiple M-protein peaks (median 2, IQR 2 to 3, range, 2 to 6) (Appendix P16–19). The isotype-specific prevalence of MS-MGUS and MGIP is described by age groups, gender, and risk groups in Appendix P20.

The MS-MGUS and MGIP prevalence increased with age in the entire cohort (P<0.0001) (Figures 2A,B). For age groups ≤50, ≥50, and ≥70 years, MS-MGUS prevalence was 5% (127/2,564), 13% (678/5,058), and 18% (173/946), respectively, and MGIP prevalence was 19% (488/2,564), 29% (1,464/5,058), and 37% (347/946), respectively. MS-MGUS was more common in males (P<0.00018), while MGIP did not differ significantly by gender (Appendix P21).

MG was detected in 36% (2,269/6,305) of high-risk individuals. The prevalence was 43% (1,788/4,207) in high-risk participants age ≥50. In this age group, the prevalence of MS-MGUS was higher in *Black* (17%, 224/1,356) and *FH* (13%, 368/2,851), compared to *Control* (10%, 38/384), following the expected relative trends although not reaching statistical significance for the latter. (P=0.0012 and P=0.1008, respectively). MGIP prevalence in each high-risk group was not significantly different from that in *Control*, for participants aged≥50 and all ages (Appendix P21). There were no significant differences in MS-MGUS and MGIP prevalence between the MGBB and PROMISE study cohorts (Appendix P22).

2,192 high-risk PROMISE participants were screened by SPEP/IFX and MS. The MGUS prevalence by SPEP/IFX was 5% (112/2,192) (95% CI, 4.3 to 6.2) and 11% (242/2,192) by MS (95% CI, 9.5 to 12). Among PROMISE participants aged ≥50 years, MGUS prevalence was 6% (101/1,714) (95% CI, 4.7 to 7.0) by SPEP/IFX and 13% (217/1,714) (95% CI, 10.9 to 14.0), which are both higher than the 3% prevalence reported for the general population age ≥50 in the Olmsted County study[4] (Appendix P23).

A summary of prevalence rates in our study is presented in Appendix P23–24.

Multivariable logistic regression models evaluated the associations of age, gender, and risk groups with screening positive for MGs. Screening positive for any MG was associated with age (odds ratio [OR], 1.49; 95% CI, 1.43 to 1.55) and *Black* (OR, 1.44; 95% CI, 1.18 to 1.75). MS-MGUS was associated with age (OR, 1.73; 95% CI, 1.62 to 1.85) and *Black* (OR, 1.79; 95% CI, 1.29 to 2.52). There was a moderate association between MS-MGUS and

male gender (OR, 1.16; 95% CI 0.99 to 1.36), which did not reach statistical significance. Age, male gender, *Black* group, and *FH* were all significantly associated with MS-MGUS on univariable analysis. MGIP was associated with age (OR, 1.41; 95% CI, 1.31 to 1.47) and *Black* group (OR, 1.31; 95% CI, 1.06 to 163) (Appendix P25).

Longitudinal clinical data were available for MGBB participants. The median follow-up from serum sample screening was 4.5 years (IQR, 2.4 to 6.7 years; range, 0 to 11 years). In a multivariable Cox proportiona-lhazards model adjusting for age, gender, risk group, and Charlson comorbidity Index (CCI), having any MG detected by MS at any concentration was associated with increased all-cause mortality (hazard ratio [HR], 1.55; 95% CI, 1.16 to 2.08, Figure 3A). When restricted to participants aged≥50, the HR for all-cause mortality for MG detected by MS was 1.68 (95% CI, 1.22 to 2.31) (Figure 3B). After stratifying MGs by concentration, MS-MGUS was significantly associated with increased all-cause mortality (HR, 2.17; 95% CI, 1.51 to 3.13), compared to having no MG. In participants aged ≥50, the HR of MS-MGUS for all-cause mortality was 2.34 (95% CI, 1.59 to 3.47). We next examined whether high-concentration MGIP mimicked the behavior of MGUS in this cohort. Using median concentration of all MGIPs (0.04g/L), we divided MGIP into MGIP-Low (L) <0.04g/L and MGIP-High (H) ≥0.04 g/L. MGIP-H was significantly associated with increased all-cause mortality (HR, 1.65; 95% CI, 1.13 to 2.43) compared to having no MG, while MGIP-L was not significantly associated with increased all-cause mortality. In participants aged>50, HR for MGIP-H for all-cause mortality was 1.80 (95% CI, 1.20 to 2.71) (Appendix P26–28).

For the MGBB cohort, age-adjusted logistic regression models evaluated the associations of MG with various comorbidities diagnosed at any point in the participants' lifetimes (Figure 4). MS-MGUS was associated with MI, SLE, UC, and lymphoid HMs, including chronic lymphocytic leukemia, all lymphoid leukemias, Hodgkin lymphoma, and non-Hodgkin lymphoma. MGIP-H was associated with CAD, MI, RA, UC, and Hodgkin lymphoma. Clinical comorbidities associated with MGs did not differ significantly when comparing our high-risk group to controls in the MGBB cohort (Appendix P29).

In age-adjusted logistic regression models, having any MG was associated with being diagnosed with lymphoid HM ≥6 months after the screening date (OR, 3.03; 95% CI, 1.95 to 4.79). MS-MGUS had nearly 8 times greater odds of being diagnosed with a lymphoid HM ≥6 months after screening (OR, 8.31; 95% CI, 5.10 to 13.66), compared to no MG. MGIP was not associated with such outcomes (Appendix P30–31). When evaluating the incidence of clinical comorbidities diagnosed ≥6 months after the screening date, MS-MGUS was associated with MI (OR, 1.75; 95% CI, 1.03 to 2.88) and systemic lupus erythematosus (OR, 4.14; 95% CI, 1.12 to 13.54) (Appendix P32).

Serial samples were available for 58 participants who screened positive for MG. The median time from baseline screening to the latest sample available was 300 days for MGIP cases (IQR, 130 to 573, range, 86 to 864 days) and 235 days for MS-MGUS cases (IQR, 130 to 573, range, 36 to 905 days). Despite a limited number of events, higher concentration of the MG detected at baseline screening was associated with the persistence of the MG over time (P<0.0001). Among the 26 baseline MGIP cases, 13 (50%) screened positive upon any

serial sampling, and 10 (38%) were positive on the latest sample available, with a maximum follow-up time of 2.5 years. One baseline MGIP case screened negative on days +589 and +689 and subsequently screened positive at +864. Two MGIP cases exhibited an increase in M-protein concentration that reached 0.2 g/L (i.e., to MS-MGUS). Among 32 baseline MS-MGUS cases, 30 (94%) screened positive upon any serial sampling. Most baseline MS-MGUS cases (23, 72%) exhibited a consistent increase in M-protein concentration, including one that progressed to SMM, defined as >30 g/L (Appendix P33).

Discussion

Prior estimates of MGUS prevalence are based on SPEP/IFX and predominantly White study populations. We present the largest screening study for serum monoclonal proteins across concentrations in high-risk individuals examined to date. Our study identifies a very high prevalence of all MGs, >40%, in high-risk individuals aged ≥50. Compared to the prevalence of 3% detected by SPEP/IFX in the general population aged ≥50 years, we found that high-risk individuals in our cohort from the same age group had an MS-MGUS prevalence over four times higher (13%). Prior studies showed that MS detects higher rates of monoclonal proteins for the diagnosis of MGUS; however, they were limited to a few hundred participants from the Olmsted County study and measured an MGUS prevalence of around 5% only, using a non-quantitative MS approach. Here, the same relative increase in MS-MGUS prevalence is maintained for at-risk individuals compared to controls, with MS detecting more cases than before in non-high-risk controls. Such rates of MS-MGUS may have been detected in our study due to the nature of the cohorts, however, we have shown that there was no difference in the prevalence of MGs across study cohorts and that the recorded comorbidities did not significantly differ across risk groups, hence not acting as a driver for the difference in prevalence rates. In our study, MG quantification allowed for stratification of outcomes, risk estimates, and clinical associations based on concentration cut points and accurate comparison to the currently widely available methods. MS-MGUS patients identified by our targeted screening approach had significantly worse survival compared to individuals with no MGs, after accounting for age, gender, risk group, and CCI. This finding builds on prior studies of more racially homogeneous populations in Sweden and southeastern Minnesota. These results, therefore, continue to motivate efforts to prospectively follow and screen a high-risk population to explore the clinical benefit of active, targeted screening strategies.

MS allowed for MG quantification at lower concentrations than was previously possible by SPEP/IFX, providing a new opportunity to explore their significance to the malignant and non-malignant clonal expansion of plasma cells. Unlike in MS-MGUS, where the prevalence was expectedly greater in high-risk groups, the prevalence of these low-level MGs, which we have termed MGIP, did not differ significantly across the defined race and family history risk groups, suggesting that these host factors may be permissive of further clonal expansion from MGIP to MGUS. The association of MGIP with increasing age may be analogous to age-associated clonal hematopoiesis of indeterminate potential (CHIP) and somatic clonal expansion in other normal tissues and may motivate future sequencing of plasma cells of study participants[17–20]. Indeed, we hypothesize that in a subset of individuals MGIP may have etiologic implications for MGUS development in combination with certain host and

environmental factors, such as race, inflammation, and genetic predisposition. However, we do not believe that all MGIP cases are premalignant as transient M-proteins have been described in the setting of immune-related disorders, infections, allogeneic hematopoietic stem cell transplant, and solid organ transplant[21–26]. Also, the oligoclonality of some MGIP cases may support future studies to test the hypothesis that an oligoclonal to monoclonal transition occurs during the development of some plasma cell disorders. Further, similar to MS-MGUS, MGIP-H was associated with worse OS, highlighting the biological continuum of MGs, with the MGs at the upper limit of MGIP (MGIP-H) potentially sharing biologic similarities with MS-MGUS. It remains unknown whether MGIP is an earlier precursor state along the MGUS-to-MM continuum. We acknowledge that by excluding patients with a diagnosis of MM prior to screening date, and the short follow-up time available for participants in the MGBB cohort, the association of MGIP with plasma cell dyscrasias could not be assessed in this study. Longer follow-up time is required to test the hypothesis that some lower-level MGIP cases carry an increased risk of developing plasma cell disorders, specifically.

Our results, from a study cohort enriched for participants of Black ancestry, necessitated an adjusted reference range for sFLC ratio for the diagnosis of LC-MGUS. After adjusting for kidney function, our analysis provides a proof-of-concept for defining population-specific reference ranges when evaluating sFLC. Further studies are needed to define appropriate reference ranges for specific patient populations, especially when using sFLC ratio for diagnosis or prognostication of patients with more advanced disease[27,28] (Appendix P35–37).

The assay used in our study is not yet available commercially or clinically across healthcare centers. However, we show data that helps establish the clinical utility and interpretation of results for clinical use of quantitative MALDI-TOF MS to screen populations at risk for myeloma. We present the first results of quantitative MS using artificial-intelligence-based software, which standardizes clinical interpretation and allow for accurate longitudinal follow-up per patient.

Our data begin to highlight the need for myeloma screening in high-risk populations using high-sensitivity methods. In summary, we found a high >40% MG prevalence using MS to screen a predominantly high-risk population, defined by self-reported Black race and family history of HM. Our study demonstrates that MGs are significantly associated with worse OS and the development of HMs. We define a new clinical entity of low-concentration MG (i.e., MGIP) that had a high prevalence of approximately 25%, a notably different risk factor profile than MGUS, and associations with age and MI. This study highlights the clinical significance of MGs, which we now have an expanded opportunity to explore with MS and may ultimately be translated to beneficial clinical and public health strategies. Future directions will include screening participants serially to determine long-term MG outcomes and next-generation sequencing to explore the molecular drivers of clonal expansion.

Limitations of our study include the lack of precise associations of MGIP detected by mass spectrometry with plasma cell disorders due to the prospective nature of the study and the immaturity of the data at this time. In our study, females exhibited a higher

propensity to participate in the PROMISE screening program and the MGBB than males. We did not conduct analyses for races or ethnicities, such as Asian and Hispanic, and relied on self-reported race rather than genetic ancestry. Also, the MGBB subgroup is not a population-based cohort and the associations drawn with overall survival and other clinical phenotypes remain to be investigated in larger studies. The prevalences described in our study were not impacted by the nature of the cohort, but remain to be generalized cautiously. Finally, the clinical implications of MGIP should be investigated in larger and more homogeneous cohorts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Research in context

Evidence before this study

Databases searched by the authors for prior evidence of the subject studied included Medline, PubMed, and Google Scholar. The search terms used included Monoclonal gammopathies, MGUS, monoclonal gammopathy of undetermined significance, prevalence, predisposition, risk factors, comorbidities, multiple myeloma, and cancer screening. Prior evidence of the prevalence of monoclonal gammopathies mainly relied on the use of conventional gel-based methods (SPEP and IFX). The prevalence of monoclonal gammopathy of undetermined significance (MGUS) was shown to be around 3–5% in the general population above the age of 50, in individuals of mostly White ancestry. MGUS was shown to be more prevalent in those who identified as being Black or had a family history of a plasma cell malignancy. There was no prior evidence of a quantitative high-sensitivity mass spectrometry assay to evaluate the prevalence of monoclonal gammopathies in general in a prospectively followed high-risk cohort.

Added value of this study

Our findings address the gap in the literature relating to the benefits of screening and early detection of monoclonal gammopathies using a novel high sensitivity quantitative mass spectrometry approach and evaluate for the first time the clinical implications of lower-level monoclonal gammopathies detected and quantified by screening.

Implications of all the available evidence

Together with future work, this will allow improved delineation of the benefits of screening, the use of a high sensitivity assay for the detection of monoclonal gammopathies and further investigate the clinical implications proposed for lower-level monoclonal gammopathies detected by this assay. In future work, we plan to further investigate the etiology of MGIP, its relation to plasma cell disorders, other comorbidities, and overall survival. We also plan to leverage germline genomic and health record data from participants in our study to further investigate factors that may predispose high-risk individuals to develop a monoclonal gammopathy.

Individual participant data, including data dictionaries, are not available for sharing, in accordance with the PROMISE study protocol (PROMISE, NCT03689595).

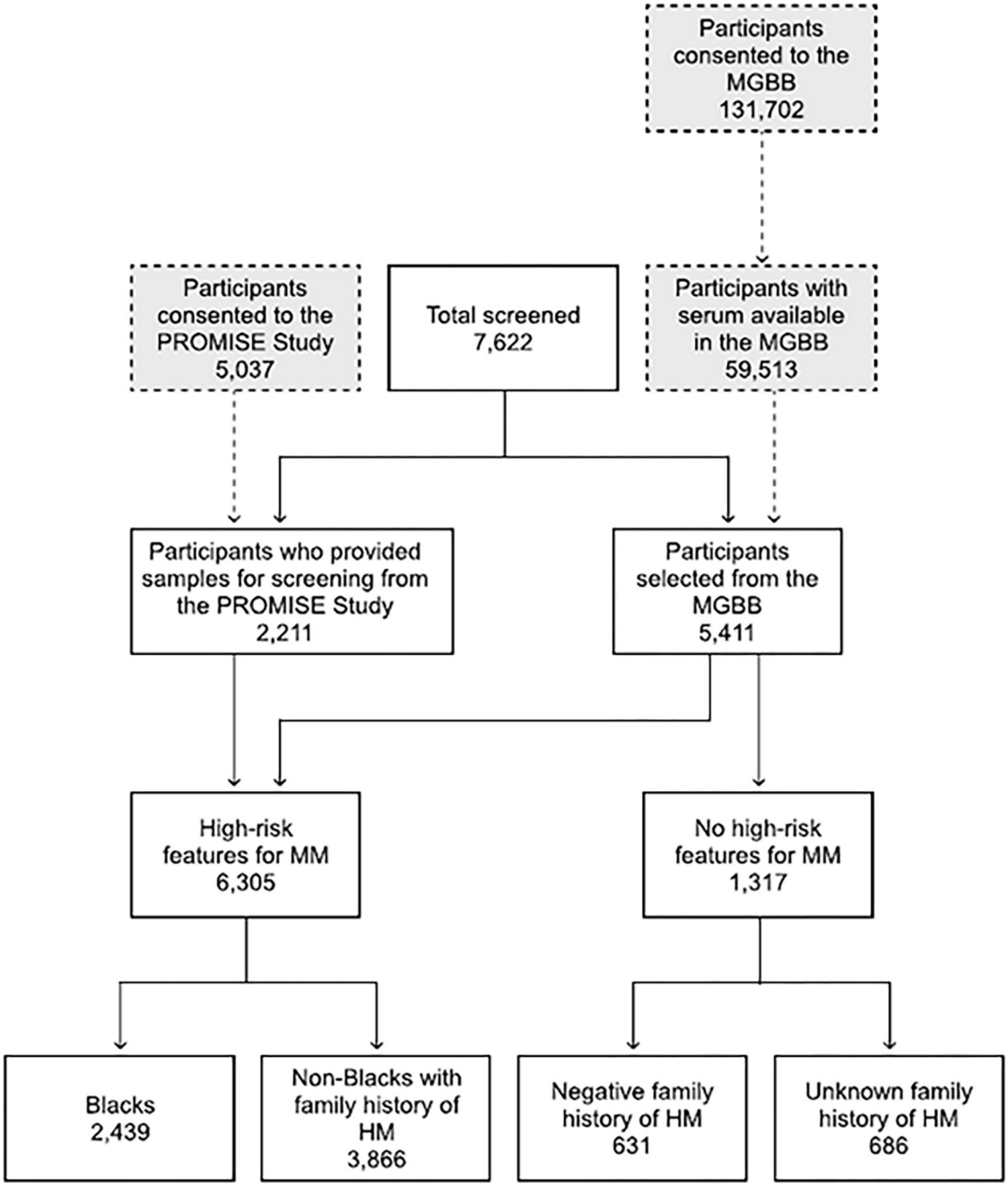


Figure 1. Study cohort composition.

Numbers reflect total participants who consented and screened from each study cohort and across risk groups until the time of analysis. Detailed methodology on recruitment of participants from both study cohorts is presented in the methods section of the manuscript and in appendix P3–4. MM: Multiple Myeloma; HM: Hematologic Malignancies

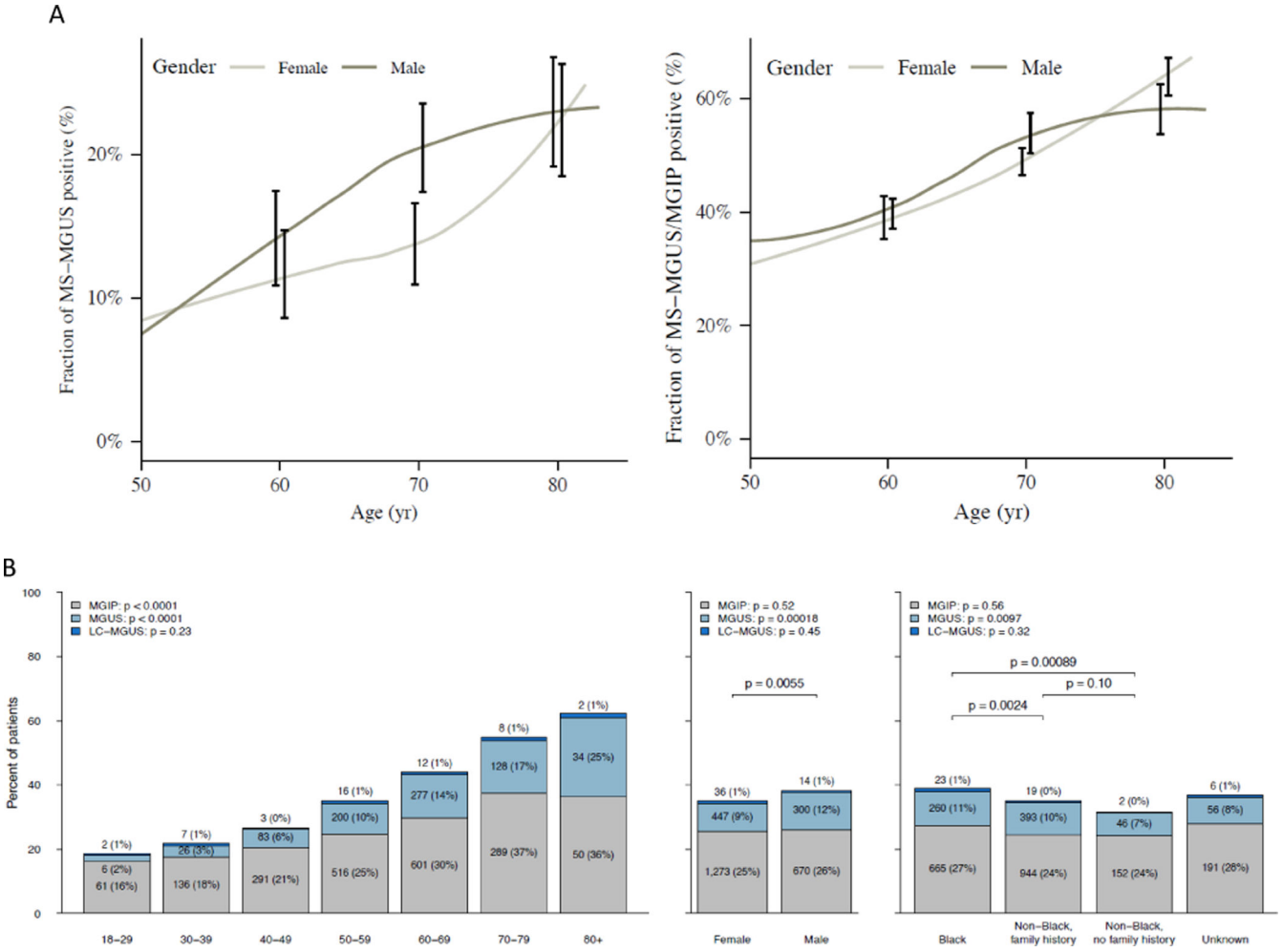
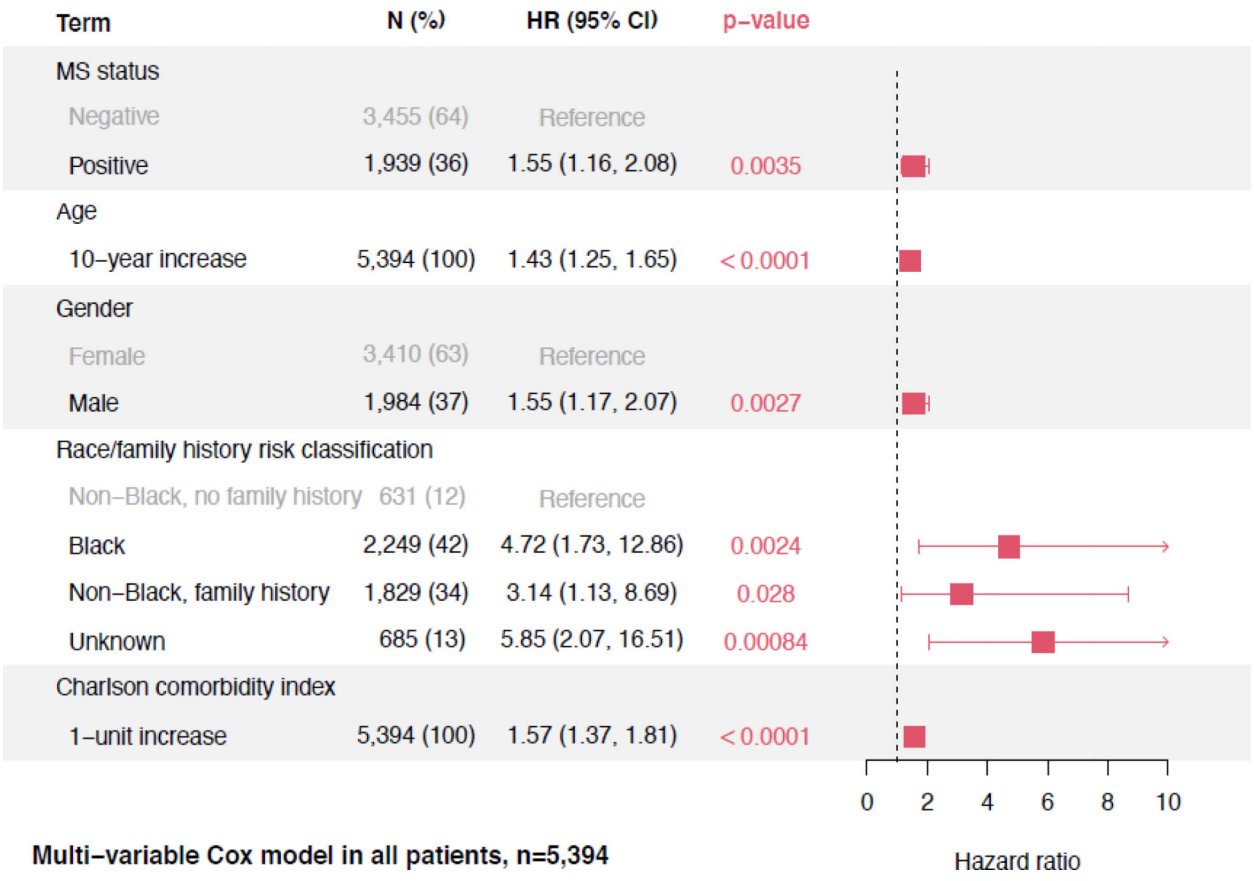


Figure 2. Description of all monoclonal gammopathies detected in our study cohort.

(A) Prevalence of MGs by age binned in 2-year intervals, modeled by local regression with 95% confidence intervals reported. (Left) Prevalence of MS-MGUS only. (Right) Prevalence of MS-MGUS and MGIP. (B) Left to right: Prevalence of all three sub-types of MGs by age, gender, and MM risk group.

A



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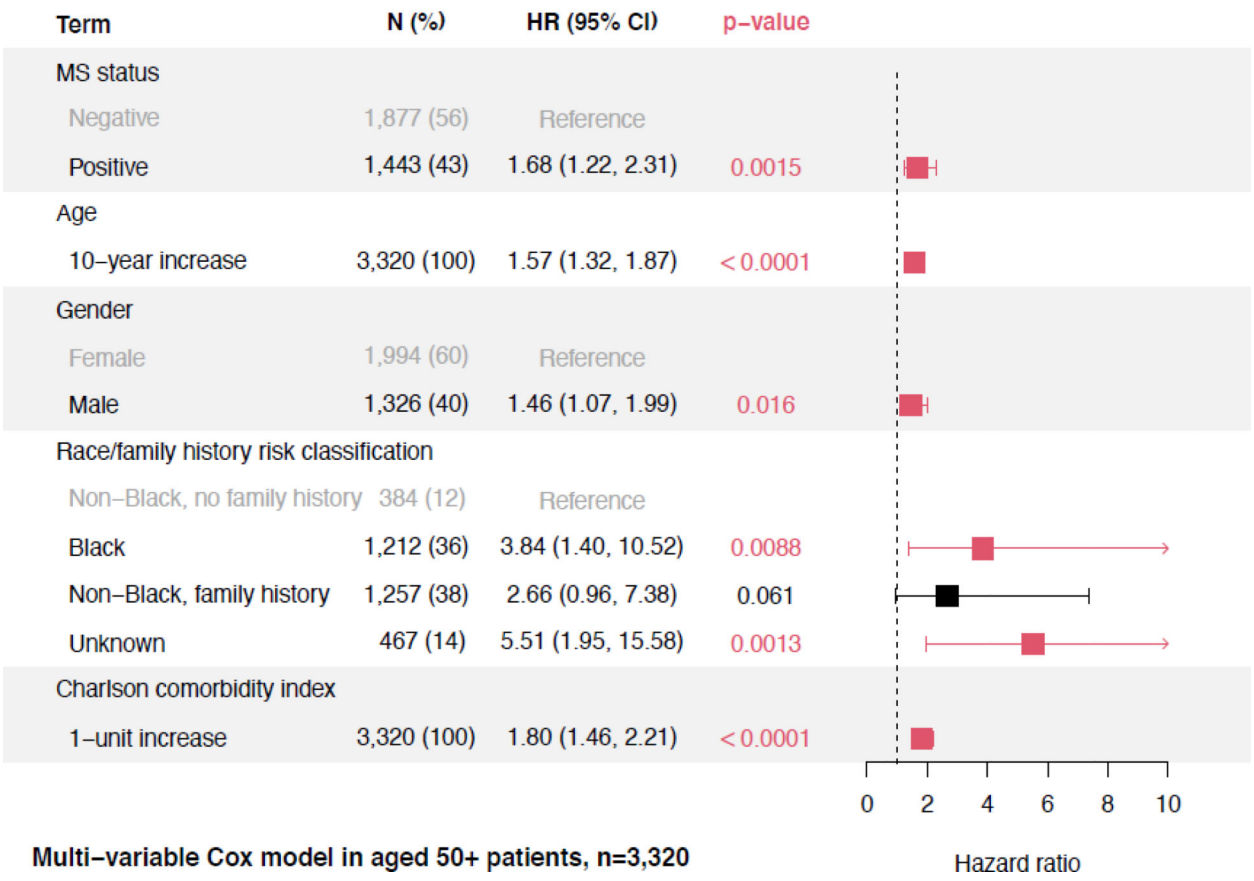

Figure 3. Association of monoclonal gammopathies with all-cause mortality.

(A) Multivariable Cox proportional-hazards model for any monoclonal gammopathy detected in all screened participants from the MGBB on overall survival adjusted for age, gender, risk group, and Charlson Comorbidiy Index. (B) Multivariable Cox proportional-hazards model for any monoclonal gammopathy detected in screened participants age ≥50, on overall survival, adjusted for age, gender, risk group, and Charlson Comorbidiy Index. CI: Confidence interval, HR: Hazard ratio, MS: Mass spectrometry.

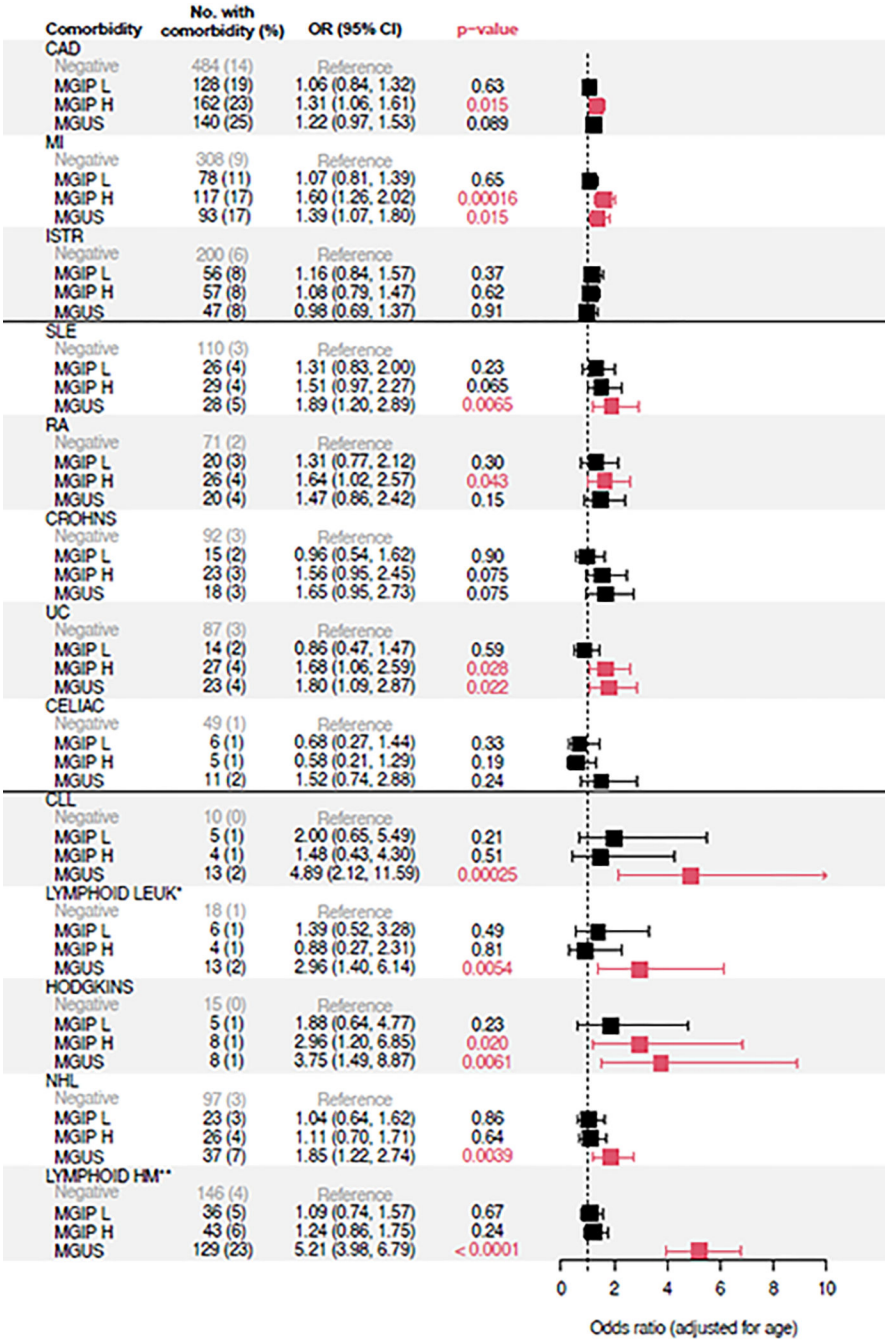

Figure 4. Association of monoclonal gammopathies with comorbidities.

Age-adjusted logistic regression models evaluating associations of monoclonal gammopathies with comorbidities diagnosed at any point in a participant's lifetime. Includes participants from MGBB only. CAD: coronary artery disease, CI: confidence interval, CLL: chronic lymphocytic leukemia, ISTR: ischemic stroke, Lymphoid HM: Lymphoid hematologic malignancies, Lymphoid Leuk: lymphoid leukemia, MI: myocardial infarction, NHL: Non-Hodgkin lymphoma, OR: odds ratio, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, UC: ulcerative colitis

*Lymphoid Leuk includes CLL and acute lymphoblastic leukemia **Lymphoid HM includes lymphoid leuk, Hodgkin lymphoma, and NHL

Table 1.

Population demographics by cohort

		All (Full cohort) (n=7622) *N* (column %)	*PROMISE* (n=2211)	*MGB BB* (n=5411)
Race				
	Black	2439 (32%)	187 (8%)	2252 (42%)
	White	4986 (65%)	1941 (88%)	3045 (56%)
	Other	119 (2%)	64 (3%)	55 (1%)
	Unknown	78 (1%)	19 (1%)	59 (1%)
Gender				
	Female	5013 (66%)	1594 (72%)	3419 (63%)
	Male	2570 (34%)	578 (26%)	1992 (37%)
	Unknown	39 (<1%)	39 (2%)	0 (0%)
Age at screening				
	Median (IQR)	56.0 years (IQR: 45.8–64.1)	58.8 years (IQR: 51.1–65.0)	54 years (IQR: 42–64)
Age class at screening				
	18–29	373 (5%)	2 (<1%)	371 (7%)
	30–39	774 (10%)	10 (<1%)	764 (14%)
	40–49	1417 (19%)	466 (21%)	951 (18%)
	50–59	2086 (27%)	710 (32%)	1376 (25%)
	60–69	2026 (27%)	772 (35%)	1254 (23%)
	70–79	774 (10%)	215 (10%)	559 (10%)
	80–89	130 (2%)	2 (<1)	128 (2%)
	90+	8 (<1%)	0 (0%)	8 (<1%)
	Unknown	34 (<1%)	34 (2%)	0 (0%)
Charlson Comorbidity Index*				
	0	558 (10%)	N/A	558 (10%)
	1	542 (10%)	N/A	542 (10%)
	2	537 (10%)	N/A	537 (10%)
	3	599 (11%)	N/A	599 (11%)
	4	533 (10%)	N/A	533 (10%)
	5	474 (9%)	N/A	474 (9%)
	6	405 (8%)	N/A	405 (8%)
	7+	1746 (32%)	N/A	1746 (32%)
	Missing	2228	2211	17
*Charlson index is missing for the PROMISE cohort				
Risk Category				

		All (Full cohort) **(n=7622)** ***N*** **(column %)**	***PROMISE*** **(n=2211)**	***MGB BB*** **(n=5411)**
	Black or African-American	2439 (32%)	187 (8%)	2252 (42%)
	Non-Black w/ + Family History	3866 (51%)	2024 (92%)	1842 (34%)
	Non-Black w/ no Family History	631 (8%)	0 (0%)	631 (12%)
	Non-Black, Unknown if family history	686 (9%)	0 (0%)	686 (13%)