Quantifying the risk of multiple myeloma from symptoms reported in primary care patients: a large case-control study using electronic records.

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ABSTRACT

Background: Myeloma patients experience the longest diagnostic delays compared with other cancers in the UK; 37% are diagnosed through emergency presentations.

Aim: To identify and quantify the risk of myeloma from specific clinical features reported by primary care patients.

Design and setting: Matched case-control study using General Practice Research Database primary care electronic records.

Methods: Putative clinical features of myeloma were identified and analysed using conditional logistic regression. Positive predictive values (PPVs) were calculated for the consulting population.

Results: 2,703 patients aged ≥40 years, diagnosed with myeloma between 2000 and 2009, and 12,157 age, sex and general practice-matched controls. Sixteen features were independently associated with myeloma: hypercalcaemia, odds ratio 11.4 (95% confidence interval 7.1,18), cytopenia 5.4 (4.6,6.4), raised inflammatory markers 4.9 (4.2,5.8), fracture 3.1 (2.3,4.2), raised mean corpuscular volume 3.1 (2.4,4.1), weight loss 3.0 (2.0,4.5), nosebleeds 3.0 (1.9,4.7), rib pain 2.5 (1.5,4.4), back pain 2.2 (2.0,2.4), other bone pain 2.1 (1.4,3.1), raised creatinine 1.8 (1.5,2.2), chest pain 1.6 (1.4,1.8), joint pain 1.6 (1.2,2.2), nausea 1.5 (1.1,2.1), chest infection 1.4 (1.2,1.6), and shortness of breath 1.3 (1.1,1.5). Individual symptom PPVs were generally below 1%, though were over 10% for some symptoms when combined with leucopenia or hypercalcaemia.

Conclusions: Individual symptoms of myeloma in primary care are generally low risk - probably explaining diagnostic delays. Once simple primary care blood tests are taken, risk estimates change.

Hypercalcaemia and leucopenia are particularly important abnormalities, and coupled with symptoms, strongly suggest myeloma. These results should aid doctors' clinical decision making in selecting relevant patients for primary care testing, thereby reducing diagnostic delay.

Keywords: Multiple Myeloma; Primary Health Care; diagnosis

HOW THIS FITS IN

What is already known on this subject?

- The UK performs poorly with respect to the European average in cancer survival. Myeloma is no exception; indeed it ranks worst of the major cancers in terms of diagnostic delay.
- Identifying myeloma in primary care is difficult as it is a multi-site cancer with varying symptoms; its salient clinical features in primary care have not previously been reported

What this study adds

- Many features may precede myeloma, but single symptoms have very low predictive values. However, when coupled with laboratory abnormalities, especially hypercalcaemia or leucopenia, the risk of myeloma is considerably increased.
- These results should aid doctors' clinical decision making in selecting relevant patients for primary care testing, thereby reducing diagnostic delay.

INTRODUCTION

Multiple myeloma is a cancer of plasma cells. Over 4,700 cases are diagnosed annually in the UK, with a male to female ratio of 1.3:1. The incidence increases with age: 71% of UK cases are diagnosed in those aged 65 or more. (1) Myeloma is usually preceded by an asymptomatic phase of paraprotein secretion, termed monoclonal gammopathy of undetermined significance (MGUS). (2) The progression rate from MGUS to myeloma is approximately 1% annually. (3) The five year UK survival percentage is 37%: furthermore, the UK had an estimated 703 'avoidable' myeloma deaths between 1995 and 1999, compared to the average European survival.(4, 5) Around 37% of UK myeloma patients are diagnosed as emergency presentations, with a poorer prognosis (51% 12-month survival compared to 81% non-emergencies). (6, 7) This is one of the highest proportions among adult cancers.

Identifying myeloma in primary care is a challenge. It is the cancer site with the highest percentage of patients consulting their GP three or more times before referral. (8) Diagnosis with advanced disease is frequent: 88% of non-emergency patients have complications at diagnosis. (9) Myeloma has myriad symptoms, which are often at multiple sites and non-specific, with musculoskeletal pain, fatigue and fractures often reported. (10) However, nearly all previous reports of the myeloma symptoms have originated from secondary care, where it is likely there is more advanced disease, with potentially different features, including hypercalcaemia, bone lesions, renal impairment and anaemia. (11) Current National Institute for Health and Clinical Excellence (NICE) diagnostic guidelines relate to haematological cancer as a whole. They recommend a full blood count and film, plus inflammatory markers for persistent unexplained fatigue, as well as investigation of spinal compression or renal failure – and, dependent upon severity - bone pain, breathlessness, recurrent infections and weight loss. (12) Early diagnosis of myeloma in primary care should be possible in theory: plasma viscosity (or other inflammatory markers) serum protein and protein electrophoresis

are generally available. (13) However, initiating investigation requires recognition of the possibility of myeloma.

This study aimed to identify and quantify the early clinical features (symptoms, diseases and abnormal investigations) of myeloma in primary care, to guide general practitioners when to consider testing.

METHODS

This was a matched case-control study using patient records from the UK's General Practice Research Database (GPRD: now called the Clinical Practice Research Datalink). The GPRD is a large computerised database of anonymised patient data from over 600 UK general practices. (14) It is broadly representative of the UK population. Information is stored for clinical events such as symptom reporting, diagnostic testing, medical diagnoses, prescriptions and specialist referrals. Data quality is assured through adherence to strict recording guidelines. (15)

Cases and controls

Cases were selected if aged ≥40 years with a diagnosis of myeloma between January 2000 and December 2009. The GPRD's master code library has twenty-three separate myeloma codes (based on READ codes; available from authors). Up to five age, sex and practice controls were matched to each case. The date of diagnosis was taken as the first myeloma code. This also served as the index date for the matched controls. Exclusion criteria were: any case or control with less than one year of records before the index date; cases without controls, controls with myeloma, and controls who had not sought medical care after registration. Some cases had paraproteinaemia ≥30g/l before their myeloma code (this level is diagnostic of myeloma, irrespective of any accompanying features). (16) There are two possible explanations for this: first, the patient was in the peri-diagnostic period, and was shortly to be given the myeloma label, or the practice had omitted to record myeloma. To accommodate both possibilities, a cut-off of 60 days was applied; retaining cases whose diagnostic-level paraproteinaemia was solely recorded within 60 days of diagnosis, but excluding those with a longer interval.

Selection of putative clinical variables

Symptoms, diseases and abnormal investigations reported in the myeloma literature and from patient online support groups were studied; these are called 'features' from now on. PubMed,

EBSCO and Google were used with the search terms 'myeloma symptoms', 'myeloma reported to GP', and 'early signs/indications/symptoms of myeloma'. The GPRD contains over 100,000 medical codes; several codes can potentially be associated with each feature. A symptom library of codes was compiled for each feature. Occurrences of features were identified in the year before the index date. Only those features present in ≥2% of cases or controls were retained (this was invariably cases). Recording bias was tested on a condition thought to have no association with myeloma – varicose veins – to identify any difference in the rate of recording between cases and controls. Abnormal investigation results were defined as the patient having a test value falling outside their local laboratory's normal range. Patients with a normal laboratory result were grouped with those who had not been tested.

Composite variables

Some tests were grouped together. The raised inflammatory markers variable was a composite of any of abnormal erythrocyte sedimentation rate, plasma viscosity, or C-reactive protein, as different local laboratories had local preferences for the inflammatory marker of choice; similarly abnormal liver function tests reflected a raised value of any of the hepatic enzymes reported by each laboratory. In clinical practice, haemoglobin, white cell count and platelets are normally requested together ('the full blood count'). For our multivariable analyses, a composite variable 'cytopenia' was deemed to be positive if any of the haemoglobin, white cell count or platelets was abnormally low; for positive predictive values (see below) the three cell types were analysed separately. Bone pain codes often had an anatomical descriptor as well as the words 'bone pain'. We retained 'rib pain', 'back pain' and 'joint pain' as separate entities; remaining bone pain codes, such as 'tibial pain' were merged with the generic 'bone pain' code, making a group we called 'combined bone pain'.

Analysis and statistical methods

Analysis used non-parametric methods as the data was not normally distributed. Testing for association used univariable and multivariable conditional logistic regression, performed in three stages. (17-20) We did not include the variable for hypergammaglobulinaemia in the multivariable analyses as it could be considered an outcome variable rather than an explanatory variable. The first stage, univariable analysis, used a p-value threshold of ≤0.1 to identify candidate variables for multivariable analysis. These were then grouped into small clinically coherent groups containing similar variables (such as back pain, rib pain and bone pain) in the first stage of multivariable analysis, with retention requiring a p-value ≤0.05. A final multivariable model used the surviving variables from the previous stages, using a p-value threshold of 0.01. Two variables, raised cholesterol and abnormally low mean corpuscular volume, were excluded from the final model as both proved to be protective, both with ORs of 0.6. Excluded variables were checked against the final model. Clinically plausible interaction terms were added to the final model and retained if their p-value was also ≤0.01. A subsidiary analysis removed patients with a MGUS code in the year before the index date. These were repeated for patients up to age 60, and for ≥60.

Risk estimates in the form of positive predictive values (PPVs) were calculated using Bayes' theorem (prior odds x likelihood ratio = posterior odds). (21) Prior odds were calculated from the age-specific national incidence of myeloma for 2008, expressed as odds. PPVs for pairs of features and repeated attendances for the same feature were calculated where indicated. PPVs were estimated for consulting patients only: thus, the posterior odds were divided by 0.911 as 1,201 (9%) of 13,358 eligible controls were non-consulters (see Figure 2).

Power calculation

The GPRD provided estimates of 3,000 cases and 15,000 controls; as this number was effectively fixed, we performed power calculations instead of sample size calculations. This provided >97%

power (5% two-sided alpha) to detect a change in a rare variable in 2% of cases and 1% of controls. For a commoner variable, the study had >95% power to detect a change in prevalence of 20% in cases to 17% in controls. Data analysis was conducted using Stata software, version 11. (22)

RESULTS

The GPRD provided 16,233 patients (2,730 cases; 13,503 controls). Application of the exclusion criteria is shown in Figure 1, leading to a final number of 14,860 (2,703 cases; 12,157 controls).

Figure 1 here

Patient demographic and consultation information is given in Table 1. Cases consulted significantly more frequently than controls in the year before diagnosis (p=<0.001; ranksum test).

Table 1 here

Clinical features

Sixty-two symptoms and twenty-two abnormal test results were considered initially. Sixteen remained significant in the final model. Their frequencies, univariable likelihood ratios and multivariable odds ratios are shown in Table 2. The proportion of patients with varicose veins did not differ between cases and controls (p<0.38). No significant interaction terms were found. From the 2,703 cases, 2,241 (83%) had at least one of the final model features from Table 2 recorded. MGUS was identified in 204 cases and 5 controls. The final model did not materially change with the exclusion of these patients. Cases aged ≥60 reported back pain significantly more than controls for up to six consultations (first occurrence, PPV 0.1(CI 0.1 to 0.2); sixth occurrence 0.9 (CI 0.4 to 1.9) – not in table). Hypercalcaemia and cytopenia had the highest odds ratios (11.4 and 5.4, respectively; see table 2).

Table 2 here

Positive predictive values

Figure 2 shows the PPVs for single and combined symptoms, for patients aged ≥60; individual symptoms have low PPVs and few combined symptoms have PPVs >=1.0. This figure omits blood tests, so that it shows the symptoms that could suggest to the GP that blood testing (for raised inflammatory markers) may be appropriate. Figure 3 shows the PPVs for symptoms combined with blood tests, again in patients aged ≥60. Hypercalcaemia in combination with almost all final model features greatly increased the risk of myeloma. PPVs for the under 60s are not shown as they are very small, and based on small numbers.

Figure 2 here

Figure 3 here

DISCUSSION

Summary

This is the first primary care study investigating the features of multiple myeloma. Eleven symptoms and five abnormal investigations were associated with the disease. The risk estimates for individual and most combinations of symptoms were low, though back pain accompanying nosebleeds or rib pain had PPVs of over 1%. However, if hypercalcaemia was present, risks were considerably higher – the highest being over 10% for hypercalcaemia accompanying fracture, or various skeletal pain variables. Although several features of bone marrow suppression, such as anaemia, thrombocytopenia and leucopenia were associated with myeloma, the strongest associations were noted with leucopenia. This has a risk of over 10% when reported with fractures or nosebleeds.

Strengths and limitations

The main study strengths are its large sample size, its representativeness of UK practice, and its primary care setting. (19, 20, 23-25) This study – the largest reported – provided ample power to identify rare but potentially clinically relevant symptoms of myeloma, and allowed sub-analyses by age. The results are highly likely to be generalisable. The study period coincided with the automatic transmission of laboratory results, thereby greatly reducing the chance of recording error.

The primary care setting is important. Up to this point, studies of the symptoms of myeloma have originated from secondary care, when patients have already been selected for referral – probably because blood tests have identified paraproteinaemia. Patients in the referred population are more likely to have advanced disease, with organ damage, particularly in the kidneys. If myeloma diagnosis is to be expedited the focus has to be on identifying the primary care features of the disease, and helping GPs to select patients for initial testing. Additionally, hypercalcaemia in primary care is rare,(26) and GPs may not always be aware of the link with myeloma.

The nature of our study meant that we were reliant upon the accuracy of GP data recording. Additionally, multiple GPRD codes can apply to each feature, though most features had a generic code which GPs used preferentially. Symptoms may have been under-recorded; this only affects the likelihood ratios (and thus the PPVs) if under-recording is more prevalent in either cases or controls: there is no reason to think this is the case. Cases attended their GP more often, so in theory, there are more opportunities for the doctor to record a symptom. Our additional analysis – of varicose veins – tested this, and identified no differential recording. Some pertinent information may have been recorded in the hidden section of the records (the so-called 'free text') but a previous cancer study suggested the loss of data in the free text was minor. (27) Again, there would have to be differential free text recording between cases and controls for this to matter, and again we have no reason to believe this is so. Finally, it is unusual to be able to calculate PPVs from a case-control study (as the population has been enriched by the study design). We side-stepped this by estimating the prior odds of myeloma from registry data. This technique is now well accepted. (28)

Comparison with existing literature

Myeloma patients experience the highest proportion of long diagnostic delays in primary care out of 24 common cancers. This is consistent with our finding of cases consulting twice as often as controls. It probably represents unfamiliarity of GPs in diagnosing myeloma, compounded by alternative benign explanations for symptoms such as back pain. In theory, myeloma should be one of the easier cancers to diagnose as near-definitive testing (raised inflammatory markers) are easily available in primary care – once the possibility is considered. Secondary care literature reports symptoms (bone pain, breathlessness, weight loss), signs (fractures, recurrent infections) and abnormal investigations (hypercalcaemia, low haemoglobin values) associated with myeloma. All were also significant in our study.

Although there are no previous primary care reports to compare, a study of Scandinavian blood donors identified low haemoglobin values in the years before myeloma was diagnosed - we

confirmed this in the present study. (29) Anaemia as a clue to myeloma was also a highlight of an audit of delayed myeloma diagnoses. (9)

Implications for practice

The relative rarity of myeloma, coupled with the non-specific nature of the symptoms, means that individual symptoms have low PPVs, although these are higher when there are multiple symptoms. PPVs of paired symptoms with abnormal tests could not be calculated due to lack of numbers. Rib pain has been regarded as a key symptom of myeloma for many years; however other skeletal pain variables, such as back pain, had odds ratios nearly as large, and they are much more common symptoms. This is even more so in the presence of a full blood count suggesting anaemia or leucopenia. Given that a quarter of people aged over 40 have a full blood count in any one year, (30) it is reasonable to suggest that a GP investigates any patient over 60 with bone pain, nosebleeds or weight loss, using a full blood count and viscosity. Backache is common, but again should be investigated, probably on a second rather than a first attendance. Hypercalcaemia *per se* has a low risk of myeloma (0.7%), but when coupled with any of the symptoms described above the risk is considerable, warranting definitive investigation.

Conclusion

No single symptom is a strong indicator of myeloma. Repeated occurrences of back pain or when combined with nosebleeds or rib pain suggest initial testing – of inflammatory markers - at the discretion of the GP. The risk of myeloma increases greatly with the presence of hypercalcaemia. Joint pain and rib pain in conjunction with leucopenia or hypercalcaemia also signify a high risk of myeloma. These findings should influence the current revision of the NICE guidelines.

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Competing interests: WH is clinical lead on the ongoing revision of the NICE guidance on investigation of suspected cancer. His contribution to this article is in a personal capacity, and is not to be interpreted as representing the view of the Guideline Development Group, or of NICE itself. PR reports personal fees from GP Update Ltd, outside the submitted work. Other than this, no competing interests.

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Table 2. Features of myeloma (all ages).

Feature	Cases, *n* (%) *n*=2703	Controls, *n* (%) *n*=12157	Likelihood ratio [a] (95% CI)	Odds ratio in multivariable analysis [b] (95% CI)
Symptoms				
Back pain:1-6	**766** (28)	**753** (6)	**4.6** (4.2-5.0)	**2.2 (2.0 to 2.4) ***
Chest pain:1-3	**397** (15)	**531** (4)	**3.4** (3.0-3.8)	**1.6 (1.4 to 1.8) ***
Chest infection:1-2	**319** (12)	**770** (6)	**1.9** (1.7-2.1)	**1.4 (1.2 to 1.6) ***
Shortness of breath:1-2	**277** (10)	**661** (5)	**1.9** (1.7-2.2)	**1.3 (1.1 to 1.5) *#**
Nausea	**162** (6)	**228** (2)	**3.2** (2.6-3.9)	**1.5 (1.1 to 2.1) ˜**
Fracture	**159** (6)	**201** (2)	**3.6** (2.9-4.6)	**3.1 (2.3 to 4.2)**
Joint pain	**118** (4)	**358** (3)	**1.5** (1.2-1.8)	**1.6 (1.2 to 2.2) §**
Combined bone pain	**108** (4)	**112** (0.7)	**4.3** (3.3-5.6)	**2.1 (1.4 to 3.1) #**
Weight loss	**107** (4)	**86** (0.7)	**5.6** (4.2-7.1)	**3.0 (2.0 to 4.5)**
Rib pain	**80** (3)	**47** (0.4)	**7.7** (5.4-11)	**2.5 (1.5 to 4.4) #**
Nosebleeds	**76** (3)	**78** (0.6)	**4.4** (3.2-6.0)	**3.0 (1.9 to 4.7)**
Investigations				
Cytopenia	**1309 (48)**	**1109 (9)**	**5.3 (5.0-5.7)**	**5.4 (4.6 to 6.4)**
Raised inflammatory markers	**1146 (42)**	**753 (6)**	**6.8 (6.3-7.4)**	**4.9 (4.2 to 5.8)**
Raised creatinine	**648 (24)**	**1021 (8)**	**2.9 (2.6-3.1)**	**1.8 (1.5 to 2.2)**
Raised mean corpuscular volume (MCV)	**347 (13)**	**250 (2)**	**6.2 (5.3-7.3)**	**3.1 (2.4 to 4.1)**
Hypercalcaemia	**246 (9)**	**44 (0.35)**	**26 (18-35)**	**11.4 (7.1 to 18)**

[a] the univariate likelihood ratio, showing the likelihood of having a specific symptom in a patient with myeloma, compared with the likelihood of having it in a patient without cancer

[b] in multivariate conditional logistic regression, containing all sixteen variables

***** The odds ratio for these four variables is for each attendance with the symptom; for back pain this is up to the sixth attendance, for chest pain the third, and for chest infection and shortness of breath to the second attendance.

 # p=0.001 § p=0.002 ˜ p=0.006

Figure 1. Application of exclusion criteria

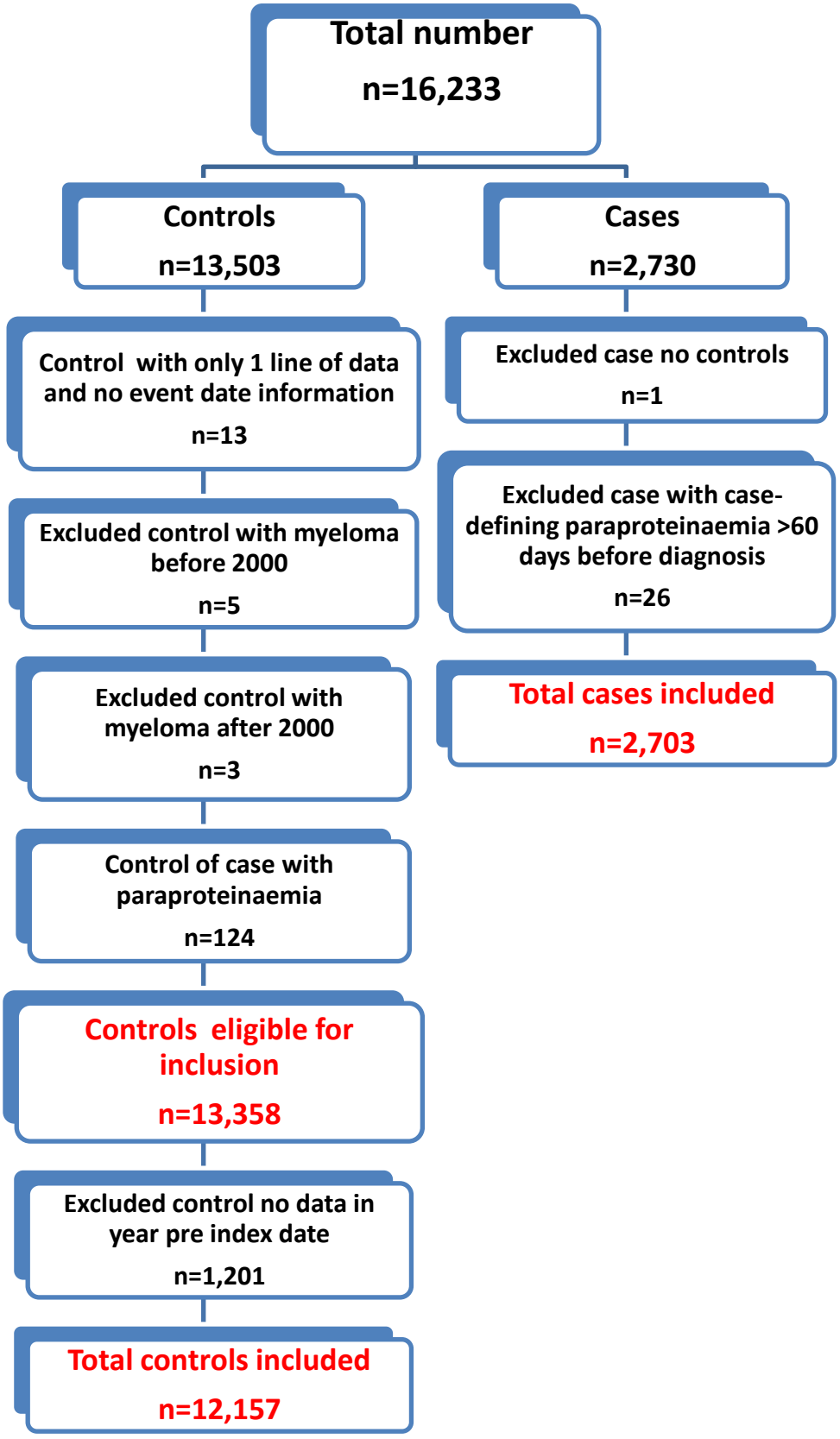

Figure 2. Positive predictive values for **myeloma symptoms** in patients *sixty* years of age and over, for single and paired features.

Joint pain	Shortness of breath	Chest infection	Chest pain	Fracture	Nausea	Combined bone pain	Nosebleeds	Back pain	Weight loss	Rib pain	
0.05 0.04, 0.06	**0.06** 0.05, 0.06	**0.06** 0.05, 0.06	**0.1** 0.09, 0.11	**0.1** 0.08, 0.12	**0.1** 0.08, 0.12	**0.1** 0.1, 0.2	**0.1** 0.1, 0.2	**0.1** 0.1, 0.2	**0.2** 0.1, 0.2	**0.2** 0.1, 0.3	**Risk as a single symptom**
	0.1 0.1, 0.2	**0.3**	**0.1**	**0.1**	**0.1**	**0.1**	**n/c**	**0.1** 0.1, 0.2	**n/c**	**0.7**	**Joint pain**
		0.1	**0.1** 0.05, 0.10	**0.1** 0.1, 0.3	**0.1** 0.1, 0.2	**0.2** 0.1, 0.3	**0.1**	**0.1** 0.1, 0.2	**0.1** 0.1, 0.3	**0.2**	**Shortness of breath**
			0.2 0.1, 0.3	**0.2** 0.1, 0.3	**0.1** 0.1, 0.2	**0.3**	**0.1**	**0.2** 0.1, 0.2	**0.3**	**0.2**	**Chest infection**
				0.3 0.2, 0.6	**0.3** 0.2, 0.4	**0.2** 0.1, 0.4	**0.3**	**0.3** 0.2, 0.4	**0.1**	**0.9**	**Chest pain**
					0.2 0.1, 0.4	**0.8**	**n/c**	**0.5** 0.3, 0.9	**0.3**	**0.7**	**Fracture**
						0.6	**n/c**	**0.4** 0.2, 0.6	**0.3**	**0.3**	**Nausea**
							n/c	**0.5** 0.3, 0.8	**n/c**	**0.5**	**Combined bone pain**
								1.5	**0.3**	**n/c**	**Nosebleeds**
									0.5	**1.1**	**Back pain**
										n/c	**Weight loss**

Notes: The PPV is shown on the first line of each cell with the 95% confidence limits shown underneath. PPVs were not calculated it fewer than 5 cases had the feature. Where fewer than 10 cases or controls had the combined features, CIs were omitted. The yellow shaded cells indicate a PPV of 1.0-1.9%; orange cells 2.0-4.9% and red cells of 5% and over. The cells showing the same feature vertically and horizontally represent a second attendance with the same investigation.

Figure 3. Positive predictive values for **myeloma blood tests with symptoms** in patients *sixty* years of age and over: risk estimate for single investigations and paired with symptoms.

Low haemoglobin	Leucopenia	Low platelets	Raised inflammatory markers	Raised creatinine	Raised MCV	Hypercalcaemia	
0.17 **0.16, 0.19**	**0.3** **0.2, 0.3**	**0.2** **0.1, 0.2**	**0.2** **0.18, 0.22**	**0.08** **0.08, 0.09**	**0.18** **0.16, 0.22**	**0.7** **0.5, 1.0**	**Risk of myeloma as a single feature**
0.5 0.4, 0.7	**0.6** **0.4, 1.2**	**0.7** 0.4, 1.3	**0.6** 0.4, 0.7	**0.3** 0.2, 0.4	**0.4** 0.3, 0.6	**4.0**	**Back pain first episode**
0.9 0.6, 1.3	**2.0**	**0.7**	**1.1** 0.7, 1.6	**0.5** 0.3, 0.7	**0.8** 0.4, 1.6	**>10**	**Back pain second episode**
0.2 0.1, 0.2	**0.3** 0.2, 0.6	**0.3** 0.1, 0.5	**0.2** 0.1, 0.2	**0.1** 0.07, 0.11	**0.2** 0.1, 0.3	**1.5**	**Shortness of breath**
0.3 0.2, 0.4	**0.3** 0.1, 0.6	**0.3** 0.2, 0.6	**0.5** 0.3, 0.6	**0.2** 0.1, 0.2	**0.3** 0.2, 0.6	**1.9**	**Chest pain**
0.2 0.2, 0.3	**0.3** 0.1, 0.5	**0.2** 0.1, 0.4	**0.3** 0.2, 0.4	**0.1** 0.1, 0.2	**0.3** 0.2, 0.4	**2.0**	**Chest infection**
0.4 0.2, 0.8	**>10**	**1.2**	**0.9**	**0.2** 0.1, 0.4	**0.3**		**Nosebleeds**
0.3 0.2, 0.4	**>10**	**0.1**	**0.4** 0.2, 0.6	**0.2** 0.1, 0.4	**0.3**	**>10**	**Fracture**
0.2 0.1, 0.3	**0.4**	**0.3**	**0.3** 0.2, 0.5	**0.2** 0.1, 0.3	**0.3** 0.2, 0.7	**1.0**	**Nausea**
0.5 0.3, 1.0	**>5**	**0.1**	**0.5** 0.3, 0.9	**0.2** 0.1, 0.4	**0.5**	**1.4**	**Combined bone pain**
0.2 0.1, 0.3	**0.3**	**0.2**	**0.1** 0.1, 0.2	**0.1** 0.05, 0.13	**0.2**	**>10**	**Joint pain**
0.9	**0.5**		**0.4** 0.2, 0.8	**0.8**	**1.1**	**>10**	**Rib pain**
0.4 0.9, 0.7	**0.5**	**0.5**	**0.6** 0.3, 1.1	**0.5**	**0.6**	**0.5**	**Weight loss**