Male sex adversely impacts survival and myeloid malignancy risk in MGUS: a real-world population-based study

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Abstract

Monoclonal gammopathy of undetermined significance (MGUS) is a common plasma cell disorder with well described risks of progression to myeloma and lymphoplasmacytic lymphoma. Using data from an established UK population-based cohort of hematological malignancies and premalignancies, we investigated patient and disease characteristics, subsequent hematological malignancy, and survival in 4,651 people diagnosed with MGUS between 2005 and 2019. The 5-year net (relative) survival (disease-specific estimate of the probability of survival) for MGUS patients was 87.8% (95% confidence interval [CI]: 85.9-89.7), with males (83.8%; 95% CI: 81.0-86.6) more affected than females (92.2%; 95% CI: 89.7-94.7). The proportion of subsequent hematological malignancies was also higher in males than females (8.8% *vs*. 5.3%; *P*<0.00001); the average annual rates of transition being 1.81% (95% CI: 1.44-2.18) and 0.99% (95% CI: 0.72-1.27), respectively. Furthermore, whilst annual rates of transformation to myeloma (1.04%) and lymphoplasmacytic lymphoma (0.11%) were as expected, both were higher in males (1.23% and 0.18%) than females (0.87% and 0.06%). With a median time to diagnosis of 40 months, the incidence of myeloid malignancy was also raised in males (relative risk=3.6; 95% CI: 2.5-4.9), but not females (relative risk=1.0; 95% CI: 0.3-1.9). No associations between MGUS and subsequent development of chronic lymphocytic leukemia were observed. Providing new data on the nature of MGUS progression, our analyses revealed previously undescribed sex disparities; including worse survival and increased rates of myeloid malignancy in males with non-IgM MGUS. These findings have implications for future research, as well as risk stratification and monitoring of patients with this highly prevalent plasma cell dyscrasia.

Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is a common plasma cell disorder characterized by the secretion of abnormal monoclonal proteins (M-proteins) or light chains, bone marrow plasma cell infiltration below 10% of nucleated cells, and absence of symptoms or end-organ manifestations.[1,2] With an estimated prevalence of around 3-5% in white populations aged 50 years or more,[3-5] MGUS incidence increases with age, and like myeloma it occurs more frequently in males,[2,6] and those of African descent.[7,8] In the clinical setting, MGUS is most frequently detected in individuals over 70 years undergoing general diagnostic investigations. Whilst overt symptoms of hematological malignancy are, by definition, absent, MGUS has the potential to transition to a number of more significant states, notably multiple myeloma (MM) at a rate of around 1% per year.[5,9,10] Additionally, as well as hematological malignancies, M-proteins are implicated in several non-malignant disorders, most commonly renal pathologies (monoclonal gammopathy of renal significance), as well as peripheral neuropathy and other neurological conditions.[11–15] Once MGUS is detected, consensus clinical guidelines recommend indefinite follow-up; with the available data showing that because MM is picked up earlier in patients who are regularly checked, those whose disease pro-

gresses tend to suffer less end-organ damage.[16,17] However, since there are currently no proven treatments to prevent or delay progression to MM, population screening is not yet recommended.[18-20] To help identify patients who are most at risk of progression to MM and other mature B-cell malignancies, stratification systems commonly use paraprotein isotype, paraprotein level and serum free light chain (sFLC) ratio (Mayo criteria[2]) or incorporate phenotyping of bone marrow plasma cells (Pethema criteria[21]). In this context, the clonal precursor relationship between non-immunglobulin M (non-IgM) MGUS isotypes and myeloma (notably IgG and IgA), and between IgM MGUS and lymphoplasmacytic lymphoma (LPL) are clear. For other mature B-cell malignancies, notably chronic lymphocytic leukemia (CLL) where indirect relationships with MGUS have been suggested,[22,23] pathogenic pathways are far less certain and data evidencing such associations are sparse and contradictory.[9,24] Likewise, although a topic of scientific interest, particularly in relation to clonal hematopoiesis and the bone marrow microenvironment,[25,26] data on myeloid malignancy development in people with MGUS is also limited.[9,27,28] This lack of information may, at least in part, be due to the comparative rarity of the conditions being examined (MGUS and myeloid malignancy), and consequent need to follow-up large numbers of people for long periods of time.

Adding significant knowledge in this challenging area, the findings presented here come from the UK's population-based Hematological Malignancy Research Network (HMRN), which was specifically designed to track newly diagnosed patients with hematological malignancies and premalignancies along their full care pathway; enumerating all progressions, transformations, and treatments (https://hmrn.org/).[29,30] Specifically, this report examines outcomes in a real-world MGUS cohort, characterizing the predictors and frequencies of subsequent hematological malignancy.

Methods

Data are from HMRN (https://hmrn.org/). Initiated in 2004 to provide robust generalizable data to inform research and clinical practice, HMRN's underpinning methods are fully described elsewhere.[29,30] Within HMRN, all diagnoses are made and coded using the latest World Health Organization classifications at a single integrated hematopathology laboratory, the Hematological Malignancy Diagnostic Service (https://hmds.info/), and all patients have diagnostic, prognostic, treatment, response and outcome information extracted from clinical and laboratory systems from diagnosis onwards. HMRN has full ethical approval (Leeds West Research Committee [REC] 04/Q1205/69) and Section 251 support from the Confidentiality Advisory Group (CAG; NHS Act 2006: 20/CAG/0149). All patients are followed up for death and subsequent cancer by the National Health Service [NHS] England (www.nhsdigital.nhs.uk/), and all are routinely linked to national Hospital Episode Statistics Admitted Patient Care (HES-APC), enabling data on preceding comorbidities to be used to calculate Charlson Comorbidity Index Scores.[31]

HMRN's catchment population has a comparable sex, age, urban/rural, and area-based deprivation (Index of Multiple Deprivation [IMD], income domain) distribution to the UK as a whole.[32,33] Served by 14 hospitals, all patients diagnosed with a hematological malignancy or a related premalignancy (~2,500 each year) within HMRN's catchment population of ~4 million people are registered into the cohort on the day they are diagnosed; irrespective of their age, treatment intent, trial entry, or management within the NHS or private sector. Population estimates are obtained from the Office for National Statistics,[34] and sub-type specific incidence rates and 95% confidence intervals (95% CI) are routinely calculated (https://hmrn.org/statistics/incidence).

Spanning the 15-year study period from the beginning of January 2005 through to the end of December 2019, 35,817 HMRN residents were newly diagnosed with a hematological neoplasm, 4,708 (13.1%) of whom were diagnosed with MGUS; defined by a serum paraprotein less than 30 g/L, and in those where a bone marrow examination was considered necessary following clinical examination, a clonal bone marrow plasma cell level <10% for those with a non-IgM paraprotein, or absence of a clonal B-cell population for those with an IgM paraprotein. Over the 15-year period, around 65% of MGUS patients had a confirmatory bone marrow; the proportion falling from over 90% in the earlier years through to around 30% in 2019, in line with increasing clinical consensus for avoiding this painful procedure where risk of malignancy is small. Fifty-seven (1.2%) MGUS patients were excluded from the present analysis because a hematological malignancy was subsequently diagnosed within 90 days of their MGUS diagnosis. The remaining 4,651 (98.8%) patients were followed up for transformation/progression and/or death until July 31, 2023; the follow-up period ranging from 3.6 to 16.6 years. For the purpose of this manuscript the closely related pathologies marginal zone lymphoma, lymphoplasmacytic lymphoma and Waldenstroms macroglobulinaemia are considered together, and referred to as lymphoplasmacytic lymphoma (LPL).

All analyses were performed in Stata 18[35] or R version 4.4.1,[36] using the tidyverse.[37] Net survival (relative survival) defined as the probability of surviving cancer in the absence of other causes of death,[38] was estimated using the Stata program stns;[39] implementing the Pohar Perme estimator[38] with age and sex-specific background mortality rates derived from national life tables.[40] Observed numbers of progressions/transformations were compared to the numbers expected on the basis of HMRN's sub-type specific incidence rates (https://hmrn.org/statistics/incidence) 2004-2022. For comparative purposes, expected frequencies were also calculated using the broad diagnostic categories used by

the national cancer registry 2016-2018 (https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type). Time-to-event analyses used the R survival library,[41] with the rms library[42] used for modeling non-linear effect of co-variates. Simple time-to-event estimates were calculated with the Kaplan-Meier method and cumulative incidence estimates were derived from intercept-only Cox models. Focusing on the first transitions only, time to myeloma transformation, treating death and other transformations as competing risks, was calculated using the multistate model illustrated in *Online Supplementary Figure S1,* which shows the structure of the model, and the number of events associated with each transition.

Results

Table 1 shows the baseline characteristics of the 4,651 patients diagnosed with MGUS over the 15-year period from 2005 to 2019 whose disease did not progress or transform in the first 90 days. With a median age of 73.3 years, 2,454 (52.8%) patients were male and 2,197 (47.2%) were female (*P*=0.0002). IgG was the most frequent M-protein isotype (N=3033, 65.2%), followed by IgM (N=772, 16.6%), and IgA (N=574, 12.3%). Other MGUS subtypes included IgD (N=5), IgE (N=3), those with multiple paraproteins (N=49), non-secretory (defined by the presence of neoplastic plasma cells in the bone marrow without serological evidence of MGUS (N=37)), and light chain disease (N=122). These paraprotein distributions and concentrations are similar in males and females, as are sFLC ratio risk category distributions, prognostic risk stratification scores, ethnicity, and area-based deprivation. Reflecting the adoption of routine light chain testing after the initiation of the cohort, the large number of missing sFLC measurements, and hence missing risk stratification scores, reflects the recency of assay incorporation into routine care. Data showing these improvements are presented in *Online Supplementary Table S1*, where baseline diagnostic/prognostic information is stratified by 5-year time period.

Despite the similarities in diagnostic ages and MGUS serological profiles, marked sex differences in survival, subsequent blood cancer development frequencies and comorbidity scores are evident in Table 1 (data distributed by M-protein isotype and sex are in *Online Supplementary Table S2A-C*). Overall survival (OS) and net survival (NS; the probability of surviving in the absence of other causes of death) estimates are stratified by M-protein isotype in Figure 1. At 87.8% (95% CI: 85.9-89.7), the 5-year NS for all M-protein subtypes combined demonstrates that people diagnosed with MGUS have poorer survival than their general population counterparts. Those with IgM MGUS had the best NS (91.2%; 95% CI: 86.4-96.1), closely followed by those with the non-IgM subtypes IgG (88.2%; 95% CI: 85.9-90.5) or IgA (85.6%; 95% CI: 80.0-91.1). Demonstrating the consistency of the sex difference in survival, Figure 2 shows sex-specific 5-year NS estimates distributed by M-protein isotype. At 83.8% (95% CI: 81.0-86.6) the NS for men is around 8 percentage points lower than that of females (92.2%; 95% CI 89.7-94.7); the median OS for males and females being 8.3 years (95% CI: 7.8-8.8) and 11.1 years (95% CI: 10.2-11.8) respectively (Table 1). This sex difference is evident within all strata of the risk stratification score and its components (*Online Supplementary Table S3*).

Over the follow-up period (minimum 3.6 years, maximum 16.6 years), 343 hematological malignancies were diagnosed in 332 of 4,651 (7.1%) individuals; 322 patients had one subsequent malignancy diagnosed, nine had two, and one had three. The proportion of MGUS patients who developed a subsequent hematological malignancy was significantly higher in males (215/2,454; 8.8%) than females (117/2,197; 5.3%) (*P*<0.00001), but at around 5 years the average time to diagnosis was similar; 59.8 months (interquartile range [IQR], 27.5-93.5) in males and 61.6 months (IQR, 34.6-98.6) in females (Table 1). With a median time to diagnosis of 61.3 months (IQR, 30.9- 94.5) and accounting for 72.3% of the total (240/332), myeloma dominates (Table 2). Around three-quarters of myeloma patients had IgG MGUS (N=181), 18.3% IgA (N=44), and 2.9% light chain disease (N=7); only one patient had IgM MGUS, one had IgA + IgM, and six had missing M-protein isotype data (*Online Supplementary Table S2A*). Again, as expected, among patients with IgM MGUS, LPL was the commonest progression (22/27). Notably, however, whilst myeloma and LPL combined accounted for 90.6% of all subsequent hematological malignancy diagnoses in females (106/117), they only accounted for 74.9% (161/215) in males.

Comparing the numbers of blood cancers (myeloid and lymphoid) that occurred in the MGUS population over the follow-up period to the numbers expected on the basis of HMRN's sex- and age-specific population-based rates, subtype-specific standardized incidence ratios (SIR) are shown in Figure 3. Confirming known lymphoid associations, relative risk estimates (SIR) for myeloma and LPL were 33.1 (95% CI: 29.0-37.4) and 7.4 (95% CI: 4.8-10.4) respectively for both sexes combined; with little variation between males and females. With the exception of post-transplant lymphoproliferative disorders (PTLD), where four diagnoses occurred in males after a previous organ transplantation (three of which were renal), the SIR for other lymphoid malignancies, including large B-cell lymphoma (LBCL), chronic lymphocytic leukemia (CLL), and follicular lymphoma (FL), are all close to one; again, no obvious sex differences are evident. At 2.5 (95% CI: 1.8-3.4), the overall SIR for myeloid malignancies is, however, raised, with increased risks for myelodysplastic syndromes (MDS; RR=4.4; 95% CI: 2.5-6.9), acute myeloid leukemia (AML; RR=2.6; 95% CI 1.2-4.4), and chronic myelomonocytic leukemia (CMML; RR=4.0; 95% CI: 1.0-8.9). As with PTLD, with a median time to diagnosis of 40.0 months (Table 2), the excess of myeloid malignancies

Table 1. Patient characteristics and outcomes: monoclonal gammopathy of undetermined significance diagnoses 2005-2019, followed up to July 2023.

Characteristics	Both sexes	Males	Females	Male : Female *P*[2]
Total diagnoses, N	4,651	2,454	2,197	0.0002
Age at diagnosis, years (% of total)				
<70	1,799 (38.7)	930 (37.9)	869 (39.6)	-
≥70	2,852 (61.3)	1,524 (62.1)	1,328 (60.5)	
Median age, years (IQR)	73.3 (64.9-80.0)	73.4 (65.5-79.8)	73.0 (63.8-80.1)	0.370
Paraprotein, N (% of total diagnoses)				
IgM	772 (16.6)	405 (16.5)	367 (16.7)	-
Non-IgM	3,879 (83.4)	2,049 (83.5)	1,830 (83.3)	-
IgG	3,033 (65.2)	1,570 (64.0)	1,463 (66.6)	-
IgA	574 (12.3)	322 (13.1)	252 (11.5)	-
Light chain only	122 (2.6)	75 (2.1)	47 (2.1)	-
Other subtypes[1]	150 (3.2)	82 (3.3)	68 (3.1)	0.102
Paraprotein concentration, g/dL, N (%)				
<1.5	3,994 (91.4)	2,089 (90.9)	1,905 (91.9)	-
>1.5	376 (8.6)	208 (9.1)	168 (8.1)	0.238[2]
Median (IQR)	0.41 (0.13-0.88)	0.50 (0.20 - 0.90)	0.40 (0.10 - 0.80)	-
Missing, N	122	68	121	-
Serum free light chain κ/λ, N (%)				
Normal (0.26-1.65)	1,603 (62.8)	831 (61.2)	772 (64.5)	-
Abnormal (<0.26 or >1.65)	951 (37.2)	526 (38.8)	425 (35.5)	0.089[2]
Missing	2,097	1,097	1,000	-
Risk stratification score,[3] N (%)				
0	1,041 (43.5)	531 (42.0)	510 (45.1)	-
1	975 (40.7)	522 (41.3)	453 (40.1)	-
2-3	378 (15.8)	211 (16.7)	167 (14.8)	0.342[2]
Missing	2,098	1,101	997	-
Ethnicity, N (%)				
White	4,021 (95.9)	2,129 (96.3)	1,892 (95.4)	-
Non-white	172 (4.1)	81 (3.7)	91 (4.6)	0.132[2]
Not known	458	244	214	-
Index of multiple deprivation,[4] N (%)				
1-3 (least deprived)	2,885 (62.3)	1,544 (63.2)	1,341 (61.3)	-
4-5 (most deprived)	1,748 (37.7)	900 (36.8)	848 (38.7)	0.315[2]
Missing	18	10	8	-
Charlson comorbidity score, N (%)				
0	2,744 (60.6)	1,373 (57.4)	1,371 (64.2)	-
1	784 (17.3)	404 (16.9)	380 (17.8)	-
≥2	1,000 (22.1)	617 (25.8)	383 (17.9)	<0.0001[2]
Missing	123	60	63	-
Subsequent blood cancer >90 days				
Total N of patients (%)	332 (7.1)	215 (8.8)	117 (5.3)	<0.001
Median months to 1st blood cancer (IQR)	60.0 (29.7-95.1)	59.8 (27.5-93.5)	61.6 (34.6-98.6)	0.91
Survival				
Deaths (%)	2,292 (49.3)	1,323 (53.9)	969 (44.1)	-
Person-years at risk	31,110.3	15,316.3	15,794.0	-
5-year overall, % (95% CI)	71.0 (69.7-72.3)	66.0 (64.1-67.9)	76.6 (74.7-78.4)	-
5-year net, % (95% CI)	87.8 (85.9-89.7)	83.8 (81.0-86.6)	92.2 (89.7-94.7)	-
Median overall, years (95% CI)	9.4 (9.1-9.8)	8.3 (7.8-8.8)	11.1 (10.2-11.8)	<0.00001
Person-years at risk (blood cancer-free)	30,180.8	14,760.3	15,420.6	-
5-year blood cancer-free, % (95% CI)	68.9 (67.5-70.2)	63.8 (61.8-65.7)	74.6 (72.6-76.4)	-
Median, blood cancer-free, years (95% CI)	8.8 (8.4-9.2)	7.5 (7.0-8.0)	10.3 (9.7-11.2)	<0.00001

[1]Immunoglobulin (Ig) D (N=5), IgE (N=3), IgA + IgG (N=13), IgA + IgM (N=2), IgG + IgM (N=34), non-secretory (N=37), not known (N=56); [2]Percentages and tests exclude missing; [3]Mayo clinic score: non-IgG isotype=1, M-protein >1.5 g/dl =1, abnormal serum free light chain=1; [4]Income domain. IQR: interquartile range; CI: confidence interval.

was driven by males; the SIR for MDS and AML being 5.5 (95% CI: 3.0-8.7) and 3.3 (95% CI: 1.4-6.0), respectively (Figure 3). Showing broadly consistent estimates to those in Figure 3; *Online Supplementary Tables S4* and *S5* present SIR for blood cancers that have national rates available; the SIR for myeloma, non-Hodgkin lymphoma (NHL), and AML being 27.3 (95% CI: 24.0-30.9), 2.1 (95% CI: 1.5-2.8) and 2.4 (95% CI: 1.2-4.2) respectively, with no association evident for CLL.

Information on the cumulative baseline hazards of tran-

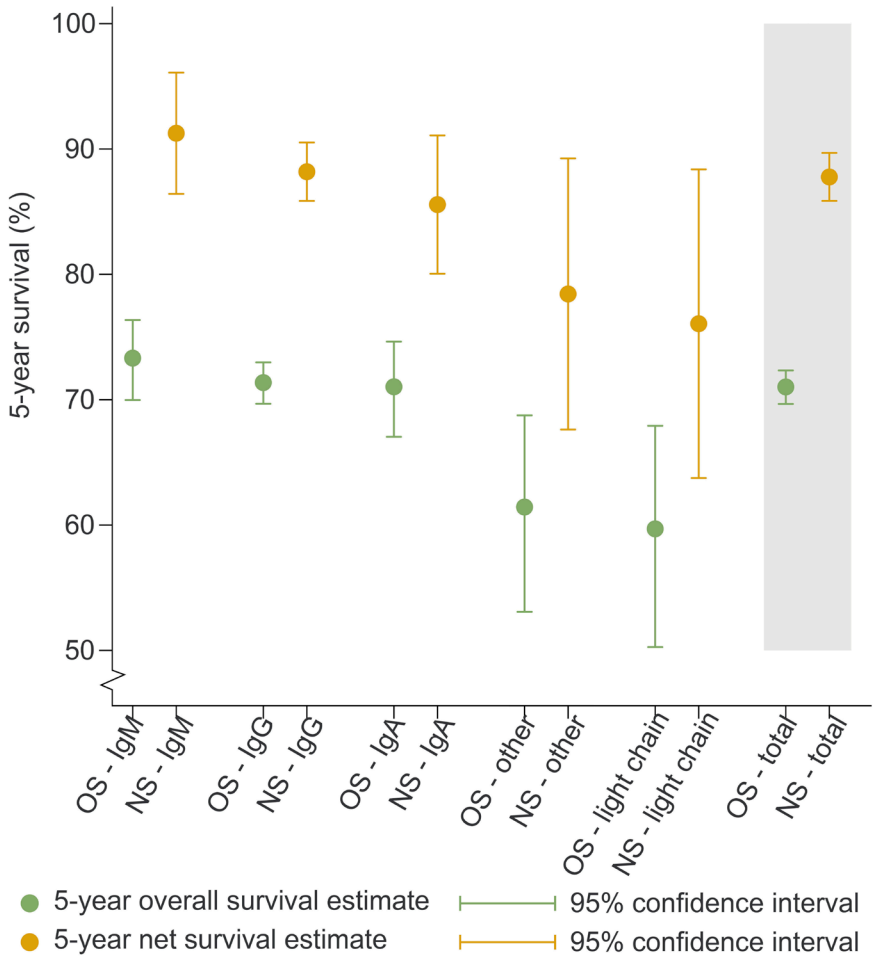


Figure 1. Five-year overall survival and net survival distributed by monoclonal gammopathy of undetermined significance M-protein isotype; monoclonal gammopathy of undetermined significance diagnoses 2005-2019, followed up to July 2023. OS: overall survival; NS: net survival.

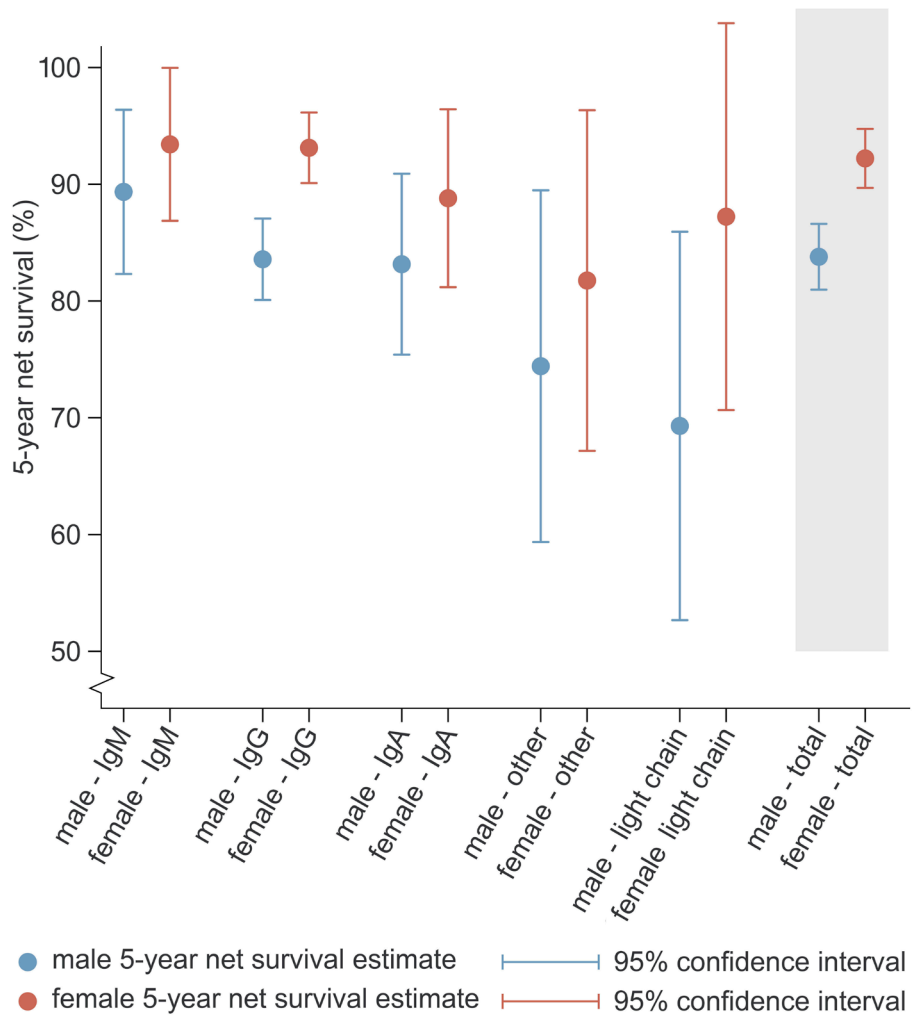


Figure 2. Five-year net survival distributed by M-protein isotype and sex; monoclonal gammopathy of undetermined significance diagnoses 2005-2019, followed up to July 2023. Ig: immunoglobulin.

Table 2. Median time (months) to first hematological malignancy (interquartile range): Hematological Malignancy Research Network monoclonal gammopathy of undetermined significance diagnoses 2005-2019, followed up to July 2023.

	Both sexes		Males		Females	
	N	Months, median (IQR)	N	Months, median (IQR)	N	Months, median (IQR)
Total hematological malignancies	332	60.0 (29.7-95.1)	215	59.8 (27.5-93.5)	117	61.6 (34.6-98.6)
Lymphoid diagnoses	292	61.7 (30.8-97.2)	181	61.8 (29.5-93.5)	111	61.6 (34.6-100.3)
Myeloma[1]	240	61.3 (30.9-94.5)	145	60.9 (29.2-93.3)	95	61.6 (37.4-100.3)
Lymphoplasmacytic lymphoma	27	65.8 (28.1-105.4)	16	49.6 (24.9-106.1)	11	72.5 (28.1-99.8)
Large B-cell lymphomas	6	53.4 (21.6-73.6)	4	68.1 (53.4-102.6)	2	13.4
Chronic lymphocytic leukemia	5	33.8 (25.8-129.8)	4	81.8 (21.7-160.9)	1	25.8
Follicular lymphoma	4	88.3 (68.7-102.6)	3	79.5 (57.8-97.1)	1	108.1
Post-transplant lymphoproliferative disorder	4	66.8 (32.4-145.7)	4	66.8 (32.4-145.7)	-	-
Other lymphoid	6	79.9 (29.0-138.3)	5	77.8 (29.0-82.1)	1	142.7
Myeloid diagnoses	40	43.3 (21.3-71.3)	34	40.0 (21.4-76.1)	6	50.0 (21.3-63.8)
Myelodysplastic syndromes	16	26.2 (19.2-53.1)	14	31.6 (21.4-56.1)	2	17.4
Acute myeloid leukemia	10	61.4 (42.3-94.7)	8	61.4 (38.9-112.5)	2	56.9
Chronic myeloproliferative neoplasms	5	54.3 (30.9-63.8)	4	42.6 (21.6-101.7)	1	63.8
Chronic myelomonocytic leukemia	4	42.0 (17.8-71.5)	4	42.0 (17.8-71.5)	-	-
Other myeloid	5	34.5 (23.7-57.7)	4	29.1 (14.7-76.6)	1	57.7

[1]Includes multiple myeloma and plasmacytoma. IQR: interquartile range.

sition to malignancy is shown in Figures 4 and 5. Over the follow-up period, transition rates for all MGUS diagnoses combined (N=4,651) are roughly linear; approximately 1.37% (95% CI: 1.15-1.60) per year for any hematological malignancy, 1.04% (95% CI: 0.84-1.24) for myeloma, 0.11% (95% CI: 0.04-0.18) for LPL, and 0.13% (95% CI: 0.07-0.19) for myeloid malignancies (Figure 4A). Rates in males (N=2,454) are consistently higher than in females (N=2197) (Figure 4B); the average annual rate for any hematological malignancy being 1.81% (95% CI: 1.44-2.18) in males and 0.99% (95% CI: 0.72-1.27) in females. While the transition to LPL is almost undetectable in Figure 4, the increase within the IgM MGUS group is clear (Figure 5C), the annual rate being 0.63 (95% CI: 0.22-1.05). Likewise, at 1.24% (95% CI: 1.00-1.48) and 0.15% (95% CI: 0.08-0.22) respectively, the annual rates of transition to myeloma and myeloid malignancies are increased in the non-IgM MGUS group (Figure 5A). In all cases, transition rates are significantly higher among males than females. Finally, to assess whether the varying rates of progression/transformation could explain the sex differences in survival multistate modeling was used (*Online Supplementary Figure S1*); the age and comorbidity adjusted hazard ratio for death-without-progression for males *versus* females was 1.35 (95% CI: 1.24-1.47; $P=<10^{-4}$), indicating that the sex imbalance of hazard-of-death is not explained by differential rates of progression/transformation.

Discussion

In addition to demonstrating the expected associations with myeloma, LPL, and PTLD, analyses of our large population-based cohort of clinically annotated MGUS patients with mature follow-up (N=4,651; excluding patients whose MGUS diagnosis was followed by hematological malignancy within 90 days) revealed a number of less well recognized,

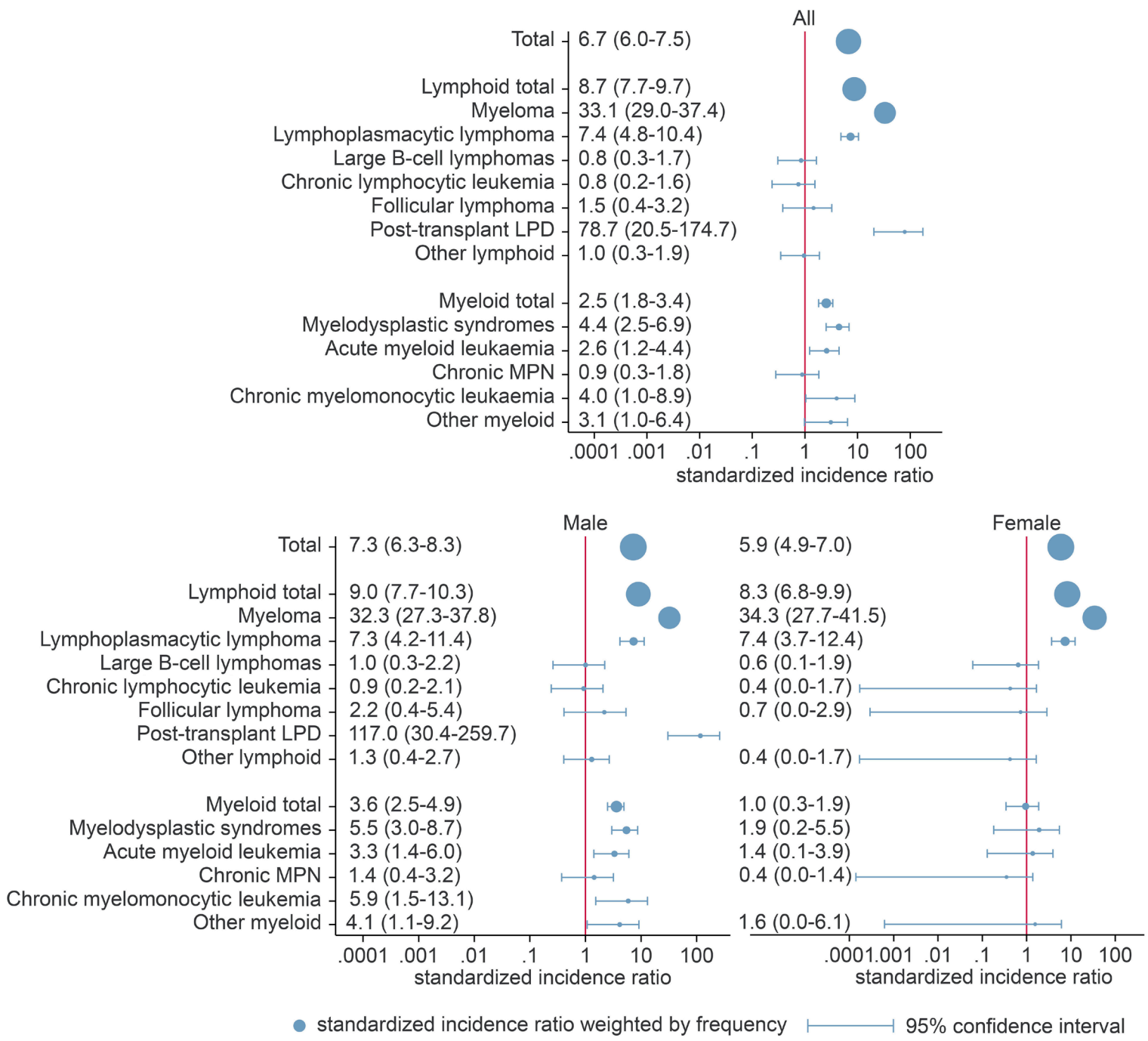


Figure 3. Standardized incidence ratios (95% confidence intervals) comparing the numbers of blood cancers diagnosed in monoclonal gammopathy of undetermined significance patients to the numbers expected on the basis of Hematological Malignancy Research Network's age and sex-specific rates. LPD: lymphoproliferative disorders; MPN: myeloproliferative neoplasm.

but potentially important relationships. Notably, whilst the sex, age, and paraprotein distributions were broadly similar to other published series, and the temporally stable annual rates of progression to myeloma (1.04 % for all isotypes combined, or 1.24% when considering non-IgM isotypes only) were as expected,[2,5,6,27,44] striking sex differences in progression, survival, and associations with myeloid malignancies were observed. Furthermore, adding to an increasing body of evidence on this topic, we found no increased risk of CLL in individuals previously diagnosed with MGUS.[2,9,27] Whilst it is well known that most hematological malignancies and premalignancies occur more frequently in males than females,[45,46] our finding that the risk of myeloid malignancy was increased in males (RR=3.6; 95% CI: 2.5-4.9) but not females (RR=1.0; 95% CI: 0.3-1.9) was surprising; particularly given the similarities in diagnostic ages, MGUS serological profiles, and time to hematological malignancy development (median ~5 years). This difference, which was driven by IgG and IgA isotypes, resulted in a 2.5-fold increase in risk when both sexes were combined; the male RR for MDS, AML and CMML being 5.5 (95% CI: 3.0-8.7; 14 cases, median time to diagnosis 31.6 months), 3.3 (95% CI: 1.4-6.0; 8 cases, median time to diagnosis 61.4 months) and 5.9 (95% CI: 1.5-13.1; 4 cases, median time to diagnosis 42.0 months), respectively, with no associations evident among females. Furthermore, the survival difference between males and females remained significant, even after considering the potentially confounding effects of comorbidity and progression.

The size and maturity of our cohort, coupled with the fact that all patients with hematological malignancies and/or premalignancies are diagnosed and monitored by a central hematopathology laboratory,[29] facilitated examination of these rarer myeloid events. Obviating the need for data linkage to national data and/or other external sources, this framework is particularly important for blood cancers like MDS which were previously classified as neoplasms of uncertain behavior in ICD-10, and are often poorly recorded in national cancer registries.[45] Although the potential etiological role of high body mass index has recently been investigated in relation to MGUS progression to myeloma,[47,48] as far as we are aware this is the first time that sex-spe-

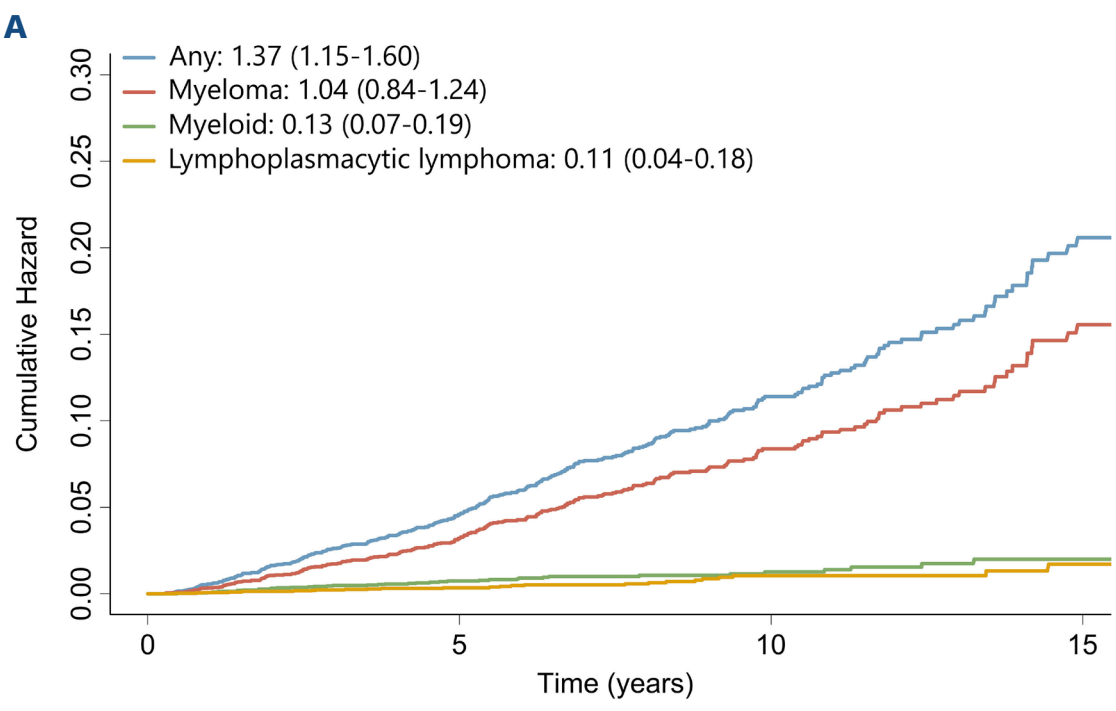


Figure 4. Average annual transition rates (95% confidence intervals) in monoclonal gammopathy of undetermined significance patients (N=4,651) whose disease did not progress or transform within the first 90 days. (A) Both sexes combined. (B) Stratified by sex. F: female; M: male.

cific data on MGUS and myeloid malignancies have been reported. Supporting the 2.5-fold overall excess seen in our cohort, data for both sexes combined have been published. A 2011 analyses of clinically accrued MGUS patients ascertained through a national hospital network in Sweden (diagnoses 1986-2005, followed until 2006) reported an 8-fold increased risk of myeloid malignancies, most notably for MDS/AML (median time to diagnosis 14.4 months), that reduced to 5-fold when patients diagnosed within a year of MGUS detection were removed.[27] Subsequently, in 2013 the USA's medical record based Olmsted County population-based screening cohort (diagnoses 1995-2001, followed until 2006) reported a 2.4-fold significantly increased risk for MDS, but not AML (RR=1.36, based on 2 cases).[28]

At present we can only speculate on the underpinning reasons behind the sex and myeloid patterns seen in our cohort. Although numbers are small, the genetic profile of the myeloid disorders detected in patients with MGUS appeared broadly similar to that expected in myeloid malignancies in the general population, and none of the patients were diagnosed or received treatment for any other blood cancer before the myeloid malignancy was diagnosed. Nonetheless, one potential area of concern relates to the fact that clinical MGUS cohorts like ours tend to contain more individuals with comorbidities than screen-detected cohorts, as we and others have shown.[11-15] Importantly, however, recent work comparing data from the Olmsted County population-based screened series to a clinically detected series from the Mayo Clinic, reported that after accounting for competing risk of death, for myeloma at least, risk of progression was independent of the method of detection.[49] Nonetheless, whether this holds for hematological malignancies where direct clonal relationships are absent has yet to be determined. As such, although the association between MGUS and myeloid cancers could reflect a yet to be determined relationship, it could also be incidentally detected in patients undergoing investigations for clinical features associated with MDS/AML. Indeed, much like MGUS, rates of clonal hematopoiesis (CH) increase with age and the two conditions may co-exist, but are not known to be clonally related.[50] Mutations associated with CH are, however, reported in 10-20% of patients with MGUS.[51] Interestingly in our MGUS cohort there was a suggestion of increased rates of thrombocytopenia and neutropenia in males who subsequently developed a myeloid malignancy. However, these data were only available for a subset of patients, and further sequencing analysis on more complete data is required to determine whether such patients also have CH.

In summary, our analysis provides new data on the nature of MGUS progression; revealing a marked and previously undescribed disparity in outcomes by sex, and a striking increased risk of myeloid malignancies in male patients with MGUS. These findings have implications for counseling, risk stratification, and monitoring of the growing number of patients with this highly prevalent plasma cell dyscrasia.

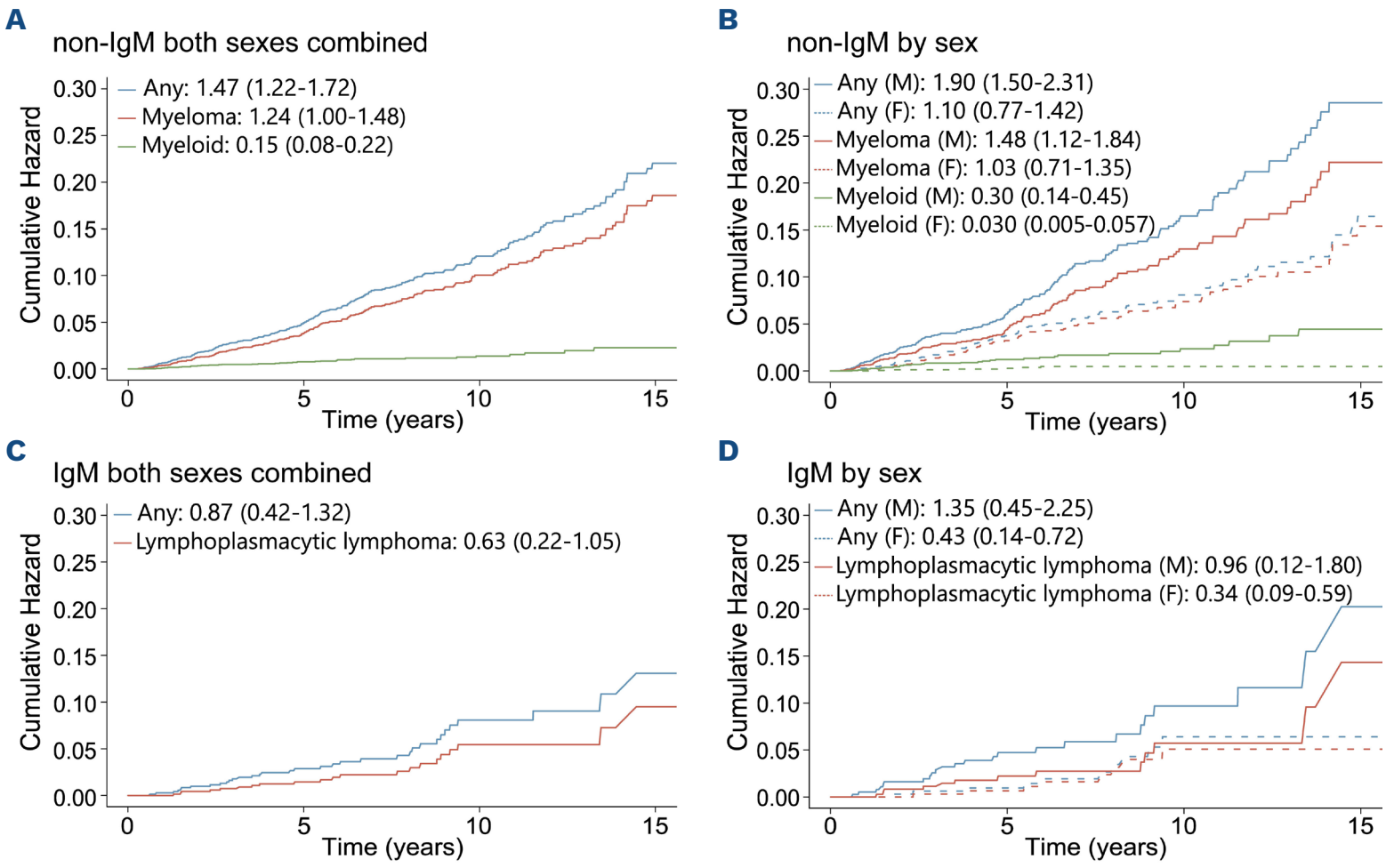


Figure 5. Average annual transition rates (95% confidence intervals) in monoclonal gammopathy of undetermined significance patients (N=4,651) whose disease did not progress or transform within the first 90 days. (A) Non-immunoglobulin M (IgM) both sexes combined. (B) Non-IgM stratified by sex. (C) IgM both sexes combined. (D) IgM stratied by sex. F: female; M: male.

A final unanswered question is whether existing prognostic scores should be refined to reflect the higher rates of progression and poorer outcomes observed in males, and predict those most at risk of progression to a myeloid malignancy. At present a pragmatic approach would be to consider bone marrow sampling with myeloid mutation panels for male MGUS patients with mild but unexplained anemia, neutropenia or thrombocytopenia.

Disclosures

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Contributions

ER, FS, CP, TB, and AS were responsible for the conception and design of the study. TB, SC, DP, AS, and DH undertook data collection, data management, and statistical analyses. FS, CP, GC, CC, RT, RdT, and AR provided diagnostic and clinical advice about the analysis and interpretation of findings. ER, FS, CP, AS, and TB drafted the paper, and all authors contributed to the final draft.

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Data-sharing statement

Ethical approvals and data restrictions mean that data cannot be shared, but collaborative projects can be undertaken. The corresponding author can be contacted for more information.

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