Incidence of first and subsequent fractures in multiple myeloma patients: a parallel cohort study using UK CPRD dataset

Authors: Rohit Vijjhalwar[1*], Kaiyang Song[2*,^], Franz Clemeno[3], Maria T Sanchez-Santos[3], Samuel Hawley[4], Bhuvan Kishore[5], Kwee Yong[6], Stella Bowcock[7], Karthik Ramasamy[3,8], Antonella Delmestri[3], Rafael Pinedo-Villanueva[3], Muhammad Kassim Javaid[3]

Affiliations

1. University Hospital Southampton NHS Foundation Trust, UK
2. Centre for Rheumatic Diseases, King's College London, UK
3. NDORMS, University of Oxford, UK
4. Musculoskeletal Research Unit, Bristol Medical School, University of Bristol, UK
5. Department of Haematology, University Hospitals Birmingham NHS Foundation Trust, UK
6. Department of Haematology, University College London, UK
7. Department of Haematology, King's College Hospital NHS Trust, UK
8. Oxford Translational Myeloma Centre, UK

*Denotes joint first authorship

^Denotes corresponding author

Corresponding author details:

Kaiyang Song, Centre for Rheumatic Diseases, King's College London, UK

Email address: kaiyang.song@kcl.ac.uk

Abstract

Purpose: Whilst multiple myeloma (MM) is known to increase fracture risk, the incidence of subsequent fractures is poorly described. Here, we describe the incidence of index and subsequent fractures in a real-world cohort of MM patients, compared to non-MM controls.

Methods: Using the UK Clinical Practice Research Datalink GOLD, we identified a MM cohort with age-, sex-, and GP-practice-matched controls from 1995-2017. The primary outcome was the incidence of fracture at major osteoporotic sites (i.e. hip, vertebral, wrist or humerus) within two years before and after MM diagnosis. The cumulative incidence of subsequent fractures up to two years post-index fracture was estimated using Cox proportional hazards models.

Results: 1,974 patients (59.6% male, median age 70 years) with MM were matched to 6,429 non-MM controls. The index fracture rate was significantly greater in the MM cohort compared to non-MM cohort from one year prior to MM diagnosis onwards. Post-index fracture, the overall 2-year subsequent major fracture rate was 16.4% (95% CI:11.1-21.5) and 12.0% (95% CI:7.50-16.30) in the MM and non-MM cohorts, respectively. Within two years post-index fracture, the risk of subsequent vertebral fracture was significantly greater in MM patients (aHR: 11.6 (95% CI:1.47-91.8), p=0.02)).

Conclusions: MM patients are at higher risk of having an index fracture from one year pre-diagnosis and a subsequent vertebral fractures in the two years post-index fracture, compared to non-MM controls. These findings highlight the potential for earlier MM diagnosis in adults presenting with a major fracture, and the need to reduce subsequent fracture risk.

Mini Abstract

Based on a UK primary care dataset, patients with Multiple Myeloma (MM) experience a significantly higher index fracture rate from one year prior to MM diagnosis onwards and a higher subsequent vertebral fracture rate, compared to non-MM controls. There is potential for earlier MM diagnosis and reducing subsequent fracture risk.

Key words

Multiple myeloma, Clinical Practice Research Datalink (CPRD) GOLD dataset, index fracture, imminent fracture risk, vertebral fracture, non-hip fracture

Introduction

Multiple myeloma (MM) is the second most common haematological malignancy with nearly 6,000 new cases are diagnosed annually in the United Kingdom (UK)[1] with approximately 43% diagnosed aged 75 years or older. Skeletal manifestations of MM include signs local lytic lesions, generalised osteoporosis, and fractures[2]. Fragility fractures are the presenting symptom in 20-30% of MM cases in the UK[3, 4] and substantially reduce the quality of life in MM and increase in the risk of mortality in patients two-fold, compared to those without fractures[5]. A US population-based cohort study of MM patients diagnosed from 1945 to 2001, demonstrated a nine-fold increase in the risk of fractures within the first two years after diagnosis as compared the general population, with the ribs and vertebrae being the most common sites of fracture around the time of MM diagnosis[2]. In patients without MM, an index major fracture rapidly increases the risk of subsequent fracture, an imminent fracture risk (IFR)[6-8]. However, given MM patients often start both glucocorticoids and monthly intravenous zoledronate soon after diagnosis, it is not known if they also have a high IFR. We aim to estimate the incidence rates of index and subsequent bone fractures in the period leading up to and following the date of MM diagnosis, and compare this to a general population matched population without MM in the UK setting.

Methods

Data sources and participants

We used primary care records from the Clinical Practice Research Datalink (CPRD) GOLD dataset from 1995 to 2017. As of 2013, CPRD GOLD covered over 11.3 million patients from 674 general practitioner (GP) practices and had a representative coverage of approximately 7% of the UK population[9]. CPRD GOLD uses the Read code system and includes more than 100,000 codes for clinical events in primary care[10], covering diagnostic codes for myeloma used by previous studies[4]. The CPRD GOLD dataset was linked to the Hospital Episode Statistics (HES), which provides admission data and ICD10 diagnosis codes for all publicly funded hospital admissions in England only. English GP practices had to agree to the join the linkage scheme and there was no

significant difference in the percentage of patients with missing linkage with HES across cases vs controls (42.19% vs 42.94% respectively, p=0.36). The CPRD dataset has previously been shown to have a high level of validity regarding fracture data[11].

MM patients were identified using the primary care record Read codes (Sup. Table 1) and were individually matched by the date of MM diagnosis, to 2-4 non-MM controls of the same sex, age band (within five years of the matched case's age) and same primary care practice. MM patients for whom there were less than two non-MM controls, were excluded. We observed a statistically significant imbalance in ages between cases and controls despite using age bands as part of the matching strategy (Table 1), and so age was added as a confounder in our models.

We defined the timepoint of two years prior to MM first diagnosis/matching date as start date for follow-up (Sup. Figure 1). Given the aim was to describe incident (rather than prevalent) fractures, we excluded patients who did not have at least one year of follow-up prior to this cohort entry, thus enabling a washout period of one year with no prior fracture. We also excluded patients without HES linkage, a diagnosis of Paget's disease, prior cancer (excluding multiple myeloma), and those having no remaining matched patients due to other exclusions.

To validate the Read codes, a questionnaire to confirm the diagnosis was sent to a sample of GPs of myeloma cases via the CPRD to maintain patient anonymity. Curator software was used to perform the pre-analytical data curation[12].The Read codes for myeloma diagnoses were validated from 125 questionnaires completed by GPs (Sup. Table 2), with a positive predictive value (PPV) for Read codes: B630.00 (Multiple Myeloma) of 87.7% and BBn0.12 (Myeloma NOS) of 78.6%.

Outcome

The primary outcome was major closed bone fracture of the hip, vertebral, humeral, or wrist (major osteoporotic fractures). Secondary outcomes were fractures of the hip, vertebra, hunerus and wrist using a combination of Read and ICD10 codes (Sup. Table 2). To avoid duplicate fracture coding, re-fractures of the same bone were only included if diagnosed after a six-month period in the primary

care records[13] and during a separate hospital spell if identified by a ICD10 code from secondary care records.

Statistical analysis

For MM patients and the control cohort, sex-specific incidence rates of fracture per 1,000 person-years (PYs) were generated for each year of follow-up (i.e., two years prior to MM diagnosis date to two year after diagnosis), We performed survival analysis using the Cox proportional hazards model to investigate the association between the covariates and the second fracture. The model was fitted using the coxph command in R, incorporating stepwise variable selection with a significance level of 0.1. The variables included in the final model were age, sex, cardiovascular disease history; smoking status; drinking status; depression history; bisphosphonate use history; diabetes history. The proportional hazards assumption was not violated using Schoenfield residual plots. Additionally, a Fine-Gray model was used to account for the competing risk of mortality. A priori we estimated that a total sample size of approximately 1200 patients was required to provide a power of 90% for our primary outcome. Statistical analyses were performed using R version 4.4.2.

Results

Following identification in CPRD GOLD and then linkage to HES, 1,972 patients with MM were identified and matched to 6,413 non-MM controls (Table 1). Mortality and index fracture rates were greater in the MM than non-MM cohorts (Table 2). Women with MM had significantly higher index major fracture rates from 12 months prior to diagnosis and onwards compared with women in the non-MM cohort (Table 2). For men, the index major fracture rates were significantly higher in the MM cohort from 24 months prior to diagnosis and onwards (Table 2). There was no statistically significant difference in index fracture incidence between men and women with MM in the two years pre- or post diagnosis.

The associations between MM and fracture events differed by fracture site and sex. Hip fracture rates were significantly higher in MM vs non-MM in the two years after diagnosis (Figure 1A). When stratified by sex, a significantly higher incidence of hip fractures was seen in females with MM (compared to controls) one year after MM diagnosis, and in males with MM two years after diagnosis (Figure 1B). For non-hip fractures, a significant difference was seen in males with MM from two years pre-diagnosis onwards, and for females this difference was observed from one year prior to diagnosis onwards (Figure 2B). There were significantly higher rates of vertebral fractures in the MM cohort (Figure 3A and B), from two years pre-index fracture onwards, but there was no significant difference between rates of wrist or humeral fractures in the MM vs non-MM cohort (Figure 4A and B).

In those with an index fracture, the risk of a subsequent fracture risk in MM and control patients is shown in Table 3**.** While the IFR for major fractures was similar between MM and non-MM patients, the IFR for spine fractures was significantly higher in MM patients by year 2, even after adjusting for the competing risk of death and potential confounders. A small proportion of patients with MM experienced more than one subsequent fracture, whilst no patients in the non-MM had more than one subsequent fracture (Sup. Table 3).

Discussion

We have demonstrated an excess fracture risk for MM patients in the years prediagnosis as well years following MM diagnosis. We have also demonstrated a comparable IFR for major fracture but a higher IFR for vertebral fracture MM patients following an index fracture compared to non-myeloma controls.

Previous studies have established that fracture risk is increased in patients with MM more than other cancers[14]. Given the significantly higher rates of index fracture in both male and female MM patients (compared to controls) from one year prior to diagnosis, clinical teams should consider MM as a potential differential diagnosis in adults presenting with a fragility fracture. These findings, support systematic inclusion of laboratory testing for myeloma (e.g. urine Bence Jones Protein or

serum free light chain analysis) in adults presenting with a fragility fracture[15], a pathway that can be effectively delivered in the fracture liaison service (FLS) setting[16].

In the non-cancer setting, it is well recognisd that a previous fracture increases subsequent fracture risk[17] and this risk is even higher in the next 2 years, the imminent fracture risk period[18]. There are few studies that have described the imminent fracture risk in MM. In a single centre study of 33 patients with MM and vertebral fractures, 61% of patients had a further vertebral fracture, with higher risk in patients with hypertension, diabetes, osteoporosis and hypercalcaemia[19]. Our study showed a significantly higher risk of imminent vertebral fractures but not other fractures in MM after an index fracture compared to the non-MM cohort. We note the cumulative incidence of imminent vertebral fractures after two years in the non-MM cohort was 0.5%, comparably lower than previous studies from other countries where this figure has ranged from 1.5%-25.5%[20, 21]. These variances may reflect differences by population[22] as well as case ascertainment.

The factors leading to a higher imminent fracture risk may include imminent falls risk[23] as well as direct effects on the bone from the fracture site. Drivers of the increased fracture risk in MM include the dysregulation of RANK, RANKL and OPG, which are known to induce osteoclastogenesis and bone destruction in myeloma[24]. Conversely, the increased expression of Wnt pathway antagonists (e.g. DKK1 and sFRP-2) in MM is known to inhibit osteoblast activity and thus new bone formation[25]. In addition, treatment-related factors such as treatment with glucocorticoids may also increase fracture risk. Bone-targeted agents, such as 4-weekly zoledronate and denosumab, are used as standard of care to prevent skeletal related events of pathological fractures, spinal cord compression, radiation therapy or surgery to the bone in newly diagnosed MM[26, 27]. However, anti-resorptive agents do not induce new bone formation or repair lytic lesions[28]. Recent work has highlighted the benefit from enhancing Wnt signalling by dual blockage of both DKK-1 and LRP6 without increasing tumour burden in murine models of myeloma[29]. In the non-cancer osteoporosis setting, anti-sclerostin therapy led to superior and earlier hip and non-hip fracture reduction in patients with a previous fracture compared with oral anti-resorptives[30]. In a clinical trial setting for patients with newly diagnosed myeloma, after 39 months, the cumulative incidence of hip fracture was 0.7%

with zoledronate and 0.2% with denosumab[27]. These rates are significantly lower than observed in this real-world study and may reflect differences in comorbidity and types of myeloma treatment received. Currently MM diagnosis does not influence type of osteoporosis treatment recommended following an index fracture. The observed residual fracture risk despite standard of care use of anti-resorptive highlight the urgent need to consider alternative therapeutic approaches to reduce fracture risk in this paitent group[28], including the potential use of anabolic agents in newly-diagnosed myeloma patients. Pre-clinical work has highlighted that romozusumab increases bone formation rate and fracture resistance in myeloma-bearing[31], whilst other anabolic therapies, including sotatercept, BHQ880 (monoclonal antibody against DDK1), and cabozantinib are being evaluated [32-34]. Future research should examine the mechanism(s) for the higher subsequent fracture risk in patients with MM.

A strength of the study is the use of real-world data and matched controls to estimate the attributable risk from myeloma. However, there are several limitations to this study. Firstly, the dataset is from 2017 to allow sufficient time to measure subsequent fracture risk outside of the COVID pandemic, which affected fracture rates in the UK[35]. In the UK, osteoporosis medications prescribed at oncology doses are invariably delivered in hospital care settings, and so data on these medications is limited in this General Practice Dataset and our analysis did not include parenteral anti-osteoporotic medication that would have been routinely used in the patients' care[36]. However, use of anti-resorptive such as bisphosphonates was standard of care during the study data collection period. Glucocorticoids are a recognised risk factor for osteoporotic fractures[37], and are commonly used as part of many induction regiments for myeloma. Our study is limited by a lack of data on steroid use within both cohorts; further work should explore the role of high dose steroids and re-fracture risk in this population. Regarding fracture data, our study is limited by the fact that the dataset analysed does not include data on the the pathological mechanisms of fracture, or the anatomical position of fracture affecting long bones (e.g. metaphysis or diaphysis). The ascertainment of fractures may be higher in the myeloma cohort than the control cohort due to their physicians being more aware of fractures in this population and may account for the excess imminent fracture risk. A more systematic assessment

of fractures in future cohort studies is required, for instance, regular radiological spine assessment to detect spine fractures[38]. Our analysis was restricted to the NHS England dataset and therefore may not be generalisable to other nations. Previous data have shown that imminent fracture risk varies across countries, with rates particularly low across Asia; further studies ought to investigate whether our findings are replicated across patients on an international scale[39]. Owing to the relatively small sample size of patients with fractures at certain sites, and data of site-specific fractures is likely to be underpowered, requiring further validation. While we validated the Read codes for myeloma, in the future we would recommend linkage of hospital and primary care data to the National Cancer Registration and Analysis Service cancer registration, if resources and time permit[40]. Finally, the study design did not include fractures that are only managed in ambulatory settings and so would underestimate fractures of the proximal humerus or wrist.

Conclusion

We have demonstrated an excees in major fractures pre-diganosis of MM and a higher IFR for vertebral fractures. These findings support systematic screening for myeloma in the FLS setting and further research is need to understand the mechanisms and develop more potent osteoporosis treatment strategies to reduce the risk of subsequent fractures, especially for vertebral fractures.

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Data availability statement

The data underlying this article were provided by Clinical Practice Research Datalink under licence. Data are not openly available, but could be shared on request subject to permission and associated conditions from the Clinical Practice Research Datalink.

Ethics Approval Statement

The Independent Scientific Advisory Committee (ISAC) approved the study (ISAC protocol application number: 18_137) and given that only de-identified routinely collected data were used, no further approvals were required.

Conflicts of interest

MTSS was supported by grants or contracts from the Oxford NIHR Musculoskeletal Biomedical Research Centre (BRC), and has received consultancy fees from Theramex. BK reports lecture fees and/or consulting honoraria from Pfizer, Sanofi, and Janssen. KR has received grant funding to their institution from Janssen, Amgen, Takeda, GSK, Celegene - Bristol Myers Squibb; honoraria from Janssen, Adaptive Biotech, Amgen, Takeda, Abbvie, Oncopeptides, Celgene – Bristol Myers Squibb, Pfizer, Recordati and GSK; support for attending meetings and/or travel from BMS, Amgen, and Takeda; is an advisor for advisor for Janssen, Adaptive Biotech, Amgen, Recordati, Takeda, Abbvie, Oncopeptides, Celgene – Bristol Myers Squibb, Pfizer, Menarini Stemline and GSK. RPV has received grants or contracts from UCB, and lecture fees and/or consultating honoraria from UCB, Amgen and IOF. MKJ has received consulting fees from UCB, Nannox AI, Naitive Technologies Limited; honoraria from Amgen Ltd, Sanofi, UCB; support for attending meetings and/or travel from UCB; and has a leadership or fiduciary role on the Royal Osteoporosis Society Clinical Research Committee. The remaining authors declare no conflicts of interest relevant to this paper.

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Figure titles

Figure 1: Incidence rate of hip fractures in MM cases and matched non-MM controls, both overall (A) and by sex (B)
Legend: p values shown comparing MM vs non-MM using the log-rank test . Bonferroni correction was used to adjust for multiple testing by sex

Figure 2: Incidence rate of non-hip fractures in MM cases and matched non-MM controls, both overall (A) and by sex (B)
Legend: p values shown comparing MM vs non-MM using the log-rank test . Bonferroni correction was used to adjust for multiple testing by sex

Figure 3: Incidence rate of vertebral fractures in MM cases and matched non-MM controls, both overall (A) and by sex (B)
Legend: p values shown comparing MM vs non-MM using the log-rank test . Bonferroni correction was used to adjust for multiple testing by sex

Figure 4: Incidence rate of wrist and humeral fractures in MM cases and matched non-MM controls, both overall (A) and by sex (B)
Legend: p values shown comparing MM vs non-MM using the log-rank test . Bonferroni correction was used to adjust for multiple testing by sex

Supplementary Figure 1: Population flow diagram

417 **Table 1: Patient characteristics of myeloma and their matched controls at their myeloma/matching date, stratified by sex.**

	Myeloma cohort (n = 1972)			Non-myeloma cohort (n = 6413)			
	All (n(%))	Male (n(%))	Female (n(%))	All (n(%))	Male (n(%))	Female (n(%))	p-value
Sex		1079 (54.7%)	893 (45.3%)		3528 (55.0%)	2885 (45.0%)	0.837
Age: median (IQR)	70 (62-78)	69 (61-77)	72 (64-79)	69 (61-77)	68 (60-76)	71 (63-79)	**0.007**
Index of Multiple Deprivation							0.251
Least deprived	496 (25.2%)	292 (27.1%)	204 (22.8%)	1543 (24.1%)	876 (24.8%)	667 (23.1%)	
Less deprived	510 (25.9%)	266 (24.7%)	244 (27.3%)	1573 (24.5%)	845 (24.0%)	728 (25.2%)	
Mid deprived	392 (19.9%)	216 (20.0%)	176 (19.7%)	1419 (22.1%)	791 (22.4%)	628 (21.8%)	
More deprived	346 (17.5%)	182 (16.9%)	164 (18.4%)	1135 (17.7%)	614 (17.4%)	521 (18.1%)	
Most deprived	225 (11.4%)	121 (11.2%)	104 (11.6%)	736 (11.5%)	398 (11.3%)	338 (11.7%)	
Missing	3 (0.2%)	2 (0.2%)	1 (0.1%)	7 (0.1%)	4 (0.1%)	3 (0.1%)	
Smoking							0.452
Yes	337 (17.1%)	207 (19.2%)	130 (14.6%)	1198 (18.7%)	733 (20.8%)	465 (16.1%)	
No	1119 (56.7%)	539 (50.0%)	580 (64.9%)	3554 (55.4%)	1711 (48.5%)	1843 (63.9%)	
Ex-	446 (22.6%)	301 (27.9%)	145 (16.2%)	1431 (22.3%)	940 (26.6%)	491 (17.0%)	
Missing	70 (3.5%)	32 (3.0%)	38 (4.3%)	230 (3.6%)	144 (4.1%)	86 (3.0%)	
Alcohol							0.167
Yes	1320 (66.9%)	786 (72.8%)	534 (59.8%)	4401 (68.6%)	2592 (73.5%)	1809 (62.7%)	
No	286 (14.5%)	97 (9.0%)	189 (21.2%)	961 (15.0%)	339 (9.6%)	622 (21.6%)	
Ex-	32 (1.6%)	16 (1.5%)	16 (1.8%)	93 (1.5%)	56 (1.6%)	37 (1.3%)	
Missing	334 (16.9%)	180 (16.7%)	154 (17.2%)	958 (14.9%)	541 (15.3%)	417 (14.5%)	

Comorbidities (ever prior)							
Angina	128 (6.5%)	75 (7.0%)	53 (5.9%)	392 (6.1%)	249 (7.1%)	143 (5.0%)	0.578
CVD	209 (10.6%)	127 (11.8%)	82 (9.2%)	659 (10.3%)	427 (12.1%)	232 (8.0%)	0.712
COPD	95 (4.8%)	65 (6.0%)	30 (3.4%)	325 (5.1%)	196 (5.6%)	129 (4.5%)	0.699
Diabetes	183 (9.3%)	103 (9.5%)	80 (9.0%)	603 (9.4%)	388 (11.0%)	215 (7.5%)	0.905
Dementia	12 (0.6%)	4 (0.4%)	8 (0.9%)	53 (0.8%)	27 (0.8%)	26 (0.9%)	0.413
Depression	298 (15.1%)	122 (11.3%)	176 (19.7%)	839 (13.1%)	340 (9.6%)	499 (17.3%)	**0.024**
Hypertension	618 (31.3%)	338 (31.3%)	280 (31.4%)	974 (29.4%)	974 (27.6%)	909 (31.5%)	0.099
Bisphosphonates (ever prior)	218 (11.1%)	53 (4.9%)	165 (18.5%)	310 (4.8%)	56 (1.6%)	254 (8.8%)	**<0.0001**
p-values were calculated using Mann-Whitney U tests or chi-squared tests. These p-values compare the demographic variables between the myeloma and non-myeloma cohorts							

Table 2: Incidence of index osteoporotic fracture and deaths in each year of study period (from 2 years before to 2 years after multiple myeloma diagnosis/matching date) by sex

Year from cohort entry date	Myeloma cohort (n=1,972)						Non-myeloma cohort (n=6,413)						p value*
	No. of patients alive at the end of the year	Index fracture count	Patients with at least 1 new fracture				No. of patients alive at the end of the year	Index fracture count	Patients with at least 1 new fracture				
			Count	Incidence rate (per 1,000 Pys)	Lower 95% CI	Upper 95% CI			Count	Incidence rate (per 1,000 Pys)	Lower 95% CI	Upper 95% CI	
Females													
year 1	893	15	16	18.1	10.3	29.3	2885	40	42	14.7	10.6	19.8	0.585
year 2	893	57	60	68.4	52.2	88.1	2885	56	60	21	16	27	<0.001
year 3	883	55	61	71.8	54.9	92.2	2884	54	59	20.7	15.7	26.7	<0.001
year 4	740	38	45	70.5	49.4	97.6	2799	59	70	50.3	36.2	68.2	<0.001
Total for females		165 (18.5%)	182					209 (7.2%)	231				
Males													
year 1	1079	12	12	11.2	5.8	19.5	3528	16	16	4.5	2.6	7.4	0.028
year 2	1079	37	41	38.2	27.4	51.9	3528	20	21	6	3.7	9.1	<0.001
year 3	1070	39	44	41.9	30.4	56.2	3528	22	24	6.8	4.4	10.2	<0.001
year 4	927	26	34	49.3	33.3	70.4	3433	20	21	9.5	4.6	17.5	<0.001
Total for males		114 (10.6%)	131					78 (2.2%)	82				
Total count		279 (14.1%)	313					287 (4.5%)	313				

Table 3: Subsequent fracture risk among patients with index fracture at any site, adjusted following stepwise variable selection: stratified by MM case or non-MM control status.

Subsequent fracture outcome following	Myeloma cohort (n=279)	Non-myeloma cohort (n=287)	Significant predictors adjusted hazard ratio[3]	CRR-adjusted hazard ratio[3]

first incident fracture during follow-up	N	Cumulative Incidence: % (95%CI)	N	Cumulative Incidence: % (95%CI)	Hazard Ratio	Lower 95% CI	Upper 95% CI	p-value	Hazard Ratio	Lower 95% CI	Upper 95% CI	p-value
Within 6 months												
Any OP fracture	19	6.8 (3.9-10)	24	8.4 (5.2-11.7)	0.889[4]	0.478	1.65	0.709	0.87[4]	0.48	1.59	0.66
Hip	5	1.8 (0.2-3.4)	2	0.7 (0-1.7)	2.34	0.438	12.5	0.320	2.30	0.54	9.72	0.26
Spine	2	0.7 (0-1.8)	1	0.3 (0-1.1)	2.19	0.188	25.5	0.531	2.09	0.19	23.0	0.55
Other	13	4.7 (2.2-7.3)	21	7.3 (4.3-10.4)	0.732[4]	0.359	1.49	0.391	0.72[4]	0.35	1.48	0.37
Within 1 year												
Any OP fracture	32	11.5 (8.1-15.9)	36	12.5 (8.8-16.7)	1.02[4]	0.625	1.67	0.932	0.99[4]	0.66	1.59	0.96
Hip	6	2.2 (0.4-4)	6	2.1 (0.4-3.9)	1.14	0.356	3.66	0.825	1.10	0.39	3.08	0.85
Spine	7	2.5 (0.7-4.7)	2	0.7 (0-1.7)	4.32	0.872	21.4	0.073	4.19	0.90	19.0	0.069
Other	22	7.9 (4.9-11.6)	28	9.8 (6.4-13.4)	0.930[4]	0.523	1.65	0.804	0.90[4]	0.51	1.61	0.73
Within 2 years												
Any OP fracture	41	14.7 (11.4-20.5)	42	14.6 (10.8-19.2)	1.17[4]	0.752	1.83	0.484	1.10[4]	0.71	1.69	0.67
Hip	8	2.9 (1-5.2)	8	2.8 (0.9-4.9)	1.27	0.465	3.49	0.638	1.18	0.49	2.84	0.72
Spine	13	4.7 (2.4-8)	2	0.7 (0-1.7)	8.80	1.95	39.7	**0.005**	8.16	1.84	36.1	**0.006**
Other	27	9.7 (6.7-14.3)	32	11.1 (7.6-15.1)	1.02[4]	0.599	1.72	0.954	0.96[4]	0.56	1.63	0.88

Legend: Final models incorporated any significant variables following stepwise variable selection (pr=0.1). CRR = Competing Risk Regression (Fine-Gray models). [1]Defined as hip, spine, humerus and wrist/forearm; [2] Defined as spine, humerus and wrist/forearm. [3]Adjusted for age and sex only given small number of outcomes, unless stated otherwise. [4]Adjusted for age, sex, and prior bisphosphonate use.

Supplementary Table 1: Read codes use to identify potential myeloma cases.

Read code	Read term
B630000	Malignant plasma cell neoplasm, extramedullary plasmacytoma
B630100	Solitary myeloma
B630200	Plasmacytoma NOS
B630300	Lambda light chain myeloma
B630400	Solitary plasmacytoma
B630.00	Multiple myeloma
B630.12	Myelomatosis
B63..00	Multiple myeloma and immunoproliferative neoplasms
B63z.00	Immunoproliferative neoplasm or myeloma NOS
B936.11	Myeloma - solitary
BBmK.00	[M]Waldenstrom's macroglobulinaemia
BBn0.11	[M]Multiple myeloma
BBn0.12	[M]Myeloma NOS
BBn2.00	[M]Plasmacytoma NOS
C330000	Waldenstrom's hypergammaglobulinaemic purpura
C333000	Waldenstrom's macroglobulinaemia
C333.00	Macroglobulinaemia

Supplementary Table 2: GP validation of myeloma, smouldering myeloma and MGUS Read codes.

Read code	Read term	No (n=5)		Yes (n=120)				TOTAL (n=125)	
		no.	%	Myeloma (n=83) [3]	Smouldering myeloma	MGUS (n=8)	Other[1] (n=22)	no.	%

							(n=7)						
				no.	%	no.	%	no.	%	no.	%		
B630000	Malignant plasma cell neoplasm, extramedullary plasmacytoma	0	0	0	0	0	0	0	0	2	9.1	2	1.6
B630100	Solitary myeloma	0	0	2	2.4	0	0	0	0	0	0	2	1.6
B630200	Plasmacytoma NOS	0	0	4	4.8	0	0	0	0	3	13.6	7	5.6
B630300	Lambda light chain myeloma	0	0	4	4.8	0	0	0	0	0	0	4	3.2
B630400	Solitary plasmacytoma	0	0	0	0	0	0	0	0	1	4.5	1	0.8
B630.00	Multiple myeloma	0	0	64	77.1	5	71.4	2	25	2	9.1	73	58.4
B630.12	Myelomatosis	0	0	1	1.2	1	14.3	0	0	0	0	2	1.6
B63..00	Multiple myeloma and immunoproliferative neoplasms	0	0	1	1.2	0	0	0	0	0	0	1	0.8
B63z.00	Immunoproliferative neoplasm or myeloma NOS	0	0	2	2.4	0	0	0	0	0	0	2	1.6
B936.11	Myeloma - solitary	0	0	3	3.6	0	0	0	0	0	0	3	2.4
BBmK.00	[M]Waldenstrom's macroglobulinaemia	1	20	0	0	0	0	2	25	10	45.5	13	10.4
BBn0.11	[M]Multiple myeloma	0	0	3	3.6	0	0	0	0	0	0	3	2.4
BBn0.12	[M]Myeloma NOS	2	40	22	26.5	1	14.3	3	37.5	0	0	28	22.4
BBn2.00	[M]Plasmacytoma NOS	0	0	1	1.2	0	0	0	0	1	4.5	2	1.6
C330000	Waldenstrom's hypergammaglobulinaemic purpura	1	20	0	0	0	0	0	0	0	0	1	0.8
C333000	Waldenstrom's macroglobulinaemia	1	20	0	0	0	0	2	25	7	31.8	10	8
C333.00	Macroglobulinaemia	0	0	0	0	0	0	0	0	1	4.5	1	0.8

Legend: [1]Includes Waldenstroem's, plasmacytoma and primary plasma cell leukaemia. Some Waldenstroem's included "and lymphoblastic lymphoma" or "with amyloidosis plaques" or "waldenstrom's lg m paraproteinaemia lamda".

Supplementary table 3: Frequency of subsequent fracture(s) in MM and non-MM cohorts

Number of subsequent fracture(s)	Non-MM cohort (n=287)	MM cohort (n=279)	Total (n=566)
0	240 (83.6%)	235 (84.2%)	475 (83.9%)
1	45 (15.7%)	35 (12.5%)	80 (14.1%)
2	2 (0.7%)	5 (1.8%)	7 (1.2%)
3	-	4 (1.4%)	4 (0.7%)