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

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Running heads: Men with MGUS have worse survival and more myeloid cancers

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Authors' contributions: *ER and *TB contributed equally as first co-authors. ER, FS, CP, TB, and AS were responsible for the conception and design of the study, and 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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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 haematological malignancies and premalignancies, we investigated patient and disease characteristics, subsequent haematological malignancy, and survival in 4651 people diagnosed with MGUS 2005-2019. The 5-year net (relative) survival (disease-specific estimate of the probability of survival) of MGUS patients was 87.8% (95% Confidence Interval 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 haematological malignancies was also higher in males than females (8.8% *versus* 5.3%; P<0.001); the average annual rates of transition being 1.81 (95% CI 1.44-218) 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 1.18%) than females (0.8% 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 (RR=1.0, 95% CI 0.3-1.9). No associations between MGUS and subsequent development of chronic lymphocytic leukaemia 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 haematological 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 haematological 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 progresses 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 ratio (Mayo criteria[2]) or incorporate phenotyping of bone marrow plasma cells (Pethema criteria[21]). In this context, the clonal precursor relationship between 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 Haematological Malignancy Research Network (HMRN), which was specifically designed to track newly diagnosed patients with haematological 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, characterising the predictors and frequencies of subsequent haematological malignancy.

Methods

Data are from the Haematological Malignancy Research Network (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 WHO classifications at a single integrated haematopathology laboratory, the Haematological 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 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 (CCI) Scores[31].

HMRN's catchment population has a comparable sex, age, urban/rural, and area-based deprivation (IMD: Index of Multiple Deprivation; income domain) distribution to the UK as a whole[32,33]. Served by 14 hospitals, all patients diagnosed with a haematological 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 National Health Service (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 haematological 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 haematological malignancy was subsequently diagnosed within 90 days of their MGUS diagnosis. The remaining 4651 (98.8%) patients were followed-up for transformation/progression and/or death until 31st July 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 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 modelling non-linear effect of covariates. Simple time-to-event estimates were calculated with the Kaplan-Meier method and cumulative incidence estimates were derived from intercept-only Cox models. Focussing 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 **Supplementary Figure 1**, 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 4651 patients diagnosed with MGUS over the 15-year period 2005-19 whose disease did not progress or transform in the first 90 days. With a median age of 73.3 years, 2454 (52.8%) patients were male and 2197 (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 serum free light chain (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 sFLCs measurements, and hence missing risk stratification scores, reflects the recency of assay incorporation into routine care. Data showing these improvements are presented in **Supplementary Table 1**, 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 **Supplementary Tables 2A-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% Confidence Interval 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 overall survival 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 (**Supplementary Table 3**).

Over the follow-up period (minimum 3.6 years, maximum 16.6 years), 343 haematological malignancies were diagnosed in 332/4651 (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 haematological malignancy was significantly higher in males (215/2454, 8.8%) than females (117/2197, 5.3%) (P<0.00001), but at around five years the average time to diagnosis was similar; 59.8 months (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 (**Supplementary Table 2A**). Again, as expected, among patients with IgM MGUS, LPL was the commonest progression (22/37). Notably, however, whilst myeloma and LPL combined accounted for 90.6% of all subsequent haematological 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 haematological malignancies) 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 (SIRs) are shown in **Figure 3**. Confirming known lymphoid associations, relative risk estimates (SIRs) 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 SIRs for other lymphoid malignancies, including large B-cell lymphoma (LBCL), chronic lymphocytic leukaemia (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=4.5, 95% CI 2.5-6.9), acute myeloid leukaemia (AML; RR=2.6, 95% CI 1.2-4.4), and chronic myelomonocytic leukaemia (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 was driven by males; the SIRs for MDS and AML being 5.5 (95% CI 3.0-8.7) and 3.3 (1.4-6.0) respectively (**Figure 3**). Showing broadly consistent estimates to those in **Figure 3, Supplementary Tables 4 and 5** present SIRs for blood cancers that have national rates available; the SIRs 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 transition to malignancy is shown in **Figures 4 and 5**. Over the follow-up period, transition rates for all MGUS diagnoses combined (n=4651) are roughly linear; approximately 1.37% (95% CI 1.15-1.60) per year for any haematological 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=2454) are consistently higher than in females (n=2197) (**Figure 4B**); the average annual rate for any haematological malignancy being 1.81% (95% CI 1.44-2.18) in males and 0.99% (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 modelling was used (**Supplementary Figure 1**); 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, lymphoplasmacytic lymphoma (LPL), and post-transplant LPD (PTLD), analyses of our large population-based cohort of clinically annotated MGUS patients with mature follow-up (n=4651; excluding patients whose MGUS diagnosis was followed by haematological malignancy within 90 days) revealed a number of less well recognised, 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 chronic lymphocytic leukaemia (CLL) in individuals previously diagnosed with MGUS[2,9,27].

Whilst it is well known that most haematological 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 haematological 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 RRs 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 haematological malignancies and/or premalignancies are diagnosed and monitored by a central haematopathology 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 behaviour in ICD-10, and are often poorly recorded in national cancer registries[45]. Although the potential aetiological role of high BMI 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-specific 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 eightfold increased risk of myeloid malignancies, most notably for MDS/AML (median time to diagnosis 14.4 months), that reduced to fivefold 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 two 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 haematological 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 haematopoiesis (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 counselling, risk stratification, and monitoring of the growing number of patients with this highly prevalent plasma cell dyscrasia. 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 anaemia, neutropenia or thrombocytopenia.

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Table 1: Patient characteristics and outcomes: MGUS diagnoses 2005-2019, followed-up to July 2023

	Both sexes	Males	Females	Male: Female p-value[2]
Total diagnoses	4651	2454	2197	
Age at diagnosis (years; % of total)				
< 70	1799 (38.7)	930 (37.9)	869 (39.6)	
≥70	2852 (61.3)	1524 (62.1)	1328 (60.5)	
Median (IQR)	73.3 (64.9-80.0)	73.4 (65.5-79.8)	73.0 (63.8-80.1)	p = 0.370
Paraprotein (% of total diagnoses)				
IgM	772 (16.6)	405 (16.5)	367 (16.7)	
Non-IgM	3879 (83.4)	2049 (83.5)	1830 (83.3)	
IgG	3033 (65.2)	1570 (64.0)	1463 (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)	p=0.102
Paraprotein concentration g/dl				
< 1.5	3994 (91.4)	2089 (90.9)	1905 (91.9)	
≥ 1.5	376 (8.6)	208 (9.1)	168 (8.1)	p= 0.238[2]
Median (IQR)	0.41 (0.13 - 0.88)	0.50 (0.20 - 0.90)	0.40 (0.10 - 0.80)	
Missing	122	68	121	
Serum free light chain (kappa/lambda)				
Normal (0.26-1.65)	1603 (62.8)	831 (61.2)	772 (64.5)	
Abnormal (<0.26 or >1.65)	951 (37.2)	526 (38.8)	425 (35.5)	p=0.089[2]
Missing	2097	1097	1000	
Risk stratification score[3]				
0	1041 (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)	p=0.342[2]
Missing	2098	1101	997	
Ethnicity				
White	4021 (95.9)	2129 (96.3)	1892 (95.4)	
Non-white	172 (4.1)	81 (3.7)	91 (4.6)	p=0.132[2]
Not known	458	244	214	
Index of multiple deprivation (IMD)[4]				
1-3 (least deprived)	2885 (62.3)	1544 (63.2)	1341 (61.3)	
4-5 (most deprived)	1748 (37.7)	900 (36.8)	848 (38.7)	p=0.315[2]
Missing	18	10	8	
Charlson comorbidity score				
0	2744 (60.6)	1373 (57.4)	1371 (64.2)	
1	784 (17.3)	404 (16.9)	380 (17.8)	
≥2	1000 (22.1)	617 (25.8)	383 (17.9)	p<0.0001[2]
Missing	123	60	63	
Subsequent blood cancer >90 days				
Total patients (%)	332 (7.1)	215 (8.8)	117 (5.3)	P<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)	P=0.91
Survival				
Deaths (%)	2292 (49.3)	1323 (53.9)	969 (44.1)	
Person-years at risk	31110.3	15316.3	15794.0	
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)	p<0.00001
Person-years at risk (blood cancer-free)	30180.8	14760.3	15420.6	
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)	

	Both sexes	Males	Females	Male: Female p-value[2]
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)	p<0.00001

[1] IgD (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 sFLC = 1; [4] Income domain

Table 2: Median time (months) to first haematological malignancy (Inter Quartile Range - IQR): HMRN MGUS diagnoses 2005-2019, followed-up to July 2023

	Both sexes		Males		Females	
Total haematological malignancies (IQR)	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 (LPL)	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 (LBCL)	6	53.4 (21.6 - 73.6)	4	68.1 (53.4 - 102.6)	2	13.4
Chronic lymphocytic leukaemia (CLL)	5	33.8 (25.8 - 129.8)	4	81.8 (21.7 - 160.9)	1	25.8
Follicular lymphoma (FL)	4	88.3 (68.7 - 102.6)	3	79.5 (57.8 - 97.1)	1	108.1
Post-transplant lymphoproliferative disorder (PTLD)	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 (MDS)	16	26.2 (19.2 - 53.1)	14	31.6 (21.4 - 56.1)	2	17.4
Acute myeloid leukaemia (AML)	10	61.4 (42.3 - 94.7)	8	61.4 (38.9 - 112.5)	2	56.9
Chronic myeloproliferative neoplasms (MPN)	5	54.3 (30.9 - 63.8)	4	42.6 (21.6 - 101.7)	1	63.8
Chronic myelomonocytic leukaemia (CMML)	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

Figure Legends

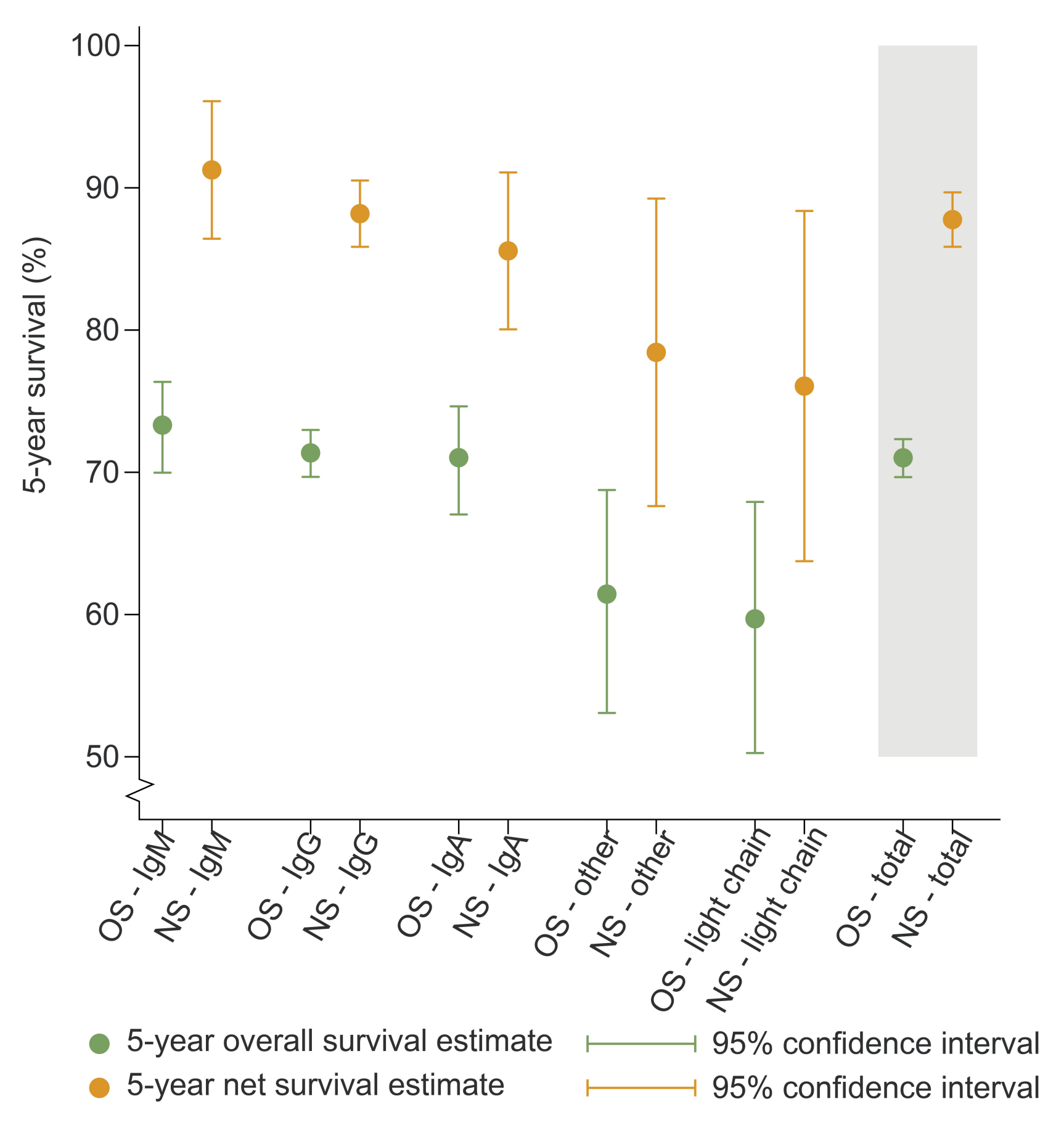
Figure 1: 5-year overall survival and net survival distributed by MGUS M-protein isotype; MGUS diagnoses 2005-2019, followed-up to July 2023

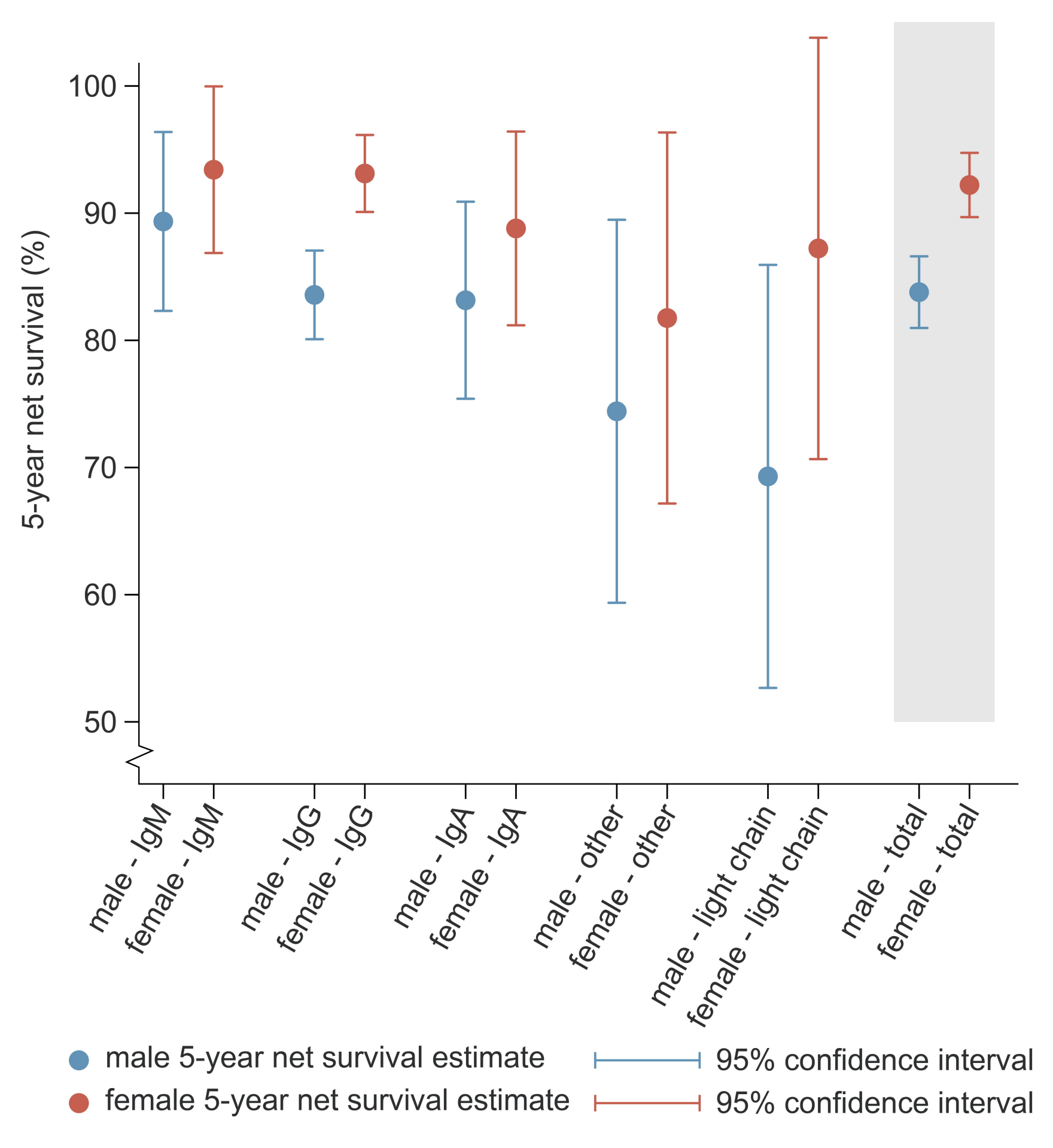
Figure 2: 5-year net survival distributed by M-protein isotype and sex; MGUS diagnoses 2005-2019, followed-up to July 2023

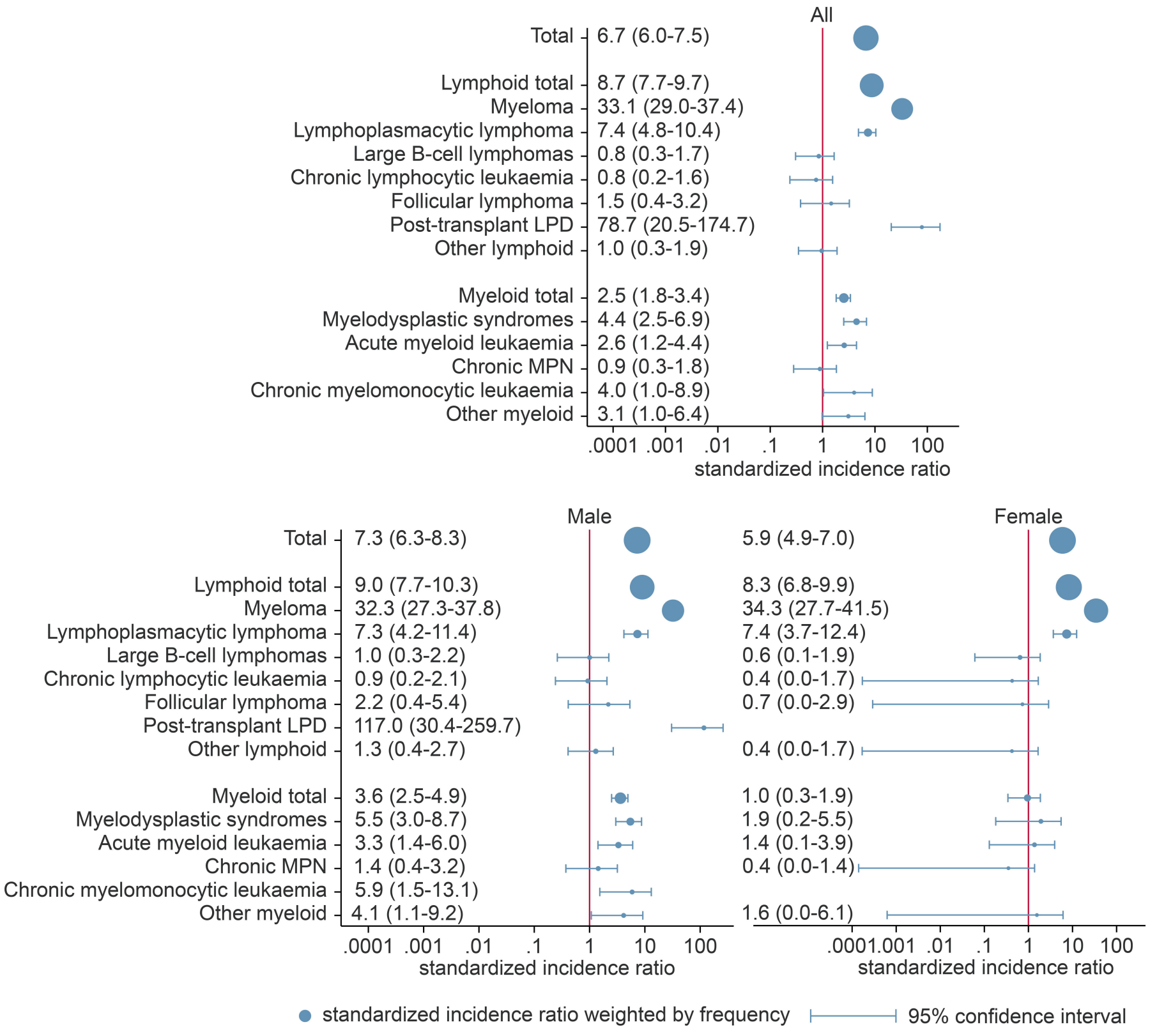
Figure 3: Standardized Incidence Ratios (95% Confidence Intervals) comparing the numbers of blood cancers diagnosed in MGUS patients to the numbers expected on the basis of HMRN's age and sex-specific rates

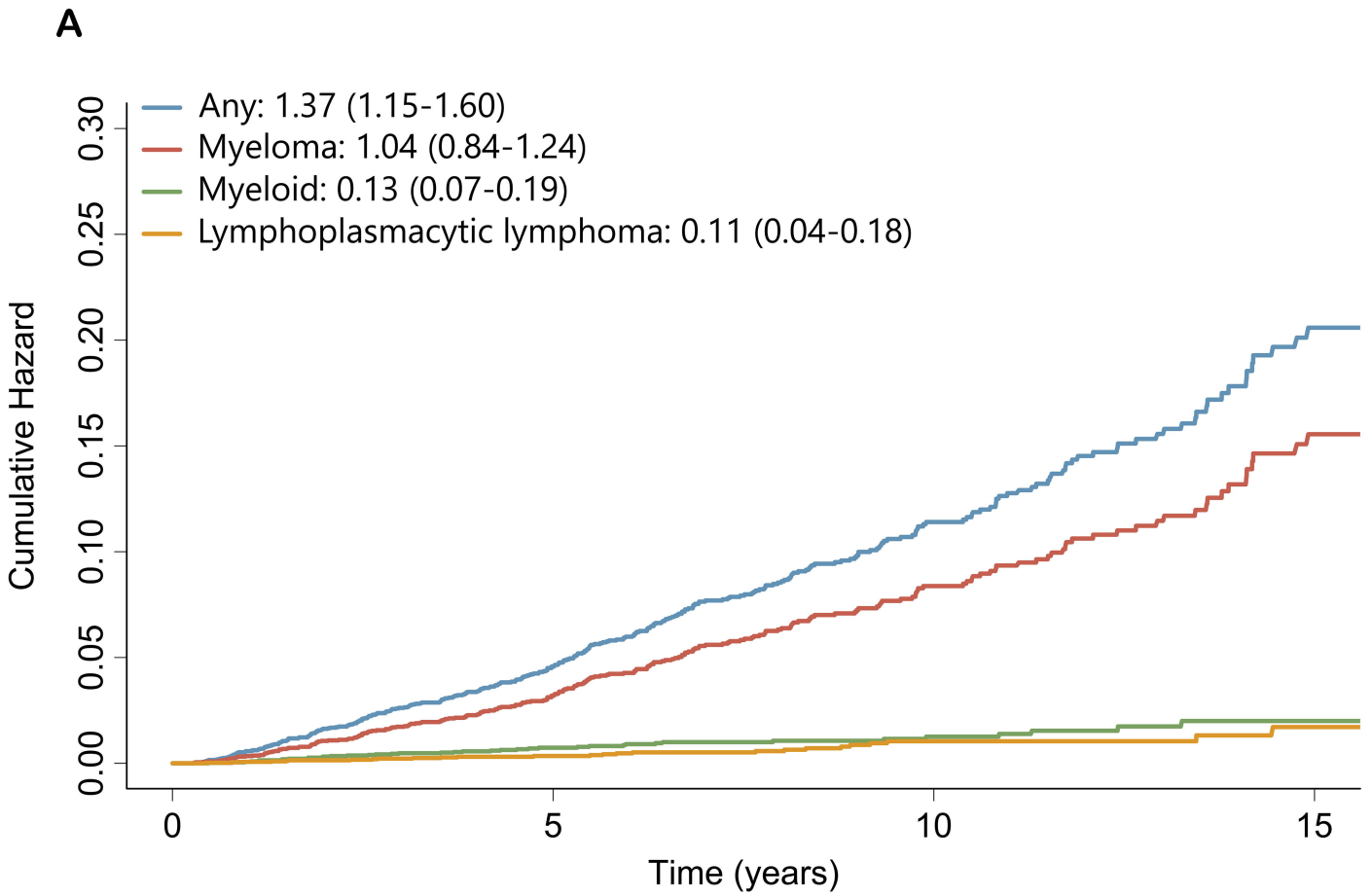
Figure 4: Average annual transition rates (95% Confidence intervals) in MGUS patients (n=4651) whose disease did not progress or transform within the first 90 days: A, both sexes combined; B, stratified by sex

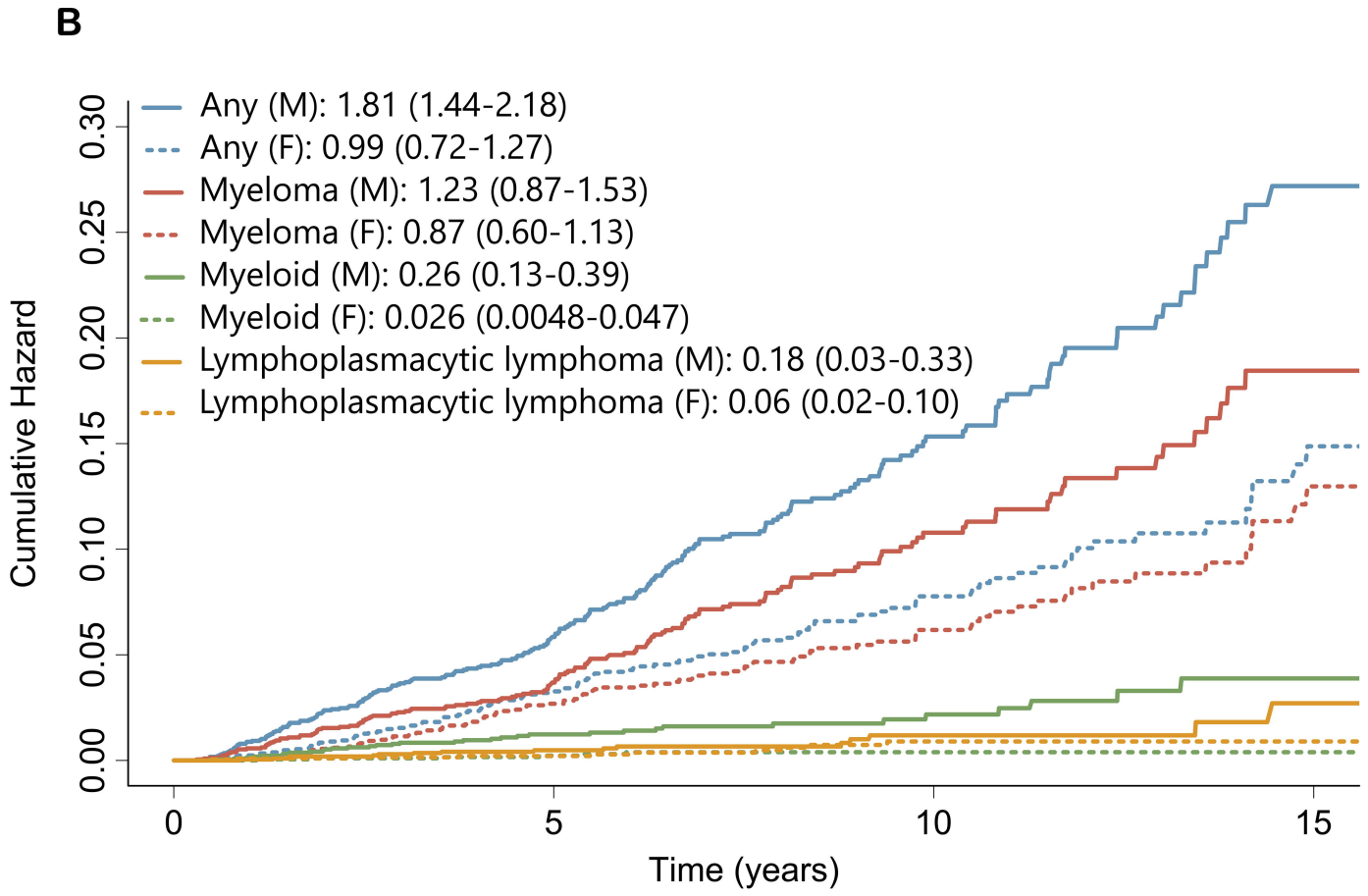
Figure 5: Average annual transition rates (95% Confidence intervals) in MGUS patients (n=4651) whose disease did not progress or transform within the first 90 days: A, non-IgM both sexes combined; B, non-IgM stratified by sex; C, IgM both sexes combined; D, IgM stratied by sex

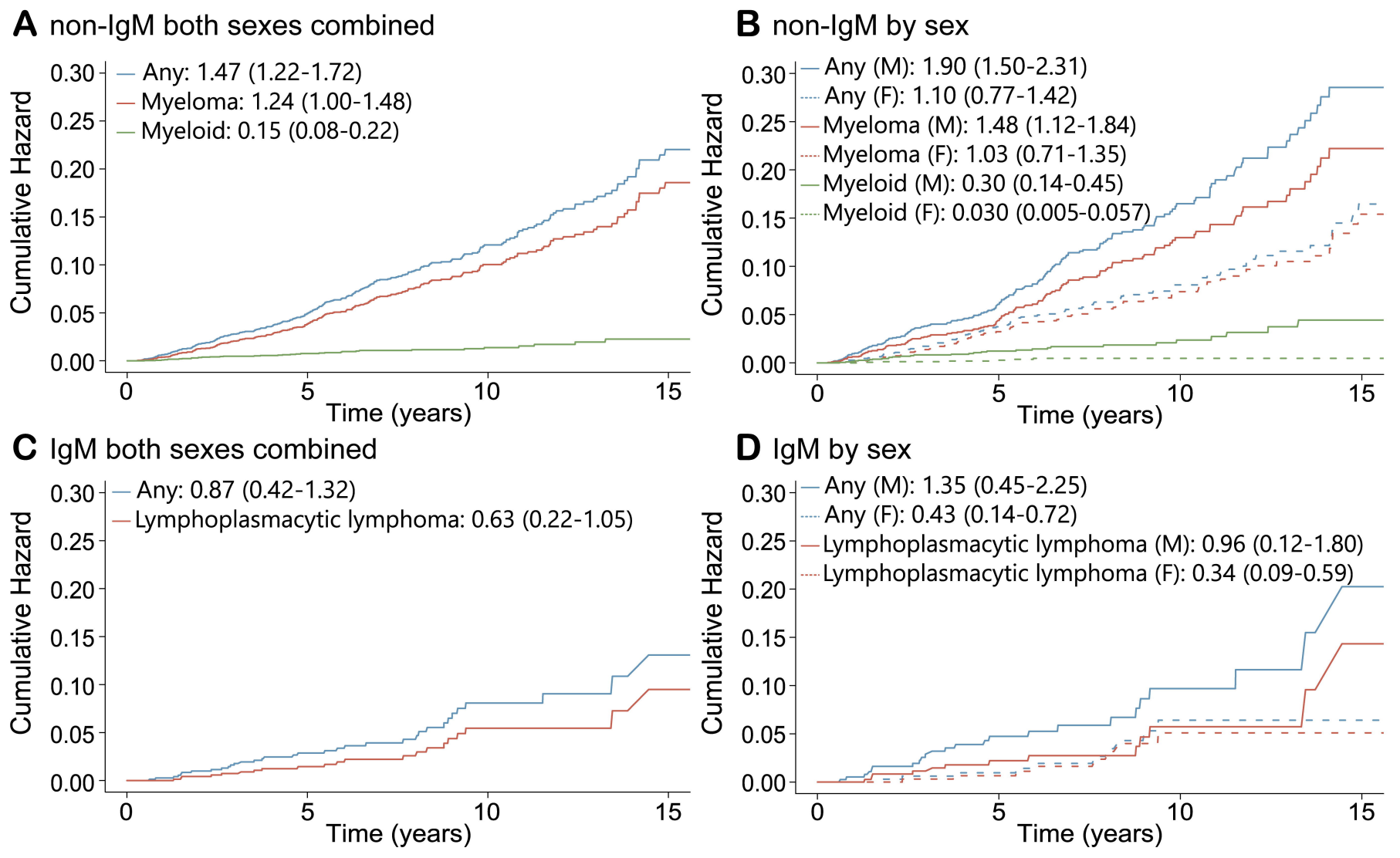

100
90
80
70
60
50
5-year survival (%)
OS - IgM
NS - IgM
OS - IgG
NS - IgG
OS - IgA
NS - IgA
OS - other
NS - other
OS - light chain
NS - light chain
OS - total
NS - total
5-year overall survival estimate
95% confidence interval
5-year net survival estimate
95% confidence interval


5-year net survival (%)
100
90
80
70
60
50
male - IgM
female - IgM
male - IgG
female - IgG
male - IgA
female - IgA
male - other
female - other
male - light chain
female - light chain
male - total
female - total
male 5-year net survival estimate
95% confidence interval
female 5-year net survival estimate
95% confidence interval


All
Total 6.7 (6.0-7.5)
Lymphoid total 8.7 (7.7-9.7)
Myeloma 33.1 (29.0-37.4)
Lymphoplasmacytic lymphoma 7.4 (4.8-10.4)
Large B-cell lymphomas 0.8 (0.3-1.7)
Chronic lymphocytic leukaemia 0.8 (0.2-1.6)
Follicular lymphoma 1.5 (0.4-3.2)
Post-transplant LPD 78.7 (20.5-174.7)
Other lymphoid 1.0 (0.3-1.9)
Myeloid total 2.5 (1.8-3.4)
Myelodysplastic syndromes 4.4 (2.5-6.9)
Acute myeloid leukaemia 2.6 (1.2-4.4)
Chronic MPN 0.9 (0.3-1.8)
Chronic myelomonocytic leukaemia 4.0 (1.0-8.9)
Other myeloid 3.1 (1.0-6.4)
.0001 .001 .01 .1 1 10 100
standardized incidence ratio
Male
Total 7.3 (6.3-8.3)
Lymphoid total 9.0 (7.7-10.3)
Myeloma 32.3 (27.3-37.8)
Lymphoplasmacytic lymphoma 7.3 (4.2-11.4)
Large B-cell lymphomas 1.0 (0.3-2.2)
Chronic lymphocytic leukaemia 0.9 (0.2-2.1)
Follicular lymphoma 2.2 (0.4-5.4)
Post-transplant LPD 117.0 (30.4-259.7)
Other lymphoid 1.3 (0.4-2.7)
Myeloid total 3.6 (2.5-4.9)
Myelodysplastic syndromes 5.5 (3.0-8.7)
Acute myeloid leukaemia 3.3 (1.4-6.0)
Chronic MPN 1.4 (0.4-3.2)
Chronic myelomonocytic leukaemia 5.9 (1.5-13.1)
Other myeloid 4.1 (1.1-9.2)
.0001 .001 .01 .1 1 10 100
standardized incidence ratio
Female
5.9 (4.9-7.0)
8.3 (6.8-9.9)
34.3 (27.7-41.5)
7.4 (3.7-12.4)
0.6 (0.1-1.9)
0.4 (0.0-1.7)
0.7 (0.0-2.9)
0.4 (0.0-1.7)
1.0 (0.3-1.9)
1.9 (0.2-5.5)
1.4 (0.1-3.9)
0.4 (0.0-1.4)
1.6 (0.0-6.1)
.0001 .001 .01 .1 1 10 100
standardized incidence ratio
standardized incidence ratio weighted by frequency
95% confidence interval


A
Any: 1.37 (1.15-1.60)
Myeloma: 1.04 (0.84-1.24)
Myeloid: 0.13 (0.07-0.19)
Lymphoplasmacytic lymphoma: 0.11 (0.04-0.18)
Cumulative Hazard
0.00
0.05
0.10
0.15
0.20
0.25
0.30
0
5
10
15
Time (years)


B
Any (M): 1.81 (1.44-2.18)
Any (F): 0.99 (0.72-1.27)
Myeloma (M): 1.23 (0.87-1.53)
Myeloma (F): 0.87 (0.60-1.13)
Myeloid (M): 0.26 (0.13-0.39)
Myeloid (F): 0.026 (0.0048-0.047)
Lymphoplasmacytic lymphoma (M): 0.18 (0.03-0.33)
Lymphoplasmacytic lymphoma (F): 0.06 (0.02-0.10)
Cumulative Hazard
0.00
0.05
0.10
0.15
0.20
0.25
0.30
0
5
10
15
Time (years)


A non-IgM both sexes combined
Any: 1.47 (1.22-1.72)
Myeloma: 1.24 (1.00-1.48)
Myeloid: 0.15 (0.08-0.22)
Cumulative Hazard
0.30
0.25
0.20
0.15
0.10
0.05
0.00
0
5
10
15
Time (years)
B non-IgM by sex
Any (M): 1.90 (1.50-2.31)
Any (F): 1.10 (0.77-1.42)
Myeloma (M): 1.48 (1.12-1.84)
Myeloma (F): 1.03 (0.71-1.35)
Myeloid (M): 0.30 (0.14-0.45)
Myeloid (F): 0.030 (0.005-0.057)
Cumulative Hazard
Time (years)
C IgM both sexes combined
Any: 0.87 (0.42-1.32)
Lymphoplasmacytic lymphoma: 0.63 (0.22-1.05)
Cumulative Hazard
Time (years)
D IgM by sex
Any (M): 1.35 (0.45-2.25)
Any (F): 0.43 (0.14-0.72)
Lymphoplasmacytic lymphoma (M): 0.96 (0.12-1.80)
Lymphoplasmacytic lymphoma (F): 0.34 (0.09-0.59)
Cumulative Hazard
Time (years)

Supplementary Results

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

Contents

Supplementary Table 1: Baseline patient characteristics distributed by year of diagnosis: MGUS diagnoses 2005-2019, followed-up to July 2023

	2005-19 (Total)		Year of MGUS diagnosis; last date of follow-up = 31st July 2023					
			2005-9		2010-14		2015-19	
	Males	Females	Males	Females	Males	Females	Males	Females
Total diagnoses	2454	2197	615	499	835	784	1004	916
Age at diagnosis								
Median, years (IQR)	73.4 (65.5 - 79.8)	73.0 (63.8 - 80.1)	72.8 (63.1 - 78.8)	72.1 (61.7 - 79.3)	72.5 (65.0 - 79.6)	72.9 (63.0 - 80.1)	74.5 (67.2 - 81.0)	73.8 (66.4 - 80.5)
Paraprotein type								
IgM	405 (16.5)	367 (16.7)	65 (10.6)	65 (13.0)	147 (17.6)	135 (17.2)	193 (19.2)	167 (18.3)
Non-IgM	2049 (83.5)	1830 (83.3)	550 (89.4)	434 (87.0)	688 (82.4)	649 (82.8)	811 (80.8)	747 (81.7)
IgG	1570 (64.0)	1463 (66.6)	433 (70.4)	326 (65.3)	534 (64.0)	530 (67.6)	603 (60.1)	607 (66.4)
IgA	322 (13.1)	252 (11.5)	72 (11.7)	67 (13.4)	108 (12.9)	79 (10.1)	142 (14.1)	106 (11.6)
Other[1]	82 (3.3)	68 (3.1)	26 (4.2)	30 (6.0)	20 (2.4)	22 (2.8)	36 (3.6)	16 (1.8)
Light chain	75 (3.1)	47 (2.1)	19 (3.1)	11 (2.2)	26 (3.1)	18 (2.3)	30 (3.0)	18 (2.0)
sFLC (kappa/lambda)								
Normal (0.26-1.65)	831 (61.2)	772 (64.5)	58 (54.2)	46 (54.8)	298 (59.4)	257 (60.2)	475 (63.5)	469 (68.4)
Abnormal (<0.26 or >1.65)	526 (38.8)	425 (35.5)	49 (45.8)	38 (45.2)	204 (40.6)	170 (39.8)	273 (36.5)	217 (31.6)
Missing	1097	1000	508	415	333	357	256	228
Paraprotein concentration g/dl								
< 1.5	2089 (90.9)	1908 (91.9)	482 (84.7)	405 (88.2)	725 (92.5)	678 (91.9)	882 (93.3)	825 (93.9)
≥ 1.5	209 (9.1)	168 (8.1)	87 (15.3)	54 (11.8)	59 (7.5)	60 (8.1)	63 (6.7)	54 (6.1)
Median (IQR)	0.50 (0.20 - 0.90)	0.40 (0.10 - 0.80)	0.69 (0.30 - 1.20)	0.60 (0.23 - 1.07)	0.50 (0.10 - 0.87)	0.40 (0.10 - 0.80)	0.40 (0.10 - 0.70)	0.30 (0.10 - 0.70)
Missing	67	53	24	21	21	20	22	12
Risk stratification score[2]								
0	531 (42.0)	510 (45.1)	41 (43.6)	23 (32.4)	198 (42.4)	163 (40.6)	292 (41.5)	324 (49.2)
1	522 (41.3)	453 (40.1)	36 (38.3)	36 (50.7)	185 (39.6)	172 (42.9)	301 (42.8)	245 (37.2)
2-3	211 (16.7)	167 (14.8)	17 (18.1)	12 (16.9)	84 (18.0)	66 (16.5)	110 (15.6)	89 (13.5)
Missing	1101	997	499	407	338	357	264	233

[1]IgD (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]Mayo clinic score: non-IgG isotype=1, M-protein ≥ 1.5 g/dl = 1, abnormal sFLC = 1

Supplementary Table 2A (Total): Baseline characteristics and subsequent haematological malignanacy frequencies (first only) >90 days after MGUS diagnosis; stratified by M-protein isotype

MALES + FEMALES	All subtypes	IgM	Non-IgM				
			Total	IgG	IgA	Other[1]	Light chain only
Total MGUS	4651	772	3879	3033	574	150	122
Males (%)	2454 (52.8)	405 (52.5)	2049 (52.8)	1570 (51.8)	322 (56.1)	82 (54.7)	75 (61.5)
Mean age at diagnosis, years (SD)	71.7 (11.5)	71.8 (10.8)	71.7 (11.6)	71.6 (11.6)	71.2 (11.8)	73.1 (11.9)	73.4 (9.8)
Paraprotein concentration g/dl							
< 1.5	3994 (91.4)	745 (98.3)	3249 (90.0)	2667 (88.9)	533 (95.2)	49 (96.1)	
≥ 1.5	376 (8.6)	13 (1.7)	363 (10.0)	334 (11.1)	27 (4.8)	2 (3.9)	
Median (IQR)	0.41 (0.13 - 0.88)	0.30 (0.01 - 0.50)	0.50 (0.20 - 0.90)	0.50 (0.20 - 1.00)	0.50 (0.12 - 0.80)	0.30 (0.01 - 0.40)	
Missing	122	14	108	32	14	62	
Risk stratification score							
0	1041 (43.5)	0 (0.0)	1041 (28.0)	1041 (60.0)	0 (0.0)	0 (0.0)	
1	975 (40.7)	185 (68.0)	790 (21.2)	570 (32.9)	205 (56.6)	15 (57.7)	
2-3	378 (15.8)	87 (32.0)	291 (7.8)	123 (7.1)	157 (43.4)	11 (42.3)	
Missing[5]	2098	500	1598	1299	212	87	
Total blood cancers >90 days after MGUS	332 (7.1%)	37 (4.8%)	295 (7.6%)	221 (7.3%)	56 (9.8%)	9 (6.0%)	9 (7.4%)
Lymphoid diagnoses (% total blood cancers)	292 (88.0)	33 (89.2)	259 (87.8)	199 (90.0)	45 (80.4)	8 (88.9)	7 (77.8)
Myeloma	240 (72.3)	1 (2.7)	239 (81.0)	181 (81.9)	44 (78.6)	7 (77.8)[2]	7 (77.8)
Lymphoplasmacytic lymphoma (LPL)	27 (8.1)	22 (59.5)	5 (1.7)	3 (1.4)	1 (1.8)	1 (11.1)[3]	-
Large B-cell lymphomas (LBCL)	6 (1.8)	1 (2.7)	5 (1.7)	5 (2.3)	-	-	-
Chronic lymphocytic leukaemia (CLL)	5 (1.5)	3 (8.1)	2 (0.7)	2 (0.9)	-	-	-
Follicular lymphoma (FL)	4(1.2)	3 (8.1)	1 (0.3)	1 (0.5)	-	-	-
Post-transplant lymphoproliferative disorder	4(1.2)	2 (5.4)	2 (0.7)	2 (0.9)	-	-	-
Other lymphoid	6 (1.8)	1 (2.7)	5 (1.7)	5 (2.3)	-	-	-
Myeloid diagnoses (% total blood cancers)	40 (12.0)	4 (10.8)	36 (12.2)	22 (10.0)	11 (19.6)	1 (11.1)	2 (22.2)
Myelodysplastic syndromes (MDS)	16 (4.8)	2 (5.4)	14 (4.7)	8 (3.6)	5 (8.9)	1 (11.1)[4]	-
Acute myeloid leukaemia (AML)	10 (3.0)	1 (2.7)	9 (3.1)	6 (2.7)	2 (3.6)	-	1 (11.1)
Chronic myeloproliferative neoplasms	5 (1.5)	-	5 (1.7)	2 (0.9)	2 (3.6)	-	1 (11.1)
Chronic myelomonocytic leukaemia	4 (1.2)	-	4 (1.4)	4 (1.8)	-	-	-
Other myeloid	5 (1.5)	1 (2.7)	4 (1.4)	2 (0.9)	2 (3.6)	-	-

[1]IgD (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]IgA & IgM (n=1), not known (n=6); [3]not known (n=1); [4] non-secretory (n=1); [5] Excludes light chain only and non-secretory

Supplementary Table 2B (Males): Baseline characteristics and subsequent haematological malignanacy frequencies (first only) >90 days after MGUS diagnosis; stratified by M-protein isotype

MALES	All subtypes	IgM	Non-IgM				
			Total	IgG	IgA	Other[1]	Light chain only
Total MGUS	2454	405	2049	1570	322	82	75
Mean age at diagnosis, years (SD)	71.9 (11.2)	71.8 (10.3)	72.0 (11.4)	71.9 (11.5)	71.4 (11.1)	73.4 (11.0)	73.6 (10.4)
Paraprotein concentration g/dl							
< 1.5	2089 (90.9)	389 (98.0)	1700 (89.5)	1363 (87.9)	302 (96.8)	35 (94.6)	
≥ 1.5	208 (9.1)	8 (2.0)	200 (10.5)	188 (12.1)	10 (3.2)	2 (5.4)	
Median (IQR)	0.50 (0.20 - 0.90)	0.30 (0.01 - 0.58)	0.50 (0.20 - 1.00)	0.50 (0.20 - 1.02)	0.49 (0.10 - 0.73)	0.30 (0.01 - 0.60)	
Missing	68	8	60	19	10	31	
Risk stratification score							
0	531 (42.0)	0 (0.0)	531 (27.1)	531 (59.0)	0 (0.0)	0 (0.0)	
1	522 (41.3)	97 (66.9)	425 (21.7)	304 (33.8)	109 (54.8)	12 (60.0)	
2-3	211 (16.7)	48 (33.1)	163 (8.3)	65 (7.2)	90 (45.2)	8 (40.0)	
Missing[5]	1101	260	841	670	123	48	
Total blood cancers >90 days after MGUS	215 (8.8)	26 (6.4)	189 (9.2)	137 (8.7)	39 (12.1)	6 (7.3)	7 (9.3)
Lymphoid diagnoses (% total blood cancers)	181 (84.2)	22 (84.6)	159 (84.1)	120 (87.6)	29 (74.4)	5 (83.3)	5 (71.4)
Myeloma	145 (67.4)	1 (3.8)	144 (76.2)	107 (78.1)	28 (71.8)	4 (66.7)[2]	5 (71.4)
Lymphoplasmacytic lymphoma (LPL)	16 (7.4)	13 (50.0)	3 (1.6)	1 (0.7)	1 (2.6)	1 (16.7)[3]	-
Large B-cell lymphomas (LBCL)	4 (1.9)	-	4 (2.1)	4 (2.9)	-	-	-
Chronic lymphocytic leukaemia (CLL)	4 (1.9)	3 (11.5)	1 (0.5)	1 (0.7)	-	-	-
Follicular lymphoma (FL)	3 (1.4)	2 (7.7)	1 (0.5)	1 (0.7)	-	-	-
Post-transplant lymphoproliferative disorder	4 (1.9)	2 (7.7)	2 (1.1)	2 (1.5)	-	-	-
Other lymphoid	5 (2.3)	1 (3.8)	4 (2.1)	4 (2.9)	-	-	-
Myeloid diagnoses (% total blood cancers)	34 (15.8)	4 (15.4)	30 (15.9)	17 (12.4)	10 (25.6)	1 (16.7)	2 (28.6)
Myelodysplastic syndromes (MDS)	14 (6.5)	2 (7.7)	12 (6.3)	7 (5.1)	4 (10.3)	1 (16.7)[4]	-
Acute myeloid leukaemia (AML)	8 (3.7)	1 (3.8)	7 (3.7)	4 (2.9)	2 (5.1)	-	1 (14.3)
Chronic myeloproliferative neoplasms	4 (1.9)	-	4 (2.1)	1 (0.7)	2 (5.1)	-	1 (14.3)
Chronic myelomonocytic leukaemia	4 (1.9)	-	4 (2.1)	4 (2.9)	-	-	-
Other myeloid	4 (1.9)	1 (3.8)	3 (1.6)	1 (0.7)	2 (5.1)	-	-

[1] IgA & IgG (n=9), IgA & IgM (n =1), IgD (n =3), IgE (n =3), IgG & IgM= (n 22), Non-secretory= (n 14), Not known (n =30); [2] IgA & IgM (n=1), not known (n=3); [3] not known (n=1); [4] non-secretory (n=1); [5] Excludes light chain only and non-secretory

Supplementary Table 2C (Females): Baseline characteristics and subsequent haematological malignanacy frequencies (first only) >90 days after MGUS diagnosis; stratified by M-protein isotype

FEMALES	All subtypes	IgM	Non-IgM				
			Total	IgG	IgA	Other[1]	Light chain only
Total MGUS	2197	367	1830	1463	252	68	47
Mean age at diagnosis, years (SD)	71.5 (11.8)	71.9 (11.3)	71.4 (11.9)	71.3 (11.8)	70.9 (12.7)	72.7 (13.1)	73.3 (8.9)
Paraprotein concentration g/dl							
< 1.5	1905 (91.9)	356 (98.6)	1549 (90.5)	1304 (89.9)	231 (93.1)	14 (100.0)	
≥ 1.5	168 (8.1)	5 (1.4)	163 (9.5)	146 (10.1)	17 (6.9)	0 (0.0)	
Median (IQR)	0.40 (0.10 - 0.80)	0.20 (0.01 - 0.50)	0.50 (0.20 - 0.90)	0.50 (0.20 - 0.90)	0.50 (0.20 - 0.80)	0.10 (0.01 - 0.30)	
Missing	54	6	48	13	4	31	
Risk stratification score							
0	510 (45.1)	0 (0.0)	510 (50.8)	510 (61.2)	0 (0.0)	0 (0.0)	
1	453 (40.1)	88 (69.3)	365 (36.4)	266 (31.9)	96 (58.9)	3 (50.0)	
2-3	167 (14.8)	39 (30.7)	128 (12.8)	58 (7.0)	67 (41.1)	3 (50.0)	
Missing[3]	997	240	757	629	89	39	
Total blood cancers >90 days after MGUS	117 (5.3)	11 (3.0)	106 (5.8)	84 (5.8)	17 (6.7)	3 (4.4)	2 (4.3)
Lymphoid diagnoses (% total blood cancers)	111 (95.0)	11 (100.0)	100 (94.3)	79 (94.0)	16 (94.1)	3 (100.0)	2 (100.0)
Myeloma	95 (81.2)	-	95 (89.6)	74 (88.1)	16 (94.1)	3 (100.0)[2]	2 (100.0)
Lymphoplasmacytic lymphoma (LPL)	11 (9.4)	9 (81.8)	2 (1.9)	2 (2.4)	-	-	-
Large B-cell lymphomas (LBCL)	2 (1.7)	1 (9.1)	1 (0.9)	1 (1.2)	-	-	-
Chronic lymphocytic leukaemia (CLL)	1 (0.9)	-	1 (0.9)	1 (1.2)	-	-	-
Follicular lymphoma (FL)	1 (0.9)	1 (9.1)	-	-	-	-	-
Post-transplant lymphoproliferative disorder	-	-	-			-	-
Other lymphoid	1 (0.9)	-	1 (0.9)	1 (1.2)	-	-	-
Myeloid diagnoses (% total blood cancers)	6 (5.1)	-	6 (5.7)	5 (6.0)	1 (5.9)	-	-
Myelodysplastic syndromes (MDS)	2 (1.7)	-	2 (1.9)	1 (1.2)	1 (5.9)	-	-
Acute myeloid leukaemia (AML)	2 (1.7)	-	2 (1.9)	2 (2.4)	-	-	-
Chronic myeloproliferative neoplasms	1 (0.9)	-	1 (0.9)	1 (1.2)	-	-	-
Chronic myelomonocytic leukaemia	-	-	-	-	-	-	-
Other myeloid	1 (0.9)	-	1 (0.9)	1 (1.2)	-	-	-

[1] IgA & IgG (n=4), IgA & IgM (n=1), IgD (n=2), IgG & IgM (n=12), Non-secretory (n=23), Not known (n=26); [2] not known (n=3); [3] Excludes light chain only and non-secretory

Supplementary Table 3: 5-year overall survival by patient diagnostic/prognostic characteristics: MGUS diagnoses 2005-2019, followed-up to July 2023

	5-year OS, % (95% CI)		
	Both sexes	**Males**	**Females**
Total diagnoses	71.0 (69.7-72.3)	66.0 (64.1-67.9)	76.6 (74.7-78.4)
Paraprotein			
IgM	73.3 (70.0-76.4)	70.8 (66.0-75.1)	76.1 (71.3-80.2)
Non-IgM	70.6 (69.1-72.0)	65.1 (62.9-67.1)	76.7 (74.7-78.6)
IgG	71.4 (69.7-73.0)	65.5 (63.0-67.8)	77.7 (75.4-79.8)
IgA	71.0 (67.0-74.6)	68.1 (62.6-72.9)	74.9 (68.8-79.9)
Light chain only	59.7 (50.3-67.9)	51.5 (39.5-62.2)	73.2 (57.6-83.8)
Other subtypes[1]	61.4 (53.1-68.8)	58.1 (46.7-68.0)	65.4 (52.7-75.5)
Paraprotein concentration g/dl			
< 1.5	71.8 (70.4-73.2)	67.1 (65.0-69.2)	77.0 (75.0-78.8)
≥ 1.5	70.2 (65.2-74.6)	62.6 (55.6-68.9)	79.6 (72.6-85.1)
Missing	60.3 (51.1-68.4)	57.4 (44.8-68.1)	64.2 (49.8-75.4)
Serum free light chain (kappa/lambda)			
Normal (0.26-1.65)	72.1 (69.7-74.3)	67.0 (63.6-70.2)	77.6 (74.3-80.5)
Abnormal (<0.26 or >1.65)	71.6 (68.5-74.4)	67.6 (63.3-71.5)	76.6 (72.0-80.5)
Missing	70.0 (68.0-72.0)	64.6 (61.6-67.4)	75.9 (73.1-78.5)
Risk stratification score[3]			
0	72.3 (69.4-75.1)	68.8 (64.5-72.7)	76.0 (71.9-79.6)
1	73.2 (70.2-76.0)	67.3 (63.0-71.3)	80.1 (75.9-83.6)
2-3	71.1 (66.1-75.5)	68.9 (62.0-74.7)	73.8 (66.1-80.0)
Missing	70.2 (68.1-72.1)	64.5 (61.6-67.3)	76.4 (73.6-78.9)

[1]IgD (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] Tests exclude missing; [3] Mayo clinic score: non-IgG isotype=1, M-protein ≥ 1.5 g/dl = 1, abnormal sFLC = 1; [4] Income domain

Supplementary Table 4: Standardized Incidence Ratios (95% Confidence Intervals) comparing the numbers of blood cancers diagnosed in MGUS patients (first transition, n=332)[1] in the HMRN region to the numbers expected on the basis of national rates (all diagnoses) Observed (O) and Expected (E[2])

	All			Male			Female		
Diagnosis	**O[1]**	**E[2]**	**Relative risk**	**O[1]**	**E[2]**	**Relative risk**	**O[1]**	**E[2]**	**Relative risk**
All	332	-	-	215	-	-	117	-	-
Myeloma[3]	240	8.8	27.3 (24.0-30.9)	145	5.4	27.0 (22.8, 31.5)	95	3.4	27.9 (22.6, 33.8)
Non-Hodgkin lymphoma	40	19.0	2.1 (1.5-2.8)	25	11.0	2.3 (1.5, 3.3)	15	8.0	1.9 (1.0, 3.0)
Hodgkin lymphoma	1	1.3	0.8 (0.0-3.0)	1	0.8	1.3 (0.0, 5.1)	0	0.5	-
Chronic lymphocytic leukaemia	5	5.6	0.9 (0.3-1.9)	4	3.7	1.1 (0.3, 2.4)	1	1.9	0.5 (0.0, 2.0)
Acute lymphoblastic leukaemia	0	0.2	-	0	0.1	-	0	0.1	-
Acute myeloid leukaemia[4]	10	4.1	2.4 (1.2-4.2)	8	2.6	3.1 (1.3, 5.7)	2	1.6	1.3 (0.1, 3.7)
Chronic myeloid leukaemia	1	0.8	1.2 (0.0-4.9)	1	0.5	2.2 (0.0, 8.6)	0	0.3	-
Other[5]	35	-	-	31			4	-	-

[1]Followed up to 01/08/2023 for progression, excluding progressions within 90 days of MGUS diagnosis ; [2]Rates used are from Cancer Research UK, UK 2016-2018 https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type; [3]includes plasmacytoma; [4]includes acute promyelocytic leukaemia; [5] n=16 myelodysplastic syndromes, n=5 chronic myeloproliferative neoplasms, n=4 chronic myelomonocytic leukaemia, n=4 post-transplant lymphoproliferative disorder, n=2 myelodysplastic / myeloproliferative neoplasms, n=2 myelofibrosis, n=1 hairy cell leukaemia, n=1 T-cell large granular lymphocytic leukaemia

Supplementary Table 5: Standardized Incidence Ratios (95% Confidence Intervals) comparing the numbers of blood cancers diagnosed in MGUS patients (all transitions, n=343)[1] in the HMRN region to the numbers expected on the basis of national rates (all diagnoses) Observed (O) and Expected (E[2])

	All			Male			Female		
Diagnosis	**O[1]**	**E[2]**	**Relative risk**	**O[1]**	**E[2]**	**Relative risk**	**O[1]**	**E[2]**	**Relative risk**
All	343	-	-	225	-	-	118	-	-
Myeloma[3]	240	8.8	27.3 (24.0, 30.9)	145	5.4	27.0 (22.8, 31.5)	95	3.4	27.9 (22.6, 33.8)
Non-Hodgkin lymphoma	43	19.0	2.3 (1.6, 3.0)	28	11.0	2.5 (1.7, 3.6)	15	8.0	1.9 (1.0, 3.0)
Hodgkin lymphoma	2	1.3	1.5 (0.1, 4.4)	2	0.8	2.6 (0.2, 7.4)	0	0.5	-
Chronic lymphocytic leukaemia	8	5.6	1.4 (0.6, 2.6)	6	3.7	1.6 (0.6, 3.2)	2	1.9	1.0 (0.1, 3.0)
Acute lymphoblastic leukaemia	0	0.2	-	0	0.1	-	0	0.1	-
Acute myeloid leukaemia[4]	12	4.1	2.9 (1.5, 4.8)	10	2.6	3.9 (1.9, 6.7)	2	1.6	1.3 (0.1, 3.7)
Chronic myeloid leukaemia	1	0.8	1.2 (0.0, 4.9)	1	0.5	2.2 (0.0, 8.6)	0	0.3	-
Other[5]	37	-	-	33	-	-	4	-	-

[1]Followed up to 01/08/2023 for progression, excluding progressions within 90 days of MGUS diagnosis ; [2]Rates used are from Cancer Research UK, UK 2016-2018 https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type; [3]includes plasmacytoma; [4]includes acute promyelocytic leukaemia; [5] n=18 myelodysplastic syndromes, n=5 chronic myeloproliferative neoplasms, n=4 chronic myelomonocytic leukaemia, n=4 post-transplant lymphoproliferative disorder, n=2 myelodysplastic / myeloproliferative neoplasms, n=2 myelofibrosis, n=1 hairy cell leukaemia, n=1 T-cell large granular lymphocytic leukaemia

Supplementary Figure 1: Multi-state model structure and number of events associated with eacjh transition