Prevalence of heavy chain MGUS by race and family history risk groups using a high-sensitivity screening method

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Key Points

- The mass spectrometry assay found over threefold numbers of individuals with MGUS than gel-based assays across 3 risk groups.

- Relative differences in MGUS using the sensitive mass spectrometry assay were similar by race, family history, and age as prior MGUS studies.

Mass-spectrometry (MS) assays detect lower levels of monoclonal proteins and result in earlier detection of monoclonal gammopathy of undetermined significance (MGUS). We examined heavy chain MGUS prevalence using matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) MS among 3 risk groups, ages 50 or older: 327 African Americans (AA) and 1223 European Americans (EA) from a clinical biobank and 1093 unaffected first-degree relatives (FDR) of patients with hematologic disorders. Age- and sex-adjusted prevalence rates were directly standardized to 2010 United States population. Prevalence ratios were estimated for comparisons of AA and FDR to the EA group using the Poisson distribution. Results were also compared with population-based prevalence using conventional gel-based methods. Risk groups had similar sex and age distributions. MALDI-TOF MGUS prevalence was higher in the AA (16.5% [95% confidence interval (CI), 12.2%, 20.8%]) and FDR (18.3% [95% CI, 16.6%, 21.6%]) than in EA (10.8% [95% CI, 8.8%, 12.7%]), translating to prevalence ratios of 1.73 (95% CI, 1.31, 2.29) and 1.90 (95% CI, 1.55, 2.34), respectively. MALDI-TOF EA prevalence was over threefold higher than conventional estimates but showed similar age trends. Thus, the MALDI-TOF assay found greater numbers with MGUS but similar relative differences by race, family history, and age as prior studies.

Introduction

Monoclonal gammopathy of undetermined significant (MGUS) is a premalignant plasma cell disorder that is common in individuals over age 50. MGUS prevalence estimates to date have generally been based on the results of serum electrophoresis (SPEP) and immunofixation (for determination of heavy chain MGUS) and, additionally, free light chain (for light chain MGUS). Population-based screening studies using these methods have shown estimates of MGUS to be 3% for those over age 50.[1,2]

However, rates of MGUS differ by race and family history, concordant with multiple myeloma (MM) risk in the respective populations. People of African American (AA) ancestry have a two- to threefold increased risk of MM and younger age at onset compared with individuals of European American (EA) ancestry.[3-5] Similarly, MGUS prevalence is highest among AAs,[6,7] and recent studies suggest the increased prevalence is even more pronounced at young ages, with up to a fourfold difference between AA and EA for ages 10 to 49 years.[6] Rates of MGUS are also high among first-degree relatives (FDRs) of MM or other lymphoid or plasma cell disorders. We and others have shown a clear familial clustering of MGUS and

The full-text version of this article contains a data supplement.

MM,[8-11] with a 2- to 2.8-fold increase in MGUS in relatives of MM and MGUS patients, compared with the general population.[9,11] FDRs of MGUS patients also have an increased risk of Walenstrom's macroglobulinemia (Relative Risk = 4.0) and chronic lymphocytic leukemia (CLL) (Relative Risk = 2.0) compared with relatives of controls.[12]

Mass-spectrometry (MS) assays have been implemented into our clinical practice over the last few years and can detect lower levels of monoclonal proteins. Using this assay, we recently showed a 5% prevalence of MGUS in adults over 50 in the Olmsted County population and also the presence of MGUS at least 10 years prior to its detection using conventional methods.[2] Thus, mass spectrometry may provide more accurate estimates of underlying MGUS and provide insight to the evolution of MGUS. We provide the first data on MGUS assessed by the sensitive assay among 3 risk groups and compare with population-based estimates using conventional methods.

Methods

Study populations and statistical analyses

Screening for MGUS was conducted among people ages 50 and older from 3 populations. The first 2 consisted of all self-reported AA participants (n = 327) and a random sample of EA participants (n = 1223) from the Mayo Clinic Biobank.[13] Briefly, the biobank consists of volunteers seen primarily in general medical practices at the Mayo Clinic campuses between the years 2009 and 2016. All biobank participants provided a baseline blood sample, completed a self-administered questionnaire, and provided access to medical records. EA participants were sampled from participants who lived within the local Olmsted County population (where the Mayo Clinic is the largest primary care clinic), whereas the AA participants were sampled across all Mayo sites. The third risk group was unaffected FDRs (n = 1093) of known cases of MM, CLL, non-Hodgkin lymphoma, amyloid light chain amyloidosis, or a precursor (monoclonal B-cell lymphocytosis, MGUS) within a large family study of hematologic malignancies.[14-16] Familial cases were recruited primarily through Mayo Clinic practices. Analyses were conducted for all relatives as well as restricted to those whose cases were from the tristate area (Minnesota, Iowa, Wisconsin) or Minnesota alone. Age- and sex-adjusted prevalence rates and age group–specific prevalence rates were calculated by direct standardization to the 2010 United States population. Ninety-five percent confidence intervals (95% CI) and comparisons were based on the Poisson distribution for EA and AA populations and estimated using bootstrapping for the unaffected relatives, given their relatedness. Prevalence ratios (and 95% CI) were also estimated, comparing the AA and FDR groups to EA populations using Poisson regression, accounting for the familial association as a clustering term in the model. Finally, prevalence rates were compared with population-based MGUS estimates from Olmsted County, Minnesota,[1] a primarily EA population, using gel-based electrophoresis assays and confirmation by immunofixation and updated to the 2010 population to be comparable to this study period.

MALDI-TOF mass spectrometry

We developed a matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry–based assay that was automatable, analytically sensitive, and applicable to analyzing the wide variety of monoclonal proteins (M-proteins) encountered clinically. This assay, known as MASS-FIX, uses the unique molecular mass signatures of the immunoglobulin (Ig) light chains in combination with nanobody immuno enrichment to generate information-rich mass spectra from which M-proteins are identified and isotyped.[17] Samples with positive MASS-FIX findings were also run by serum electrophoresis to obtain M-protein concentration.

Heavy chain MGUS was defined as the presence of a monoclonal protein with a heavy chain immunoglobulin component. We consider these screened MGUS as we did not perform comprehensive clinical assessment of kidney function, anemia, or bone marrow involvement but used screening definitions comparable to other cohort studies.[1,6,18]

All participants provided written informed consent for this study, and the research was approved by the Mayo Clinic institutional review board.

Results and discussion

The 3 risk groups had similar sex and age distributions (Table 1), with 42% to 44% male and mean age 64 to 65 years. Age- and sex-adjusted MGUS prevalence using the MASS-FIX was higher in the AA (16.5% [95% CI, 12.2%, 20.8%]) and unaffected FDR (18.3% [95% CI, 16.6%, 21.6%]) compared with EA populations (10.8% [95% CI, 8.8%, 12.7%]) (both P values < .0001), resulting in higher prevalence ratios (PR) for AA (PR, 1.73 [95% CI, 1.31, 2.29] and FDR (PR, 1.90 [95% CI, 1.55, 2.34]) compared with the EA population. Among the unaffected FDR, MGUS prevalence was similar for unaffected FDR of MM or MGUS (17.9% [95% CI, 9.5%, 30.6%]) compared with unaffected FDR of CLL, non-Hodgkin lymphoma, myloid light chain amyloidosis, or monoclonal B-cell lymphocytosis cases (19.3% [95% CI, 5.0%, 35.3%]), including sensitivity analyses restricted to the tristate and Minnesota populations (supplemental Tables 2-3).

MGUS estimates using MASS-FIX were at least threefold higher (Table 1) than prevalence estimates of those age 50 and older from Olmsted County using conventional methods alone (ie, 3.0% [95% CI, 2.8% to 3.2%]). M-protein size did not vary greatly among the 3 groups, with a low-level clone not quantifiable by SPEP (<0.2 g/dL) found among 80.3% EA compared with 74.5% for AA and 81.3% for FDR MGUS populations (Table 1). Isotype differed across groups, with the highest proportion of IgG MGUS among EA, IgA MGUS among AA, and IgM MGUS among FDR (Table 1). Due to the conventional MGUS assays within the Olmsted County population, almost all had a detectable M-protein, and the proportion of IgG was similar to those of the EA group (Table 1).

When comparing MGUS prevalence across age groups, the rates among EA using MASS-FIX were increased but parallel to rates of MGUS among Olmsted County screened using conventional methods (Figure 1; supplemental Table 1). Age-specific rates for AA and FDR, however, were similar to EA for ages 50 to 59 but had steeper slopes for ages 60 to 69 and 70-plus age groups compared with EA (Figure 1; supplemental Table 1).

In summary, we provide some of the first data on prevalence of heavy chain MGUS across risk groups using a sensitive method for detecting monoclonal proteins. We found at least threefold increased prevalence of MGUS in EA using the MASS-FIX

Table 1. Age, sex, and MGUS characteristics by 3 risk groups and Olmsted County reference population

	EA	AA	FDR	Olmsted County
Full sample	N = 1223	N = 327	N = 1093	N = 21 463
Age (mean, SD)	64.4 (8.9)	64.5 (9.5)	65.2 (10.5)	64.9 (10.5)
Sex (% Male)	532 (43.5%)	137 (41.9%)	474 (43.4%)	9469 (44.1%)
MGUS prevalence (%, CI)	10.8% (8.8, 12.7)	16.5% (12.2, 20.8)	18.3% (15.8, 20.8)	3.0% (2.8, 3.2)
MGUS characteristics*	N = 127	N = 58	N = 215	N = 694
M-protein size (g/dL)†				
Negligible (<0.2)	94 (80.3%)	41 (74.5%)	161 (81.3%)	55 (9.4%)
0.2-1.5	22 (18.8%)	13 (23.6%)	32 (16.2%)	411 (70.4%)
≥1.5	1 (0.9%)	0 (0%)	5 (2.5%)	118 (20.2%)
Not done	1	1	12	82
Isotype				
IgG	83 (65.4%)	32 (55.2%)	120 (55.8%)	474 (68.5%)
IgA	19 (15.0%)	17 (29.3%)	31 (14.4%)	75 (10.8%)
IgM	16 (12.6%)	6 (10.3%)	47 (21.9%)	117 (16.9%)
Biclonal	9 (7.1%)	3 (5.2%)	17 (7.9%)	26 (3.8%)
Missing	0	0	0	2

*MGUS for AA, EA, and FDR assessed using MALDI (MASS-FIX). MGUS for Olmsted County assessed using SPEP followed by immunofixation.
†Excludes biclonal MGUS.

compared with conventional gel-based methods for MGUS assessment. However, the relative increases of MGUS in AA and FDR of hematologic malignancies vs EA populations were similar to the literature. Also, the differential rates of AA and FDR vs EA were most pronounced among ages 60 and older.

The majority of the screened MGUS across all groups had a low-level clone, noting the expected low risk for progression to myeloma or other lymphoproliferative disorders. We recognize that the use of more sensitive assays would result in a great number of MGUS diagnoses with low probability of progression and identified at a younger age. It will be important to understand the disease implications of these low-risk MGUS prior to their use in a screening setting, including associations with not only malignancies but also infection and other disorders.[19] Further, any screening recommendations will need to be balanced with potential harms that may result from identifying a precursor lesion that has very low risk of progression to malignant disease. Randomized trials are underway to inform the potential harms of wide-scale screening for MGUS.[20] Thus, more sensitive MGUS screening may be less relevant for identifying high-risk MGUS but will clearly be important for etiology studies as well as providing more accurate ages of MGUS initiation

We recognize limitations of sampling from a clinical biobank with members seeking health care for general or specific medical conditions. Although we can't rule out that our absolute MGUS prevalence rates are higher than expected in the general population, we attempted to reduce potential bias by sampling for the EA group from the local Olmsted County population who enrolled in the biobank and represent those who seek their general medical care at Mayo. The midwest biobank participants have been shown to have comparable race and ethnicity to the underlying source populations of the Upper Midwest using data from the Behavioral Risk Factor Surveillance System,[21] although biobank participants may be more obese. We also performed sensitivity analyses including FDR of only tristate and Minnesota cases, showing similar findings to all relatives. However, relative differences between the AA and FDR vs EA (1.7-1.9) are in line with differences seen in the literature using conventional MGUS assays across the higher-risk groups.[16,22,23] Further, our numbers of AA participants were limited and may have resulted in the skew in isotype seen in this group. Finally, we did not have comprehensive free light chain values; thus, our results are generalizable to heavy chain MGUS in these populations.
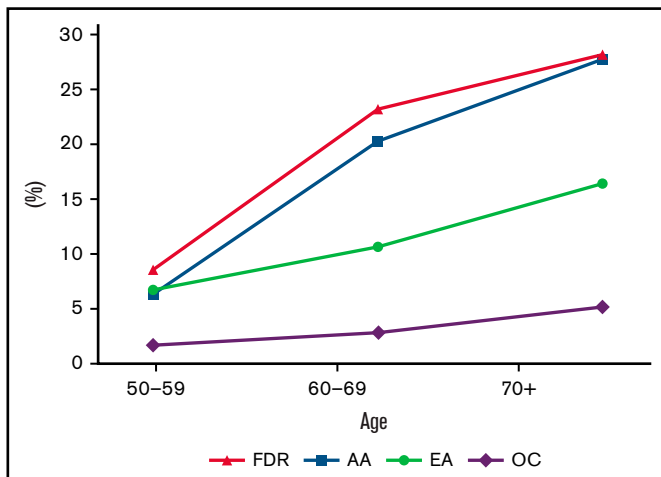

Figure 1. Age-specific MGUS prevalence estimates for risk groups (AA, FDR, and EA) using MASS-FIX compared with conventional (gel-based) estimates (Olmsted County [OC], Minnesota population).

Authorship

Contribution: C.M.V., A.D.N., and S.K.K. contributed to research design; C.M.V., J.M., R.A.K., V.R., S.L.S., and S.K.K. performed research; D.L.M. contributed vital new reagents or analytical tools; C.M.V., J.M., A.D.N., A.D., R.A.K., V.R., S.L.S., and D.L.M. collected data; C.M.V., J.M., C.A., J.P.S., A.D., G.K., V.R., S.L.S., and S.K.K. analyzed and interpreted data; C.A., D.L., J.P.S., and D.L.M. performed statistical analysis; C.M.V. wrote the manuscript; and all authors reviewed and approved the draft of the manuscript.

Conflict-of-interest disclosure: A.D. is on the advisory board and independent review committee with Janssen, is on the data monitoring safety committee with Oncopeptides, Sorrento, and receives research dollars from Alynlam, Pfizer, Takeda, and BMS. D.L. has patent rights issued to the Mayo Clinic that are licensed to the binding site for detecting PCDs by mass spectrometry. S.J. receives research funding for clinical trials to the institutions Abbvie, Amgen, BMS, Carsgen, Janssen, Astra-Zeneca, Novartis, Roche-Genentech, Takeda, Tenebio, and Molecular Templates. He is on the consulting/advisory board (with no personal payments) for Abbvie, Amgen, BMS, Janssen, Roche-Genentech, Takeda, Astra-Zeneca, Bluebird Bio, Epizyme, Secure Biotherapeutics, Oncopeptides, Beigene, and Antengene. The remaining authors declare no competing financial interests.

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