DIAGNOSTIC DELAY IN PLASMA CELL DYSCRASIAS

BY

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ABSTRACT

Background: Multiple myeloma is associated with significant diagnostic delay, and early mortality, particularly after emergency presentation. Given the varied symptoms of myeloma, symptom-based strategies to improve diagnosis may be ineffective - alternative strategies are needed.

Methods:

1) Symptoms and diagnostic pathway were assessed in patients with myeloma. Analysis considered those with and without prior knowledge of monoclonal gammopathy of undetermined significance (MGUS).

2) Blood test results prior to diagnosis were assessed in a cohort of myeloma patients.

3) Patients presenting acutely to hospital with medical complaints were recruited to assess the prevalence of detectable paraproteinemia.

Results:

1) Those diagnosed via acute services had more end organ damage and more advanced disease without a longer diagnostic pathway, suggesting faster disease progression. Prior knowledge of MGUS was associated with less end organ damage.
2) Change in blood test results was demonstrated in the two years before diagnosis
3) There was a higher prevalence of paraproteinemia in acute hospital admissions compared to expected population rates (5.3% vs 3.2%)

Discussion: Multiple factors affect the diagnostic pathway, including aggressiveness of disease. Feasible strategies to improve diagnosis could be developed, including automated processes to test based on routine blood test results, and identification of MGUS, for instance in acute medical admissions.

Dedication

To my husband Tom, for his endless support

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LIST OF FREQUENTLY USED ABBREVIATIONS

AIH	Autoimmune hepatitis
AKI	Acute kidney injury
CG	Calculated globulin
CKD	Chronic kidney disease
CRAB	Hypercalcaemia, renal impairment, anaemia, bone disease
ESR	Erythrocyte sedimentation rate
GP	General practice/practitioner
Ig	Immunoglobulin
ISS	International Staging System
MCV	Mean corpuscular volume
MGUS	Monoclonal Gammopathy of Undetermined Significance
PS	Performance status
SFLC	Serum free light chains
SMM	Smouldering Multiple Myeloma
SPE	Serum protein electrophoresis
UHB	University Hospitals Birmingham
WCC	White cell count

1 INTRODUCTION

1.1 Multiple myeloma

1.1.1 Background

Multiple myeloma, a malignancy of plasma cells, is the 19th most common cancer in the UK with around 5700 new cases diagnosed each year.(1) Myeloma mainly occurs in older adults, and the median age at diagnosis is over 70 years.(2) The highest incidence is in those aged 85-89 years old (1) although 30% of cases are diagnosed in those under 65.(3) Myeloma is common in both genders, with a 13:10 male to female ratio, and as age increases the incidence becomes higher in men than in women.(1)

Myeloma is caused by a clonal proliferation of plasma cells within the bone marrow.(4) Plasma cells are long lived, differentiated B cells that play a central role in humoral immunity through the production of immunoglobulin.(5) In health, plasma cells produce a range of immunoglobulins. Immunoglobulins are formed of four polypeptide chains – two heavy chains of the same class (IgG, IgA, IgM, IgD or IgE) and two light chains (both either κ or λ). Immunoglobulins have a constant region and a variable region; as part of the normal immune response, immunoglobulins bind to antigen at the variable region of the immunoglobulin.(6) In myeloma, there is monoclonal proliferation of plasma cells, and so the immunoglobulin produced by these clonal cells is identical. This can be detected in serum as a monoclonal paraprotein.(7)

1.1.2 Diagnosis

Initial investigations for suspected myeloma aim to identify whether a monoclonal paraprotein is present. This involves:

- serum protein electrophoresis to identify a monoclonal spike
- immunofixation to identify the type of paraprotein (both light chain and heavy chain component)
- measurement of the levels of different immunoglobulins classes (e.g. serum IgG, IgA and IgM)
- measurement of serum free light chains, including levels of κ and λ light chains, as well as the ratio between these levels (the κ:λ ratio).(8)

When a monoclonal paraprotein is identified, then the concentration is determined to allow diagnosis and monitoring.

In most cases of myeloma, the paraprotein produced has a heavy chain and a light chain component, which is used to describe the type of myeloma e.g. IgG myeloma. Light chain myeloma accounts for 15-20% of cases, (9-11) where only a light chain paraprotein component is produced.

1.1.3 Diagnostic criteria

The diagnosis of myeloma is based on several key features, as defined by the International Myeloma Working Group shown in Figure 1.1. (12, 13) For a diagnosis of active myeloma to be made, patients need 10% or more of the bone marrow to comprise of clonal plasma cells or to have biopsy proven plasmacytoma (a localised tumour of plasma cells), either of the bone or extramedullary, as well as evidence of a 'myeloma defining event'.

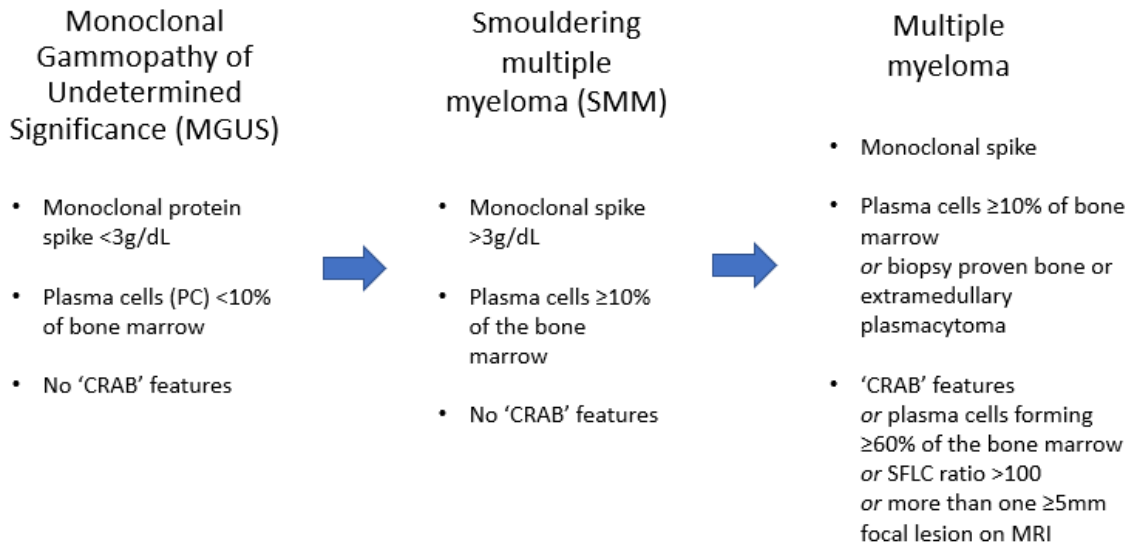


Figure 1.1: Definitions of multiple myeloma, smouldering multiple myeloma and monoclonal gammopathy of undetermined significance
The International Myeloma Working Group Criteria for diagnosis of plasma cell dyscrasias. CRAB features: hypercalcaemia, renal impairment, anaemia, bone disease. SFLC: serum free light chains. MRI: magnetic resonance imaging.

Myeloma defining events include end organ damage related to myeloma, as well as biomarkers of malignancy that predict the development of end organ damage. End organ damage is defined by 'CRAB' features which include the presence of hyper**c**alcaemia, **r**enal impairment, **a**naemia, or **b**one lesions, as outlined in Table 1.1. For many years the presence of these 'CRAB' features was necessary for diagnosis of the disease. The definition of symptomatic multiple myeloma was updated in 2014 to include biomarkers of malignancy that signify active myeloma in those without end organ damage. These newer myeloma defining events are: proportion of plasma cells in the bone marrow >60%, serum free light chain (SFLC) ratio of over 100, or more than one 5mm or larger focal lesion on MRI, as additional diagnostic criteria. (13) Including these markers of disease as myeloma defining events allows earlier initiation of treatment, before complications develop.

Patients with a detectable paraprotein who don't satisfy the criteria for diagnosis of multiple myeloma have either monoclonal gammopathy of undetermined significance, or smouldering/asymptomatic multiple myeloma, as shown in Figure 1.1, which will be discussed later.

'CRAB' features	**International Myeloma Working Group definition (13)**
Hypercalcaemia	Serum calcium >0.25 mmol/L (>1mg/dL) above the upper limit of normal *or* >2.75 mmol/L (>11mg/dL)
Renal insufficiency	Creatinine clearance <40 mL per minute *or* serum creatinine >177μmol/L (>2mg/dL)
Anaemia	Haemoglobin value of >20g/L below the lower limit of normal, or a haemoglobin value <100g/L
Bone disease	One or more osteolytic lesion on skeletal radiography, CT, or PET/CT.

Table 1.1: Features of end organ damage in multiple myeloma.
International Myeloma Working Group criteria for end organ damage in multiple myeloma as signified by the presence of CRAB features (hypercalcaemia, renal impairment, anaemia, bone disease). CT: computerised tomography. PET: positron emission tomography.

1.1.4 Staging and prognosis

Prognosis can be predicted based on stage of disease. Myeloma is currently staged according to the International Staging System (ISS). (8) This staging system divides patients into three groups, based on serum β_2-microglobulin level and serum albumin level, as shown in Table 1.2.(14) Serum β_2-microglobulin and serum albumin are thought to reflect tumour burden and renal impairment and may also reflect changes in pro-inflammatory cytokines such as interleukin-6 (IL-6). (14) Those with Stage III disease have the poorest predicted survival, at 29 months.

International Staging System (14)	Definition	Prognosis: median survival
Stage 1	ß2-microglobulin < 3.5 mg/L and albumin ≥35 g/L	62 months
Stage 2	ß2-microglobulin < 3.5 mg/L and albumin <35g/L or ß2-microglobulin 3.5 - 5.5mg/L, with any albumin level	45 months
Stage 3	ß2-microglobulin ≥ 5.5 mg/L, with any albumin level	29 months

Table 1.2: International Staging System for multiple myeloma.

Since the adoption of the ISS, it has been shown that some genetic abnormalities are associated with poorer survival. (15) Combining the ISS with high-risk genetic abnormalities provides a more accurate prediction of survival (16) as used in the revised International Staging System (R-ISS), shown in Table 1.3. This was proposed for use in research, and combines the ISS with high risk chromosomal abnormalities and serum lactate dehydrogenase (LDH) level. (17) For risk stratification, high risk chromosomal abnormalities detected by fluorescence in situ hybridization (FISH) are: del(17p), translocation t(4;14)(p16;q32), or translocation t(14;16)(q32;q23). (17)

Prior to the development of the ISS in 2005, myeloma was staged according to the Durie-Salmon staging system, shown in Table 1.4. (18)

Revised International Staging System (17)	Definition	Prognosis: 5-year overall survival
Stage I	• ß2-microglobulin < 3.5 mg/L • Albumin ≥3.5 g/dL • No high-risk chromosomal abnormality • Normal LDH	82%
Stage II	Does not meet criteria for Stage I or Stage III	62%
Stage III	• ß2-microglobulin ≥ 5.5 mg/L AND • High-risk chromosomal abnormality *or* • Raised LDH level	40%

Table 1.3: The Revised International Staging System for multiple myeloma (R-ISS)
Shown with prognosis measured by 5-year survival by stage of disease. LDH: lactate dehydrogenase

Durie Salmon staging system (18)	Definition	Prognosis: median survival (19)
Stage I	All of: • Haemoglobin >100g/L • Serum calcium normal • Low paraprotein level (IgG <50g/L, IgA <30g/L, urine light chain paraprotein <4g/24hours) • No bone lesions/solitary plasmacytoma only	53 months
Stage II	Does not meet criteria for Stage I or Stage III	31 months
Stage III	Any of: • Haemoglobin <85g/L • Serum calcium >3mmol/L • Advanced lytic bone lesions • High paraprotein level (IgG >70g/L, IgA >50g/L, urine light chain >12g/24hours)	24 months

Table 1.4: Durie-Salmon staging system for multiple myeloma
The Durie-Salmon staging system for multiple myeloma, which was used prior to the introduction of the International Staging System.

Myeloma remains an incurable disease, with a median overall survival of around 5 years. (1) Overall survival has improved over the last 20 years,(20) however these improvements have mainly been in the under 65 age group, (21) with only small improvements in survival in those over 70 years old. This improvement in the younger age group may reflect the use of high

dose melphalan and autologous stem cell transplantation, which is more commonly used in younger patients. (22) Younger patients are more likely to be Stage I at diagnosis, and to have a performance status of 0 or 1, while those over 70 are more likely to be Stage II or III at diagnosis, and so have a poorer prognosis. (23)

Patients often have a poor performance status at diagnosis due to end organ damage associated with the disease. Reported rates of renal disease at diagnosis vary, with renal impairment reported in up to 50% of patients at diagnosis. (24) Renal failure is frequently reversible with appropriate treatment, although 2-3% of patients require dialysis during the course of the disease and a small number of patients have dialysis dependent renal failure. Bone disease is also common at presentation, affecting 70% of patients, (25) with associated increased fracture risk, especially around the time of diagnosis. (26)

There is significant early mortality after diagnosis, with 10% of patients dying within 60 days of starting anti-myeloma treatment. (25) The most common cause of early mortality is infection, with up to 50% of early deaths related to bacterial infection. (25) Other common causes of early mortality include renal failure, myocardial infarction, cardiac failure and cerebrovascular accident.

This early mortality is particularly pronounced in patients presenting as an emergency, for example via accident & emergency (A&E). The 12 month survival if diagnosed via an acute route is 61.3%, compared to 86.7% if diagnosed via referral to haematology from a general practitioner (GP). (27) In the UK, 34% of myeloma patients present through acute services (27) and so this increased mortality affects a large proportion of patients. The reasons for this higher mortality in patients with myeloma presenting through acute services have not been fully explained by current research but has been explored in other cancers.

Patients diagnosed through emergency routes may have more advanced disease at initial presentation, as in colorectal cancer. Colorectal cancer is diagnosed by emergency presentation in 24% of patients, and this is associated with poorer 5 year survival and higher post-op mortality.(28) There are however notable differences in the emergency management of myeloma and of colorectal cancer – emergency presentation in colorectal cancer is frequently equated with the need for emergency surgery, which is associated with a risk of post-operative medical and surgical complications,(29) which may not be comparable to the experiences of myeloma patients.

Patients presenting through emergency routes may have a different demographic mix leading to higher mortality. Socioeconomic factors have been shown to be associated with emergency presentation.(30) Those presenting through emergency routes also have higher rates of comorbidity.(31) Different sources have found conflicting data regarding gender differences in emergency presentation,(32) with some suggesting those diagnosed via an acute route were more likely to be male (33) and some suggesting they were more likely to be female.(31) Age may also be a factor, with diagnosis due to emergency presentation more likely in older age groups.(31)

However, demographic differences do not completely account for the increased mortality. A study including patients with colorectal, cervical, breast, lung and prostate cancers demonstrated that those who presented through emergency routes had a higher mortality in the first month and the first year after diagnosis, after adjusting the mortality rates for age, gender, comorbidity and stage of disease.(31)

1.1.5 Presenting symptoms of myeloma

Myeloma presents with a wide variety of symptoms, and these symptoms are often non-specific. The symptoms of myeloma reported in previous research are shown in Table 1.5.

The commonest presenting symptoms reported in a study of 92 patients by Kariyawasan et al were bone pain (67%), 'a global feeling of ill health' (14%), fatigue (9%), shortness of breath (5%) and weight loss (5%). (34) This study included patients presenting through both primary and secondary care. These findings are similar to those by Kyle et al who found that the most commonly reported presenting symptoms were bone pain (58%), fatigue (32%) and weight loss (24%). (35)

Flanagan et al (36) also found a high percentage of patients presenting with bone pain (68%), with radiological changes showing skeletal involvement in 52.5%. Anaemia was present in 30% of patients at diagnosis, and renal impairment in 19.2%.

These three studies (34-36) all assessed presenting symptoms retrospectively and used data from hospital records. This may bias the results, as not all symptoms reported by patients may have been documented. The healthcare provider recording the symptoms may be more likely to document only those symptoms that they already recognise as related to the disease, and more unusual symptoms may be missed.

Symptom / Study	Bone pain	Pain	Tiredness or fatigue	Generally unwell	Systemic symptoms	Shortness of breath	Weight loss	Paraesthesia	Fever	Lump/ swelling	Bleeding	Urinary symptoms	Change in bowel habit	Skin symptoms	Nausea, vomiting, indigestion	Night sweats	Anaemia	Renal impairment
Howell, UK, 2015 (n=150)*	73.7%	77.1%	43.2%		52.5%	18.6%	16.9%		0.8%	4.2%	12.7%		1.7%	3.4% *itch*		10.2%		
Forbes, UK, 2014 (n=134)*		65.7% *MSK, chest, abdominal*			47% *fatigue, weight loss, loss of appetite*	20.1% *SOB and cough*				3%	6%	0.7%	1.5%	9.7%	1.5%			
Kariyawasan UK, 2007 (n=92)	67%		9% *fatigue*	14% *asthenia*	.	5%	5%										54%	36%
Kyle, USA, 2003 (n=1027)	58%		32% *fatigue*				24%	5%	0.7%								73%	1.86%
Flanagan, UK, 1998 (n=	68%																30%	19.2%

Table 1.5: Symptoms of multiple myeloma reported in previous research.
For each study, the percentage of participants who reported each symptom. Empty cells indicate that no information was provided on the rate of that symptom for that study.
MSK: musculoskeletal
** These two studies both used patients randomly selected from the same cohort of patients (National Cancer Patient Experience Survey).*

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A study of 134 patients with myeloma by Forbes et al found the most common symptom at presentation was pain (65.7%), with systemic symptoms (47%) and shortness of breath or cough (20.1%) also being common. (37)

In 2013, Howell et al reported that of 493 myeloma patients, 69.2% reported symptoms at diagnosis, most frequently pain, tiredness, fractures or joint problems, shortness of breath, and infections. (38) A similar study by Howell et al in 2015 showed that the most common symptoms were 'pain or discomfort in bones' (73.7%), extreme fatigue or tiredness (43.2%), shortness of breath (18.6%) and unexpected weight loss (16.9%). Of those who were symptomatic at presentation, 52.5% had systemic symptoms and 77.1% had pain symptoms. (39) Both studies demonstrated that a large proportion of patients are asymptomatic at diagnosis (30.8% in the 2013 study, 21.3% in the 2015 study) and are diagnosed incidentally. In this group, their myeloma may have been active for some time before diagnosis, but unrecognised due to lack of symptoms.

These three studies used data collected via patient questionnaire. The 2013 Howell study allowed patients to enter free-text symptoms, whereas the 2015 Howell study and Forbes' 2014 study allowed patients to select from a list of symptoms which had been chosen by clinicians.

Referral guidelines currently focus on pain and bone disease as presenting symptoms. The British Society of Haematology guidelines for the diagnosis of myeloma state that presenting symptoms '*include symptoms of: bone disease, impaired renal function, anaemia, hypercalcaemia, recurrent or persistent bacterial infection, hyperviscosity*' although the guideline does not specify particular symptoms. (8) The National Institute for Health and Care Excellence (NICE) guideline on suspected cancer (last updated in July 2017) recommends

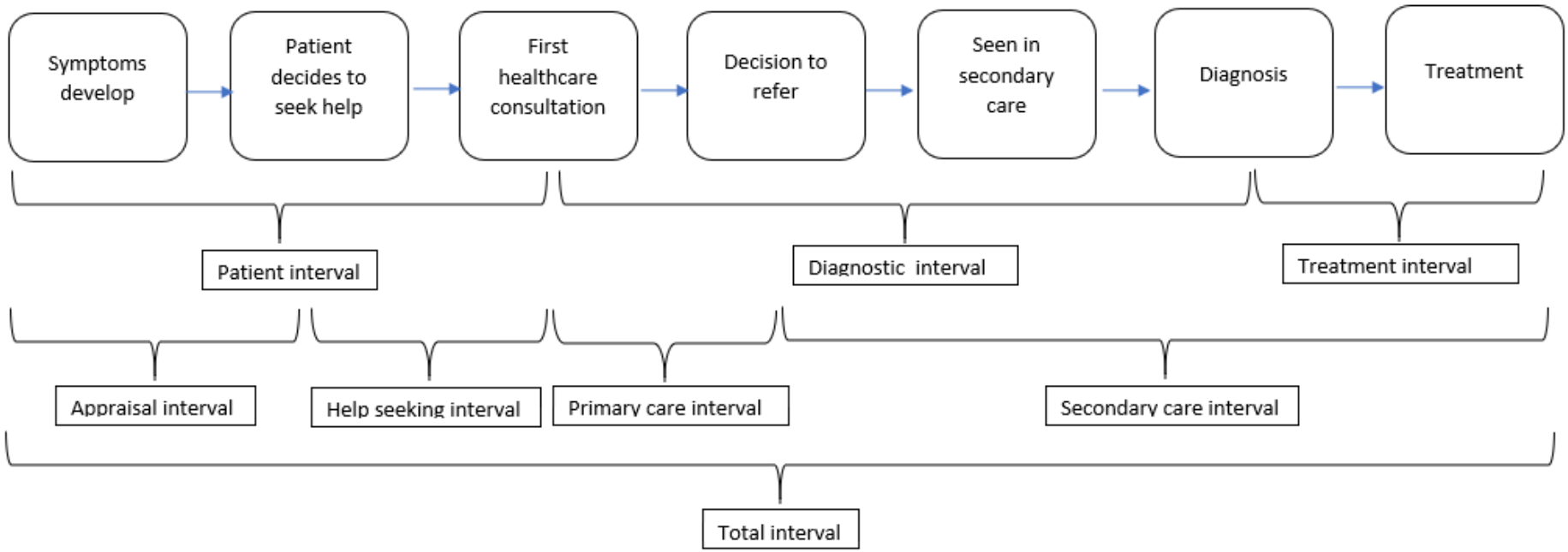
measurement of full blood count, calcium and plasma viscosity or ESR in those with '*persistent bone pain, particularly back pain, or unexplained fracture*'. (40)

Myeloma occurs most often in an older age group, where symptoms such as back pain, anaemia or renal impairment are common and have many potential causes. Patients often have one or more comorbidities, and these may cause similar symptoms. Studies have shown comorbidity rates of 33.8% to 48.8%, commonly including diabetes, cardiovascular disease, neurological disease and other malignancies. (41, 42) This high rate of comorbidity may reflect a higher rate of incidental diagnoses in patients undergoing blood tests for monitoring of other diseases. In patients with multiple comorbidities, myeloma symptoms may be misattributed to other causes by both the patient and healthcare professionals.

The non-specific nature of the presentation of myeloma may contribute to a long pathway to diagnosis, with delay at different stages of the diagnostic process.

1.1.6 Delay in the diagnostic process

Early diagnosis is recognised as an important factor to improve outcomes from cancer nationally (43, 44) and early diagnosis has been shown to improve outcomes in several malignancies. (45, 46) To reduce delays in diagnosis, it is important to characterise where within the diagnostic process that delay occurs. The diagnostic process can be split into several stages or intervals as shown in Figure 1.2. These intervals were defined in the Aarhus statement, to ensure consistency in reporting of diagnostic intervals in research into early diagnosis in malignancy. (47)



<u>Figure 1.2:</u> Diagnostic pathway intervals
Showing how the diagnostic pathway can be divided into intervals. This diagram assumes a one-way direction of travel, and does not account for multiple referrals. First healthcare consultation is assumed to be in primary care for the primary care interval

The ‘total interval’ reflects the overall diagnostic process, from symptom onset to initiation of treatment. This can then be broken down into further intervals, including:

- the **patient interval**:
- the appraisal interval
- the help-seeking interval
- the **diagnostic interval**
- the primary care interval
- the secondary care interval

By breaking down the diagnostic process into these intervals, it allows better assessment of where delays are occurring, and points to potential reasons for these delays, as each interval is affected by different factors. Some of the intervals described overlap, and dependent on the possible causative factors in any delay, a selection of the intervals may be chosen for measurement.

1.1.6.1 Patient interval

The patient interval occurs between initial onset of symptoms and first presentation to a medical professional. This can be divided further into the appraisal interval, from the time the patient first notices symptoms until the time the decision is made to seek medical advice, and the help-seeking interval, from when a patient recognises the need for assessment to the date when they first see a medical professional for their symptoms.

Delay can occur in this interval due to delay in recognition of significance of the symptoms by the patient in the attribution interval. This can occur if the symptoms are not recognised as abnormal or are misattributed to a pre-existing condition. This may be particularly relevant in

myeloma, as patients often have multiple comorbidities, and are in an older age group where they may misattribute their symptoms to normal ageing or to co-existing conditions.(48-50) The patient interval is also affected by patient decisions regarding temporalization of their symptoms – patients may choose to delay help-seeking until the symptoms remain past a self-appointed deadline for resolution.(51)

The help-seeking interval is affected by factors related to healthcare systems and processes, such as how quickly an appointment can be made within primary care. (50)

1.1.6.2 Diagnostic interval

The diagnostic interval is from first consultation to definitive diagnosis. This interval measures the time to diagnosis from the first opportunity for recognition of the disease by a healthcare professional. This interval is affected by processes in both primary and secondary care, as well as the referral pathways and interface between the two. (50) Like the patient interval, it may be affected by misattribution of the symptoms by the healthcare provider. (52, 53) It may also be affected by the length of time needed for appropriate investigations to be arranged, performed and acted on. (54)

1.1.6.3 Secondary care interval

The secondary care interval begins when referral to secondary care is made and ends when treatment begins. (55) This interval may be prolonged if the patient is initially referred to another 'incorrect' secondary care specialty before referral to the most appropriate specialty for the definitive diagnosis. (56, 57)

1.1.6.4 Treatment interval

The treatment interval measures time from diagnosis to treatment initiation. This interval is likely to be affected by system related factors such as time to next available appointment.

This may vary from hospital to hospital, due to variation in demand and in local processes. (58)

1.1.6.5 Primary care interval

The primary care interval measures the time from first consultation to decision to refer to secondary care. This interval may include repeated consultations within primary care, as well as investigations being performed in primary care, prior to the decision to refer.(59) The length of the primary care interval is affected by recognition of the presenting symptoms as being due to the underlying malignancy, and delays in this recognition can prolong the primary care interval. (60)

1.1.7 Issues with intervals

Although these standardised intervals have the benefit of allowing easier comparison between studies, there are several potential issues that need to be considered when using these diagnostic intervals to assess pathways to diagnosis in those with myeloma.

These intervals do not fully reflect the development of multiple symptoms at different time points, both before presentation and between consultations. The development of multiple symptoms may be used by the patient as a prompt to initial consultation. (61) Similarly, assessing diagnostic pathways using these intervals does not provide data on repeated consultations within primary care, which often occur in those with myeloma. (59) For myeloma patients, those who are initially referred to a secondary care specialty other than haematology may have a prolonged diagnostic interval, but the extra healthcare consultations may be missed if studies do not record events occurring within the interval in more detail.

Patients who are asymptomatic, as many of those with myeloma are, (38) may follow a very different pathway. They do not have a 'patient interval' as they have no symptoms but are found incidentally. For these patients their diagnostic pathway starts with a healthcare consultation for a different reason. Similarly, patients who are under follow-up for MGUS or SMM may not follow these intervals, but be picked up on routine monitoring. (34)

This is important information that is missed if the pathways to diagnosis are assessed using only the intervals discussed above.

Accurate definitions of diagnostic intervals are needed to allow comparison between studies, as there may be considerable variation dependent on many different factors, including variation in how you record symptom onset, decision to refer or other events that mark a transition between the various intervals. To assess dates of consultation, data may be gathered from the patients themselves, from healthcare records, or from a combination.(38, 62) These options have advantages and disadvantages to be considered. Data reported by the patients themselves can provide detailed information on symptoms and on the patient experience of the diagnostic process, however is more subjective, and may be affected by recall bias.(63) Data gathered from patient-level healthcare data may be able to provide accurate dates of consultation, particularly from electronic systems, however it may be incomplete, particularly in symptom duration prior to consultation. (64, 65) One study using electronic data from primary care found that in 37,588 patients with a new diagnosis of cancer, only 54.6% had a recorded symptom coded onto the electronic database.(66) When interpreting data obtained in this way, it is difficult to determine the true number of symptomatic patients without further information. Data may be needed from several

different systems and from different services to capture the pathway completely, particularly if data is needed from both primary and secondary care.

1.1.8 Diagnostic delay in myeloma

Previous studies have assessed parts of the diagnostic pathway in myeloma and demonstrated delay at several different stages.

Lyratzopoulos et al collected data for 10,953 patients with a known malignancy, including 124 patients with myeloma, from the English National Audit of Cancer Diagnosis in Primary Care (2009-2010). (62) This study assessed intervals using data collected from primary care records. For myeloma patients, the median combined patient interval and primary care interval was 46 days, with an interquartile range of 22 to 110.5 days. Many patients had a prolonged time from symptom onset to referral, with 10% waiting over 213 days. Of the 28 cancers included in this study, myeloma had the longest primary care interval (median 20.5 days, IQR 5-62). The median patient interval was comparatively shorter at 13.5 days.

Howell et al showed a median total time to diagnosis of 163 days, with an IQR of 84-306 days in 493 patients with myeloma. (38) This range shows the considerable variation in total interval that myeloma patients may experience. On average, the diagnostic interval was longer than the patient interval, with a median of 83 days (IQR 34-167) for diagnostic interval but only 31 days (IQR 1-122) for patient interval.

A retrospective case review by Kariyawasan et al of 92 myeloma patients found most patients had a total interval of over 3 months from symptoms to diagnosis; 21 (22.8%) received a diagnosis within 3-6 months of first symptoms, and 43 (46.7%) waited over 6 months from symptom onset to diagnosis. (34) In patients who had a total interval of over 6 months, 79% (23 out of 29) had consulted a GP within 2 weeks of initial symptom onset, suggesting that

the patient interval was shorter than the diagnostic interval and that there may have been an opportunity for earlier referral and diagnosis. (34) However, this study was small, and included patients from only one centre.

A 2015 study including 118 participants with symptomatic myeloma found that 15% had a patient interval of over 3 months. Patients were asked for factors that influenced them to wait before consulting a doctor - the most common reason reported was lack of recognition that their symptoms could reflect serious disease. (39) Similar findings were demonstrated by Forbes et al. (37) In this study those who had systemic symptoms were significantly more likely to delay visiting a doctor, which may reflect lack of recognition of the importance of these symptoms.

Neal et al demonstrated that for some cancers, the diagnostic interval had reduced between 2002 and 2007, suspecting that this improvement may have been related to the NICE guidelines for suspected cancer that were released in 2005. (66) Using primary care data to assess cancer at 15 sites, they demonstrated that the total interval to diagnosis had significantly reduced for six cancers, including bladder cancer, head and neck cancer and pancreatic cancer. When looking at the total interval for the myeloma patients however, they found that there was no difference in the median time to diagnosis between 2001-2002 and 2007-2008 (144 days and 156 days respectively).

In a study comparing patterns of GP consultation prior to diagnosis in patients with 24 different cancers, 50.6% of patients with myeloma had seen their GP three or more times prior to referral, the highest rate from all cancers included in this study. (59)

These studies suggest that delay in diagnosis is due to delay in the patient presenting to a doctor, and also to delays in recognition or investigation within primary or secondary care.

1.1.9 Delay in diagnosis and stage of disease

Delay in diagnosis is linked to higher rates of complications and more advanced stage of disease.

In the study by Kariyawasan et al, all patients with a total interval of over 6 months had complications, either anaemia, bone disease, infection, neurological complications or renal impairment. Of those diagnosed within 3 months of symptom onset, 39% had no complications. There was a significant difference in the Durie-Salmon stage at diagnosis between those diagnosed in under 3 months and those diagnosed after over 6 months. Those with a total interval of more than 6 months were more likely to be Stage III. Those who had a longer diagnostic pathway had a shorter disease-free survival from symptom onset than those who were diagnosed within 3 months ($p = 0.043$).

The problem of prolonged time to diagnosis in myeloma is longstanding. Flanagan et al described 120 cases of myeloma diagnosed between 1981 and 1986. (36) Of the 120 participants, 20% waited over 3 months from first symptoms to investigation. Of these, 20 (83%) were classified as Stage III at diagnosis. Of those who waited less than 3 months, only 29% were Stage III at diagnosis, suggesting that earlier identification could identify disease before it progresses.

These results support the hypothesis that delay in diagnosis is leading to higher rates of complications and more advanced disease. Prompt diagnosis may reduce the number with advanced myeloma at diagnosis and may improve survival. To assess this, strategies are needed to reduce this delay, in both the patient interval and diagnostic interval.

1.1.10 Abnormal results prior to myeloma diagnosis

Potential strategies to tackle diagnostic delay in myeloma include the development of algorithms to prompt appropriate investigation. Suggested approaches include identification of a specific pattern of abnormalities by recognition of particular blood test results being outside the normal range (e.g. calculated globulin), identification of change or rate of change in certain results, or a combination of blood test results and high-risk symptoms. Reflex testing involves the creation of automatic rules that add further tests based on the detection of pre-specified abnormalities. (67)

1.1.10.1 Calculated globulin

Calculated globulin, sometimes referred to as the serum globulin fraction or the 'gamma gap', (68, 69) reflects the total level of non-albumin protein within the serum. It is calculated from routine liver function tests: total protein minus serum albumin. (70) The non-albumin proteins or globulins that this measures include carrier proteins, complement, enzymes and immunoglobulin. Globulins are classified based on how they migrate during electrophoresis into α_1, α_2, β and γ.(69) The α_1 component is mainly α_1-antitrypsin, α_2 includes α_2-macroglobulin and haptoglobin, β globulins include transferrin and complement (including C3, C4 and C5), and the γ globulins are the immunoglobulins.

After albumin, the most common proteins found in the blood are the immunoglobulins,(71) constituting around 30% of non-albumin proteins by mass. (70) Calculated globulin therefore gives an estimation of the total immunoglobulin level in the blood, with IgG having the highest concentration, at an average of 10g/L. (71) A measurable change has been shown in the serum total protein levels of patients before and after giving intravenous immunoglobulin, giving further evidence for its use as a surrogate marker of immunoglobulin levels. (72) Where

abnormal globulin levels are suspected from the calculated globulin result, this can then be further investigated with serum protein electrophoresis (SPE), immunofixation and quantification of immunoglobulin levels of each class.

There is no agreed definition of the normal range for calculated globulin. Different sources have defined calculated globulin as elevated above anywhere from 35g/L up to 45g/L. (68, 73-75). Thakkinstian et al defined an abnormal calculated globulin as 41g/L based on data from 10,062 patients by using receiver-operator characteristic analysis to compare calculated globulin levels with the likelihood of an abnormal electrophoresis result. (76) Juraschek et al used a 99th centile cut-off to give an upper limit of 42g/l. (68) Mattana et al found that in patients with acute kidney injury, an abnormal immunofixation result was more likely in those with a calculated globulin of >44g/L (p = 0.0459). (77)

Causes of an abnormal calculated globulin are shown in Table 1.6.

High calculated globulin	**Low calculated globulin**
<u>Monoclonal increases in immunoglobulins:</u> Haematological malignancy *(including multiple myeloma, Waldenstrom's macroglobulinaemia, B cell lymphoproliferative disease)* <u>Polyclonal increases in immunoglobulin:</u> Liver disease *(including autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis)* Viral infection *(including HIV, EBV, hepatitis B)* Rheumatological disease Infection *(acute and chronic)* Connective tissue disease Sarcoidosis	Hypogammaglobulinaemia: Primary Immunodeficiency *e.g. CVID* Secondary immunodeficiency *e.g. haematological malignancy, immunosuppressive medication, medication side effect*

<u>Table 1.6:</u> Causes of abnormal calculated globulin.
Divided into causes of high calculated globulin and low calculated globulin. HIV: human immunodeficiency virus; EBV: Epstein-Barr virus; CVID: common variable immune deficiency.

1.1.10.1.1 High calculated globulin

Patients with myeloma or MGUS have been shown to have a significantly higher mean serum total protein than those with no evidence of myeloma or MGUS, (78) but raised calculated globulin has many underlying causes. This includes plasma cell dyscrasias such as myeloma, as well as other lymphoproliferative diseases, (79) but it can also represent polyclonally raised immunoglobulins, for example due to chronic inflammatory conditions including rheumatological disease. (74) Other causes include viral infection (including HIV, EBV, and Hepatitis B); chronic infection; sarcoidosis; connective tissue diseases; and liver disease including autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis. (69, 73)

1.1.10.1.2 Using high calculated globulin to identify those with myeloma

Several studies have assessed the utility of elevated calculated globulin as a screening test to identify those with paraproteinaemia.

Thakkinstian et al constructed a model to predict the likelihood of patients having a detectable paraprotein based on routinely collected information. This model contained calculated globulin as well as age, haemoglobin, gender and renal function. Patients with a calculated globulin of over 41g/L were five times more likely to have a detectable paraprotein that those with a calculated globulin of 41g/L or lower. (76) This was combined with other factors into a score for 'risk' of an abnormal result, with points also gained for age over 60, male gender, anaemia, and renal impairment, although the score was more heavily weighted towards abnormal calculated globulin.

Protocols for testing can also include negative modifiers, to reduce unnecessary or repeat testing.

One study where this strategy was used tested samples with a globulin of over 45g/L. (80) Only 16% of identified samples required SPE after the use of negative modifiers – this involved excluding those: under haematology follow-up, with a previous electrophoresis result, or with clinical details suggesting infection, chronic inflammation or liver disease. A paraprotein was detected in 5.4% of these samples. Of these patients, 42 patients had further follow-up: 19 were found to have MGUS, 3 had smouldering myeloma, 3 had Waldenstrom's macroglobulinaemia and 9 had symptomatic myeloma. As a result, 12 patients were started on treatment, and two patients avoided unnecessary invasive investigations that were previously planned.

1.1.10.1.3 Current practice

Some centres already have strategies to prompt SPE testing in those with high calculated globulin, with the aim of identifying cases of myeloma that weren't suspected clinically. Screening based on raised calculated globulin introduced locally within an NHS Trust in Northumberland detected 15 new cases of myeloma within the first year, and 9 cases in the second year, doubling the number of new diagnoses of myeloma per year within their hospital. (81)

The Association of Clinical Biochemists Audit Committee found that 64 out of 78 centres offered discretionary testing of SPE based at least partly on raised globulin level, however a variety of criteria were used to prompt testing, some based on raised total protein and some based on raised globulin. (82) A variety of negative modifiers were also used to identify those who didn't require testing, including known inflammatory disease, or other blood test results indicating acute infection, aiming to reduce the considerable number of SPE that would be performed in those with a polyclonal increase in immunoglobulins. (83)

Calculated globulin is suggested for use rather than using total protein alone, as using total protein alone to prompt SPE will miss some cases of paraproteinaemia where the globulin levels are high but low albumin results in a normal total protein. Similarly, the calculated globulin is not raised in all cases of myeloma. Sandle et al analysed 561 matched SPE and liver function tests (LFTs), and found abnormal paraproteins in 7 patients with a normal calculated globulin. (83) Although an abnormally high calculated globulin is a good indication of a raised immunoglobulin level, a normal calculated globulin does not exclude the presence of a paraprotein.

In a large hospital, using high calculated globulin as a screening test is likely to identify many samples for testing. The number requiring an extra SPE can be reduced by utilising additional criteria to identify those where it will not provide additional information, such as those with a prior SPE result. A potential drawback is that these criteria may exclude some patients with an unidentified paraprotein, for instance excluding those with active infection would miss patients with infection related to underlying myeloma.

The use of calculated globulin for screening in combination with modifying factors is a balance between reducing unnecessary testing, while capturing as many patients as possible who may benefit from investigation for myeloma. As not all patients with myeloma have a high calculated globulin, this cannot be used alone as a strategy for diagnosis.

1.1.10.1.4 Low calculated globulin

Calculated globulin can also be used to identify those with low immunoglobulin levels. (73) As well as detecting those with other causes of immunodeficiency, this may identify those with immunoparesis secondary to myeloma. Holding et al implemented a screening strategy for hypogammaglobulinaemia, with immunoglobulin levels measured in all those with a

calculated globulin of less than 18g/L as calculated from their LFTs, excluding those who were likely to have a secondary cause for low immunoglobulins to try to focus on primary immunodeficiency. Those excluded were haematology & oncology patients and those who were post-operative or post-transfusion. (70)

Applying this system prospectively to almost 3 million samples, they found 292 patients with IgG levels below 5g/L, 186 below 4g/L, and 80 below 3g/L. This resulted in the identification of 3 cases of lymphoma, one case of amyloidosis, one MGUS and 5 cases of myeloma, highlighting the importance of excluding haematological malignancy in patients with low calculated globulin. They also diagnosed twelve new cases of common variable immunodeficiency (CVID), as well as twenty-six patients who likely had secondary hypogammaglobulinaemia due to medication, including immunosuppression and rituximab.

Jolles et al also used calculated globulin to screen for immunodeficiency. (73) From 826 samples with low CG, they found 89% had an IgG below normal (<6g/L), with 56% having an IgG <4g/L. They found that low CG, and low immunoglobulins, were found most frequently in post-operative patients, haematology patients (including those with myeloma and lymphoma) and oncology patients. Of the samples they tested, ten (1.2%) had a previously undiagnosed paraprotein, with an associated immunoparesis, again demonstrating that plasma cell dyscrasias may be identified by low CG, as well as high CG.

1.1.10.2 Other abnormal blood tests

Strategies based on other abnormal blood tests may be successful in detecting disease earlier as patients may have abnormal test results for years prior to diagnosis. Edgren et al retrospectively analysed haemoglobin concentrations prior to diagnosis for patients with active malignancy, including myeloma. They found a decline in haemoglobin concentration

for 3 years prior to diagnosis in patients with myeloma. (84) Detection at this point could allow earlier treatment, before complications develop. However, anaemia developing over a number of years prior to diagnosis may also been seen in other conditions, such as colorectal cancer, (85) and so in isolation this may not be a useful marker.

1.1.10.3 Combining abnormal blood results and symptoms

Strategies that combine symptoms with abnormal investigation results have also been suggested. A recent study by Shephard et al calculated odds ratios for abnormal laboratory findings to assess which tests could be used to prompt testing for myeloma. (86) Using logistic regression to compare results for myeloma patients to controls, they demonstrated that eleven symptoms and five abnormal test results were more likely in those with myeloma, shown in Table 1.7. The highest positive predictive value amongst the symptoms considered was for the combinations of back pain & epistaxis (PPV 1.5) and back pain & rib pain (PPV 1.1). Combining patient reported symptoms and abnormal blood results, they identified that hypercalcaemia had a high positive predictive value (PPV >10) when found in combination with: recurrent back pain, fracture, joint pain or rib pain. Leukopenia in combination with fracture or epistaxis also had a high positive predictive value (PPV >10). They suggested that these combinations of features can be utilised in primary care to prompt earlier testing. These combinations, however, may only identify a small number of patients. Although this study included more than 2730 cases and 13,503 controls, the combinations that were shown to have a high PPV occurred in less than 10 of the cases or controls. Another drawback with using strategies involving investigations is that the diagnosis already needs to have been suspected based on symptoms to request the appropriate tests.

Features identified as suggestive of myeloma (86)	
Symptoms	**Test results**
Fracture Weight loss Nosebleeds Rib pain Back pain Other bone pain Chest pain Joint pain Nausea Chest infection Shortness of breath	Hypercalcaemia Cytopenia Raised inflammatory markers Raised mean corpuscular volume (MCV) Raised creatinine

Table 1.7: Features identified by Shephard et al as suggestive of myeloma
Features independently associated with myeloma in 2015 case-control study by Shephard et al (86)

1.2 Monoclonal Gammopathy of Undetermined Significance (MGUS)

An alternative strategy to reduce delay in diagnosis may be diagnose patients while they are still in a pre-malignant stage. Monoclonal gammopathy of undetermined significance (MGUS) consistently occurs before multiple myeloma. A retrospective study of 30 myeloma patients detected an abnormal paraprotein in prior blood samples from 90% of these patients, from at least two years prior to their diagnosis. Some patients had detectable paraproteins 15 years prior to their myeloma diagnosis. (87) Myeloma was diagnosed in 71 patients enrolled in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial who had stored serum available for analysis from 2 years or more prior to diagnosis. (88) Of 58 patients with a stored sample from three years before diagnosis, 98.3% had a detectable abnormality, with either a measurable paraprotein or an abnormal serum free light chain ratio. Again, this showed that the abnormalities may have been present for many years, with paraproteins found in 82.4% of samples from 8 or more years prior to their myeloma diagnosis.

1.2.1 Diagnostic criteria

MGUS is defined by a low level of paraprotein (<30g/L), and a low percentage of plasma cells within the bone marrow (<10%), with no evidence of end organ damage attributable to the paraprotein, as defined by the IMWG criteria for myeloma shown in Table 1.1. (13) Like myeloma, the paraprotein detected in MGUS can have a heavy chain and/or light chain component, classified in the same way as myeloma. Although still classified by the IMWG criteria as 'MGUS', IgM MGUS is most likely to progress to Waldenstrom's macroglobulinaemia. (89) This is a form of lymphoplasmacytic lymphoma and is less common than multiple myeloma, only occurring at an age standardised annual incidence of 0.55 per 100,000.(90) Multiple myeloma can have an IgM subtype, however this accounts for only 1% of cases. (91)

The cytogenetic abnormalities and bone marrow microenvironment changes that occur in multiple myeloma are also seen during the development of MGUS. As in myeloma, chromosomal translocations are common, often involving regions responsible for the heavy chain component of immunoglobulin. The most common translocation is t(11;14)(q13;q32), a translocation between the Ig heavy chain locus on chromosome 14 and chromosome 11, which has been demonstrated in 25% of patients with MGUS. (92, 93) This leads to dysregulation of cyclin D proteins, which are involved in cell cycle progression. (94) This is a frequently occurring event in those with MGUS as well as those with multiple myeloma. (95) A specific step prompting the transformation of MGUS to myeloma has yet to be identified. Abnormalities that were thought to be candidates for a transforming event have been found to occur only in a proportion of patients, suggesting that the process is more heterogenous and results from an accumulation of many events. (96, 97)

1.2.2 Prevalence of MGUS

MGUS is common. Several studies have aimed to determine the prevalence of MGUS, which are summarised in Table 1.8. The most accurate estimate of MGUS prevalence in the general population is found by screening a large population. Some studies used registry data of recorded diagnoses of MGUS to determine the rate of prevalence or incidence (98, 99) however this approach may under- or over-estimate the true rate of disease, as only those with a clinical reason for performing SPE would have been identified.

Kyle et al (100) conducted the largest study of prevalence in the general population, testing for MGUS in residents over the age of 50 in Olmsted County, Minnesota. Participants were screened for MGUS with agarose gel electrophoresis, followed by immunofixation to identify paraprotein in samples with a discrete or localised band on electrophoresis. Most samples tested were surplus serum collected from clinical samples. Residents in the target area who did not have a clinical sample during the time frame of the study were approached to provide a sample. This resulted in a high participation rate, with samples available from 21,463 out of 28,038 eligible residents. MGUS was detected in 3.2% of participants overall. Higher rates were found in men than women (4.0% vs 2.7%, age adjusted for the US population). The prevalence increased with age, with rates of 1.7% in the 50-59 age group, 3.0% in the 60-69s, 4.6% in the 70-79s, and 6.6% in the over 80s.

Following observation of an abnormally high rate of MM in the small town of Thief River Falls, Minnesota, a study was conducted looking at the population prevalence of MGUS. Forty-five percent of the over 50 population were tested (1200/2676). Overall, the prevalence was 1.25% in those tested. As with the other studies, higher rates were found with increasing age, from 0.5% in 50-59 year olds, to 4.8% in over 80s. (101)

Study	Population	Age group	Rates of MGUS	
Kyle, 2006	General population, Olmsted County, Minnesota, USA	50 years or older	Overall: By age group: 50-59 60-69 70-79 80+	3.2% 1.7% 3.0% 4.6% 6.6%
Kyle, 1972	General population, Thief River Falls, Minnesota, USA	50 years or older	Overall: By age group: 50-59 60-69 70-79 80+	1.25% 0.5% 0.3% 1.8% 4.8%
Anagnostopoulos, 2002	Hospital patients, University of Athens School of Medicine, Greece	50 years or older	By age group: 50-59 60-69 70+	 1% 4.5% 5%
Eisele, 2012	Heinz Nixdorf Recall Study population, Germany	45-75 years	Overall: By age group: 40-49 50-59 60-69 70-79	3.5% 1.3% 2.8% 4.2% 5.5%
Malacrida, 1987	Hospital inpatients and outpatients, Northern Italy	All	Overall:	0.26%
Fine, 1972	Donors at blood transfusion service, France	20-60 years	Overall: By age group: 31-40 41-50 51-60	0.12% 0.1% 0.19% 0.49%
Landgren, 2017	Participants in National Health and Nutritional Examination Survey, USA	10-49 years	Overall: By age group: 10-19 20-29 30-39 40-49	0.34% 0.01% 0.03% 0.49% 0.88%
Cohen, 1998	Duke Established Populations for the Epidemiological Study of the Elderly, North Carolina, USA	70 years or older	Overall: By age group: 70-79 80-89 90+	6.1% 5.4% 7.4% 9.1%
Aguzzi, 1992	Hospital inpatients and outpatients with a clinical requested SPE sample, Northern Italy	All	Overall: By age group: 0-10 11-24 25-34 35-44 45-54 55-64 65-74 75+	2.9% 0% 0.4% 0.8% 2.3% 5.6% 6.6% 7.8% 7.6%
Saleun, 1982	Routine health screening, Finistere, France	All	Overall: In over 50s: By age group: 30-39 40-49 50-59 60-69 70-79 80+	1.1% 1.68% 0.13% 0.35% 0.72% 1.61% 2.78% 4.17%

Table 1.8: Prevalence of monoclonal gammopathy of undetermined significance in previous research

A higher population rate was demonstrated by Eisele et al, in a study utilising a population identified for a previous study into cardiovascular risk. (102) In 4708 samples taken from participants aged 45-75 years old, 165 new cases of MGUS were detected. Increased rates were shown with increasing age. The higher rate in this study may have partly been due to the methods used, as immunofixation was performed on all samples, including those with a normal SPE result.

The prevalence of monoclonal proteins in hospital patients was assessed by Aguzzi et al (103), including both inpatients and outpatients over a period of 4 years (1987-1990). No additional tests were requested – their study population was patients where electrophoresis had been performed by the clinical team, and their rates were based on how likely these samples were to have a detectable paraprotein. A similar method to Kyle et al was used, with serum electrophoresis on cellulose acetate, followed by immunofixation if a monoclonal protein was found on electrophoresis. Over 4 years, 35,003 tests were performed. A rate of 2.9% was found overall, with increasing prevalence rates in older age groups (0-10 0%, 11-24 0.4%, 25-34 0.8%, 35-44 2.3%, 45-54 5.6%, 55-64 6.6%, 65-74 7.8%, over 75s 7.6%). This was a higher rate than that shown in other studies. It is difficult to generalise these rates to other populations as electrophoresis in this study was performed based on clinical need, therefore higher rates of monoclonal protein would be expected, as these were patients that were thought likely to have an underlying paraprotein related disease.

The rate in hospital patients was also assessed in consecutive patients attending Clinical Therapeutics at University of Athens School of Medicine. (104) Again SPE was performed using agarose gel, followed by immunofixation. If the SPE was abnormal, patients also underwent urine protein electrophoresis, skeletal survey and bone marrow examination. In total, 1564

patients over the age of 50 were included. Again, the rate of MGUS varied by age group, increasing from 1% in those aged 50-59, 4.5% in those aged 60-69, and 5% in the over 70s. The rate was slightly higher in men than women (4.7% vs 3.1%). The rate was not higher in those with infection (2%) although this was only small numbers of patients, with 2 MGUS found out of 129 patients with infection. As well as 60 cases of MGUS, 10 cases of multiple myeloma, 2 cases of Waldenstrom's macroglobulinaemia, 2 cases of amyloidosis, and 1 other lymphoproliferative disorder were identified.

Another study that recruited from hospital patients (both inpatient and outpatient) screened 102,000 samples between 1973 and 1983. (105) A detectable paraprotein was identified in 730 patients; 114 patients had a B cell malignancy including 96 cases of myeloma, and 261 patients had MGUS. In this study, the rate of MGUS was 0.26% (261 in 102,000). This may be an underestimate of the true rate, as 355 patients with a detectable paraprotein were excluded: 160 due to incomplete clinical data, and 195 as the paraprotein concentration was less the 2g/L. As the definitions of myeloma have changed substantially since this study, there were also patients classified as 'MGUS' that may now have fit the diagnostic criteria for asymptomatic or symptomatic myeloma - four patients had a paraprotein concentration of over 30g/L, and on bone marrow examination (performed on 64 of those patients with MGUS) seventeen had a plasma cell percentage of over 10%.

Cohen et al (106) also demonstrated increasing prevalence with increasing age. Only limited comparisons can be made from this study, as this study over-sampled black participants to assess the effect of racial background on MGUS rates, although it did demonstrate a significantly higher rate of MGUS in black participants.

Fine et al (107) tested a younger population, assessing samples from French blood donors aged 25 to 60, and found an overall rate of 0.12% (16/13,400). Again, increased frequency was seen with increasing age, with a rate of 0.1% in those aged 31-40 years, 0.19% in those 41-50 years, and 0.49% in those aged 51-60 years.

Low rates were also found in young participants by Langren et al. (108) They tested serum samples from 12,372 participants in the National Health and Nutritional Examination Survey, USA, aged 10-49 years. Overall, only a small number of participants were found to have MGUS, with 63 cases detected. Ethnicity was again demonstrated to influence prevalence rates, with significantly higher prevalence in black participants.

Saleun et al (109) tested patients attending for routine health screening for monoclonal paraproteinaemia, however they did not separate MGUS from malignant conditions. In 30,279 participants, they found an overall prevalence of paraproteinaemia of 1.1%. Increasing prevalence was seen with increasing age. An overall rate of 1.68% was found in the over 50s, with 303 cases in 17,968 participants. As MGUS was not differentiated from paraproteinaemia due to active malignancy, this study cannot be used to estimate prevalence, but provides further evidence for increasing rates in older age groups.

The rate of MGUS reported previously is very varied, which is likely to reflect the different populations sampled by these studies, as well as changes in the way that paraproteins are detected and changes in definitions of MGUS and myeloma.

1.2.3 Management of MGUS

Current guidance recommends that patients who are known to have MGUS undergo annual monitoring. Overall, the risk of progression to myeloma is 1% per year and does not decrease with time. (110) Although the timing of transformation to malignant disease is unpredictable,

patients can be risk stratified to identify those at highest risk of progression to active malignancy. Factors that confer a higher risk include:

- serum monoclonal paraprotein concentration over 15g/l (111, 112)
- abnormal serum free light chain ratio (112)
- IgA or IgM (non-IgG) subtype of monoclonal protein. (111-113)

If all three of these risk markers are present, then the risk of progression within 20 years is 58% - conversely, if none of these three markers is present then the 20-year risk of progression is only 5%. (112) Light chain MGUS has a low risk of progression to myeloma.(114)

The stratification of patients into low-risk and high-risk groups allows monitoring to be tailored to the risk of progression. It is recommended that patients with high risk features have blood tests every 3-4 months for the first 12 months after diagnosis, with referral to secondary care haematology services if the level of paraprotein rises by 25% over a 3-month period. (7) As well as monitoring of paraprotein concentrations, patients need to be assessed for evidence of paraprotein related end-organ damage ('CRAB' features), as patients have been known to progress from MGUS to active myeloma without a detectable rise in their serum paraprotein levels. (115) Patients should also be advised of the common symptoms of myeloma, as progression may occur between monitoring, for example in patients on yearly surveillance. (7) Progression can also occur in those at low-risk, and progression has previously been seen in those with low level paraproteins that have been stable for many years. (115)

1.2.4 Impact of MGUS diagnosis on outcomes from myeloma

Detecting MGUS may prompt earlier diagnosis of myeloma, and there is some evidence that those already under follow-up for MGUS have better outcomes from their myeloma.

Kyle et al analysed records for 1027 patients diagnosed with myeloma in the USA between 1985 and 1998. Those who were under follow-up for a preceding plasma cell disorder, including MGUS, had a significantly longer survival, with 9 months difference. (35) Significant changes in the treatments available for myeloma and in the expected survival rates have occurred since this study was performed, which may extend this survival advantage further.

Survival after myeloma diagnosis was also assessed in a retrospective population-based study in Sweden by Sigurdardottir et al using universal healthcare registry data. (116) Of 14,978 patients with myeloma, only 394 (2.7%) had a preceding MGUS diagnosis. Those with a prior knowledge of MGUS had significantly longer survival, corrected for age and gender. The median survival was 2.79 years for those with known MGUS, compared to 2.14 years for those without prior knowledge, with a hazard ratio for death of 0.86. Within the study, the results were also analysed as a nested case-control study, to account for improvements in myeloma treatment over time. The study included patients from 1976 to 2005, and there were considerable improvements in survival during this period. This was particularly relevant as a higher percentage of patients in the most recent year groups (1996-2005) had prior knowledge of MGUS. Those with prior to knowledge of MGUS were matched to cases without prior knowledge based on sex, year of myeloma diagnosis and age at myeloma diagnosis. This analysis still demonstrated improved survival in those with prior knowledge of MGUS, with a hazard ratio of 0.85.

A consideration for both studies (35, 116) is the effect of lead time bias, as this can cause an apparent improvement in survival, as the date of diagnosis is brought forward. In the population-based study, median age at diagnosis was similar between groups, with a median age at myeloma diagnosis of 73 in those with prior knowledge of MGUS and 72 in those

without. The authors felt that lead time was unlikely to be having a large effect, as this would be expected to lower the age at diagnosis. (116) Also, comparing the two groups, there was a significantly higher rate of several comorbidities including heart failure, ischaemic heart disease, and renal disease in the MGUS cohort. Given this higher burden of comorbidity, the MGUS cohort may have been expected to have reduced survival compared to the other group and so the improvement in survival may be greater than demonstrated.

Increased survival was also demonstrated in a more recent retrospective cohort study by Go et al in the United States, who used registry data from those diagnosed with malignancy that is known to have a preceding stage of monoclonal gammopathy - either multiple myeloma, Waldenstrom's macroglobulinaemia or another lymphoplasmacytic lymphoma. (117) Data was obtained for 17,457 patients between 1994 and 2007. As expected, most patients had multiple myeloma (89.7%), rather than Waldenstrom's macroglobulinaemia or lymphoplasmacytic lymphoma. As the data used in this study was obtained from records from Medicare, a health insurance program where eligibility generally starts at 65 years old, only those over 67 were included to ensure data was available for at least 15 months of follow-up for any MGUS prior to the diagnosis of a malignancy. The two groups used for comparison were those that had a recorded MGUS claim between 4-15 months before diagnosis of malignancy, compared to all others. Those with MGUS recorded less than 4 months prior to diagnosis were grouped into the 'no follow-up' group, as it was felt that this consultation likely reflected undiagnosed malignant process, rather than MGUS. This is in keeping with other studies of MGUS and myeloma, where diagnosis of myeloma within up to 24 months of MGUS diagnosis has been used as a criterion to exclude patients from the 'MGUS' group. (88) Only 6% of patients diagnosed with myeloma had received recent follow-up for MGUS, but these patients had an average survival time of 23 months compared to 19 months survival in the

94% of patients who were not known to have MGUS or had MGUS but had not received follow-up in the previous 15 months. The rate of myeloma-related complications at diagnosis was also assessed, looking specifically at: hypercalcaemia, acute kidney injury (AKI), dialysis use, pathological or compression fracture, or spinal cord compression. Those under follow-up for MGUS were less likely to have complications at diagnosis of active malignancy than those not under follow-up, with an odds ratio of 0.67. Taking each complication individually, rather than dividing into 'any complication' vs 'no complication', those under MGUS follow-up were less likely to have hypercalcaemia, AKI or fracture, however the difference in rates of spinal cord compression and dialysis use were not statistically significant. This may in part be due to the small numbers involved, as there were lower rates of spinal cord compression and dialysis use in both groups, compared to the other complications.

1.2.5 MGUS complications

Many complications that are associated with myeloma are also found in a proportion of MGUS patients before transformation to myeloma. If those with MGUS can be identified, then it offers an opportunity to manage these complications, as well as monitoring for progression to myeloma. The complications of MGUS are summarised in Table 1.9.

Complication	Risk compared to population	Suggested pathological mechanism	Potential treatment
Fracture (118)	1.7	Increased osteoclast activity, Increased bone resorption (119-122)	Bone protection with bisphosphonates
Osteoporosis (123, 124)	1.2 (or higher)		
Infection (125, 126)	2.2	Hypogammaglobulinaemia (125) Reduction in specific antibody (127)	Early treatment of infective symptoms Vaccinations
Renal disease (128, 129)		Monoclonal immunoglobulin deposition disease, (128-130), proliferative glomerulonephritis (131), light chain proximal tubulopathy.(132)	Dependent on mechanism – chemotherapy
Neuropathy (123, 133)	5.9 (CIDP) 3.2 (autonomic)	Antibodies against myelin-associated glycoprotein (MAG) in myelin sheath of peripheral nerves (134)	Intravenous immunoglobulin Chemotherapy Rituximab (in clinical trials)
Thrombosis (135)	2.1	Inflammation related – raised inflammatory mediators including IL-6 (136)	Consideration of thromboprophylaxis in high risk situations

Table 1.9: Complications of monoclonal gammopathy of undetermined significance
The recognised complications of monoclonal gammopathy of undetermined significance (MGUS). CIPD: chronic inflammatory demyelinating polyneuropathy; IL-6: interleukin-6.

1.2.5.1 Bone disease

Although the presence of bone disease is often used as a marker of end organ damage representative of myeloma, an increased risk of skeletal fracture and osteoporosis is also found in MGUS.

1.2.5.1.1 Evidence

Pepe et al investigated the rate of vertebral fractures in post-menopausal women with MGUS. They were matched to a control group based on age and years since menopause. There was

a higher rate of vertebral fracture in those with MGUS, with 52.3% of MGUS cases having vertebral fracture, compared to 23.8% of controls. (137)

This finding is not limited to vertebral fractures. Retrospective data looking at the risk of fracture, not restricted to vertebral fracture, demonstrated a 1.7 times higher risk of fracture over 5 years, and 1.6 times higher risk over 10 years in those with MGUS compared to a control population. (118) Hazard ratios showed increased risk at multiple sites, including vertebrae, pelvis, sternum, ribs, and long bones. The risk of fracture was higher for axial sites than for distal long bones. There was no significant difference in the risk of fracture depending on the Ig class of MGUS, or the concentration of paraprotein. This suggests all MGUS patients, including those who have been classified as 'low risk' MGUS, have an increased risk of fracture.

A study comparing observed and expected fracture rates in MGUS patients calculated a 20-year risk of fracture of 50%, which was significantly higher than the expected fracture rate of 43%. (138) The largest increase in fracture risk was for vertebral and pelvic fractures at 6.3 and 3.3 times higher respectively.

1.2.5.1.2 Mechanism

The increased risk of skeletal fracture seen in those with MGUS may be due to alterations in bone metabolism, decreased bone mineral density and osteoporosis.

A study of 1012 patients aged over 65 showed that those with MGUS had a significantly lower bone mineral density than those without MGUS, and a higher prevalence of osteoporosis in those with MGUS compared to those without (65% vs 24%). (139) Bida et al also demonstrated an association between MGUS and osteoporosis in a population based study (relative risk 1.2).(123) Pepe et al found that in their cohort of 65 patients with MGUS, only 20% had normal bone mineral density, whereas 53.8% were osteopenic and 26.2% had

osteoporosis. Those with lower bone mineral density were more likely to have had vertebral fractures. (137)

Imaging based studies have shown that compared to matched controls, MGUS patients have more porous cortical bone, (140) and lower trabecular thickness, which may affect bone strength. (141) Studies have also suggested that MGUS is associated with abnormal bone turnover, with increased bone resorption. (119-121) Markers of bone turnover including serum levels of carboxyterminal telopeptide of type I collagen (ICTP), indicating bone resorption, and serum levels of osteocalcin and bone-related alkaline phosphatase, indicating bone formation, have been found to be abnormal in a proportion of patients with MGUS. (119) Levels of several cytokines involved in the regulation of bone turnover are also abnormal in patients with MGUS. Serum levels of macrophage protein 1-alpha (MIP-1α), which increases osteoclast function, have been shown to be higher in MGUS patients compared to matched controls. (141) Patients with MGUS also have higher levels of interleukin-6 (IL-6) compared to healthy controls, (142) another cytokine known to increase osteoclast activity (122) and bone resorption. (143)

1.2.5.1.3 Management

Some small studies have demonstrated that bisphosphonates can be used to treat osteoporosis in patients with MGUS to improve bone mineral density.

Pepe et al used alendronate to treat MGUS patients with osteoporosis. They demonstrated a mean improvement in bone mineral density (BMD) at the lumbar spine of 6.1% (+/- 1.1%) after 18 months of treatment. (144) This study did only include a small number of patients, and there was significant attrition in both arms of the study (those on alendronate and those

on calcium & vitamin D supplementation) due to medication intolerances and progression to multiple myeloma which led to their withdrawal from the study.

Similarly, Berenson et al demonstrated an improvement in lumbar spine bone mineral density in patients treated with zoledronic acid for 12 months, (124) and here patients with MGUS and known osteoporosis or osteopenia showed a median increase in lumbar spine BMD of 21.8%.

Benefit may also be seen from the identification of fractures. Diagnosis of vertebral fractures allows appropriate treatment, for instance vertebroplasty for uncontrolled pain. (145) Currently, there is no guidance to recommend routine screening for osteoporosis or fracture in new cases of MGUS, however strategies for appropriate screening for osteoporosis may permit effective treatment.

1.2.5.2 Infection & alterations in immune system

1.2.5.2.1 Evidence

Patients with MGUS are at increased risk of infection. In one study, rates of bacteraemia in patients with MGUS compared to expected rates based on age- and sex-matched registry data found the incidence ratio was 2.2. (125) Bida et al also demonstrated an association between MGUS and an increased risk of upper respiratory tract bacterial infection. (123)

1.2.5.2.2 Mechanism

This increased risk of infection may have several underlying mechanisms. Antibody deficiency, or hypogammaglobulinaemia, has been shown to occur in those with MGUS, although reported rates vary between studies. Gregersen et al found hypogammaglobulinaemia in a quarter of patients with MGUS who had a diagnosed bacteraemia. (125) Other studies have also shown this reduction in levels of uninvolved immunoglobulins, with rates varying from

13% in a population from a Hong Kong (146) to 38% in a population from the United States. (111)

Antibody deficiency places patients at increased risk of sinopulmonary infections, in particular with encapsulated bacteria, such as Streptococcus pneumoniae and Haemophilus influenzae. (147, 148)

Levels of specific antibody have also been shown to be lower in MGUS patients compared to controls, including antibody to staphylococcal antigens, Moraxella, varicella zoster virus and candida. (127)

1.2.5.2.3 Management

Through recognition of the increased infection risk in these patients, management strategies could be implemented to encourage early antibiotic use when infective symptoms first develop, aiming to treat localised infection before it progresses to bacteraemia. These patients could also undergo vaccination, and be referred if necessary for specialist input if recurrent infections occur, although there are currently no guidelines regarding management of this increased infection risk.

Trials of vaccination in patients with myeloma have been small, but these studies suggest only 40-50% of patients display protective antibody levels following vaccination.(149) Response rates are much higher in patients with MGUS however, (126) and early vaccination before transformation to myeloma may confer a degree of protection to this “at risk” group.

1.2.5.3 Renal disease

Like myeloma, MGUS is a cause of renal impairment. Although the presence of renal disease is used as a diagnostic criterion for multiple myeloma, renal impairment has also been shown

to occur in patients who do not meet the other criteria necessary for them to be diagnosed with myeloma as per the IMWG criteria for diagnosis. (130, 131, 150, 151) This has been referred to as 'monoclonal gammopathy of renal significance' (MGRS). (152, 153)

1.2.5.3.1 Mechanism

MGUS has been demonstrated to cause renal disease via several mechanisms, including monoclonal immunoglobulin deposition disease, (128, 129) proliferative glomerulonephritis due to deposition of monoclonal IgG (131), and light chain proximal tubulopathy.(132) On kidney biopsy, patients with these complications are found to have monoclonal protein deposits within the kidney. (154)

1.2.5.3.2 Management

These complications are important to recognise as selected cases may benefit from the use of chemotherapy to reduce the level of monoclonal protein present, which can improve outcomes.

Untreated, light chain deposition disease can lead to end stage renal disease in 63% of patients within 5 years, with the subsequent requirement for dialysis or transplantation, and its associated morbidity and mortality.

A small study collected retrospective data on patients with light chain deposition disease who were treated with melphalan and prednisolone. This showed that renal function was maintained or improved in 60% of those with serum creatinine less than 354 μmol/L. In those with a creatinine level above 354 μmol/L, 82% progressed to end stage renal failure. (128)

Patients with renal disease due to a monoclonal paraprotein have a high rate of disease recurrence post-transplantation unless the underlying monoclonal protein is treated, (132,

155) therefore treatment may be necessary to prevent recurrence of renal disease in patients requiring a renal transplant for renal disease related to MGRS.

1.2.5.4 Neuropathy

1.2.5.4.1 Evidence

MGUS can cause neuropathy. Bida et al showed that those with MGUS had an increased risk of chronic inflammatory demyelinating polyradiculoneuropathy (relative risk 5.9) and autonomic neuropathy (relative risk 3.2). (123)

1.2.5.4.2 Mechanism

MGUS producing an IgM monoclonal protein is more commonly associated with neuropathy than IgG or IgA producing disease. (156) These IgM paraproteins cause neuropathy by interacting as an antibody against myelin-associated glycoprotein (MAG) in the myelin sheath of peripheral nerves. (134) This leads to a distal mixed sensorimotor neuropathy.

1.2.5.4.3 Management

Several treatment options have been suggested for IgM paraprotein associated neuropathy, including intravenous immunoglobulin (IVIg), chemotherapy, and rituximab, (133) but the trials in this area have only included small numbers.

Comi et al reported an improvement in disability after 4 weeks in a small trial of treatment with short term IVIg. However, this study included only 22 patients, half of patients in the treatment arm did not report any improvement, and the study did not assess for long term benefits of the treatment. (157)

A randomised controlled trial of cyclophosphamide and prednisolone versus placebo did not show any improvement in outcomes when assessing function, but suggested benefits in

sensation and muscle strength. Again, this study may have lacked sufficient power, as there were only 16 patients in the treatment arm and 19 in the control arm. (158)

Two small randomised controlled trials of rituximab suggested that this may lead to improvement in symptoms (159, 160) and there are further trials ongoing regarding the use of rituximab in this setting.

1.2.5.5 Thrombosis

1.2.5.5.1 Evidence

As with other recognised complications of myeloma, the risk of venous thrombosis is increased in patients with MGUS. (136) This has been demonstrated in several studies, with one study giving hazard ratios of 3.4 (95% CI, 2.5-4.6) at one year, 2.1 (95% CI, 1.7-1.5) at 5 years, and 2.1 (95% CI, 1.8-2.4) at 10 years. (135)

1.2.5.5.2 Mechanism

This increased risk of venous thromboembolism (VTE) may be due to changes in inflammatory mediators such as IL-6. Levels of IL-6 are raised in some patients with MGUS, even before progression to myeloma. (136)

1.2.5.5.3 Management

Recognition of this increased risk is important to ensure that symptoms are investigated appropriately and that patients receive appropriate thromboprophylaxis in high risk situations. Routine prophylactic treatment is not recommended.

1.2.6 Current stance on screening for MGUS

Population based screening for MGUS has not been recommended on the current evidence, as advised by the European Myeloma Network,(161) and joint recommendations from the UK

Myeloma Forum and Nordic Myeloma Study Group. (7) Both recommendations were produced through consultation with an expert panel, with a representative from MyelomaUK contributing to the UK Myeloma Forum recommendations.

The main justification for this recommendation is that a non-toxic, economically viable treatment is not currently available to prevent progression to multiple myeloma. It was felt that knowledge of a potentially pre-malignant condition would cause unnecessary anxiety for patients, particularly without treatment available to prevent progression. (7, 162)

There is some evidence from other pre-cancerous conditions that diagnosis leads to increased anxiety, however there is currently no specific evidence regarding the impact of an MGUS diagnosis on patient's anxiety levels.

Increased anxiety and depression have been shown in the first 6 months after diagnosis in patients with ductal carcinoma in situ (DCIS), (163) however generalising this finding to MGUS is likely to be inappropriate. There are significant differences in how DCIS and MGUS are managed immediately after diagnosis; as previously stated, there is currently no immediate treatment given for MGUS, however those with DCIS undergo breast surgery similar to those with invasive breast cancer. (164) For some patients with DCIS, the psychological impact seen is related to body image concerns, which would not be applicable to those with MGUS. (163)

Evidence from those with a new diagnosis of Type 2 diabetes suggests that the psychological impact of a diagnosis may in part be related to the information & support given to patients at the time of diagnosis. A new diagnosis of diabetes may provide a more appropriate comparison than DCIS, as although immediate invasive treatment is not required, these patients have reduced life expectancy (165) and a significant risk of serious complications. (166) Several studies have screened patients for diabetes in primary care, testing those at

high risk. Eborall et al collected information on anxiety, depression and self-perception of health in those undergoing screening. Those that were diagnosed with type 2 diabetes on screening had significantly higher levels of anxiety after diagnosis, however the size of the change was not felt to be clinically significant. (167)

Without evidence from patient and public involvement, a paternalistic approach deciding that screening may not be acceptable to patients may be out-dated, particularly in the context of our evolving understanding of the complications of MGUS itself. The diagnosis of MGUS necessitates monitoring to identify conversion to myeloma. A number of pre-malignant or potentially life-threatening conditions have been included in voluntary screening programs with evidence of improved patient outcomes (168) for example, the aortic aneurysm screening program (169), oral cavity lesions (170) and screening and surveillance of Barrett's oesophagus.(171) The UK population spent £135M on private health screening in 2011 (172) suggesting an appetite for personal health knowledge and a number of Royal Colleges provide guidance to assist doctors to empower patients to understand risk during screening processes (173, 174)

In the UK, screening programs that are provided within the NHS are evaluated by the National Screening Committee, (175) and are implemented after consultation and assessment against specific criteria based around 5 broad areas (176):

1. the medical condition in question
2. the method of testing
3. the interventions available
4. the proposed screening program itself
5. how the program would be implemented.

1.2.6.1 The medical condition

Screening programs need to focus on a condition that is an 'important health problem', particularly those that are common or serious. (176) Although rates of MGUS may be low in the population as a whole, MGUS is common in those over 50, becoming more common in older age groups.(110) As discussed, the potential for severe complications from MGUS itself is now recognised, as well as the risk of progression to malignancy.

The screening committee requires clear evidence of association with serious disease, which is well documented in MGUS for both complications and for risk of progression to myeloma. There is also increasing knowledge of the natural history of the disease, although there are still unanswered questions in how to predict who with MGUS will progress to myeloma.

1.2.6.2 The method of testing

The method of testing for MGUS fulfils most required elements for a screening test. The criteria specify a safe, simple, validated screening test, which is performed in a way acceptable to the target population.(176) Testing for MGUS involves a simple blood test, which is widely acceptable to the general population, and the tests required to identify MGUS (serum protein electrophoresis, paraprotein identification and serum free light chain testing) are validated tests already performed routinely in NHS laboratories nationally. A clear pathway for further investigation of abnormal results is needed and is available through current national and international recommendations for investigation and monitoring of MGUS.(7)

1.2.6.3 The intervention available

The screening criteria require evidence of improved outcomes with intervention at a pre-symptomatic stage. MGUS remains a condition that is largely identified in asymptomatic patients, but, as discussed, there is increasing evidence of complications that may require

intervention secondary to the condition. As mentioned previously, there is concern that diagnosing a pre-malignant condition with no treatment available to prevent progression may cause unnecessary anxiety, as seen in patients with ductal carcinoma in situ (DCIS). (163) Currently there is variation in the way that a diagnosis of MGUS is communicated to patients, and so inconsistent information on the risk of progression may be given. (177) However, in a system focused on patient centered care and shared decision making, further public and patient involvement is needed to determine the views of patients themselves.

Although there is no current treatment available to prevent progression from MGUS to myeloma, there are ongoing studies regarding the treatment of smouldering myeloma, which is also asymptomatic and would be identified through the same methods as MGUS. In 2013, Mateos et al conducted a phase 3 randomised trial in patients with smouldering myeloma at high risk of progression to active multiple myeloma, comparing treatment with lenalidomide and dexamethasone with observation. (178) They demonstrated that those who received treatment had a significantly longer median time to progression, and significantly higher overall survival at three years (94% vs 80%). This suggests that there may be a role for treatment of selected groups of asymptomatic patients before progression to symptomatic disease. Newer treatments for myeloma, such as daratumumab, an anti-CD38 monoclonal antibody, are also being used in patients with smouldering myeloma in ongoing trials. (179) The development of new treatments with potential benefits for selected groups of patients may lead to changes in the way the risk of progression from MGUS to myeloma is managed in the future, particularly for high-risk groups.

1.2.6.4 Proposed screening program

There is currently no evidence available showing direct benefit from screening for MGUS. National screening recommendations ask for 'high quality randomised controlled trials' showing impacts on morbidity or mortality, however there have been no published randomised trials in MGUS screening or follow-up to date. To demonstrate an impact on outcomes in myeloma, any randomised study would require a large study population, followed up over a prolonged period, likely decades. These studies would be costly, and like the current evidence, the outcome would be affected by any future improvements in myeloma outcomes or changes in routine practice that occur during such a long study. The economic impact of screening also needs to be considered (176) – currently the full extent of the economic impact of MGUS has not been fully assessed, and further evidence is needed which may be provided by longer studies of MGUS follow-up. The cost of any potential screening program could be reduced by narrowing the population where screening is implemented and indeed, this is a common practice during screening. For example, aortic aneurysm screening is currently offered to all men in England when aged 65.(180) For MGUS, targeted screening would be supported through identification of a high-risk population where the rate of MGUS is higher, for instance in those with comorbidities that are known to be associated with MGUS. As MGUS is uncommon in those under 50,(108) age-based criteria may be used to help define a group for screening, however recommendations would be needed regarding how often screening should be repeated.

1.2.6.5 Implementation of the screening program

If a screening program for MGUS were implemented, a clear structure would need to be established for local follow-up and investigation of identified patients. This is particularly

important as the tests being performed have the potential to identify patients with myeloma, which can be asymptomatic at diagnosis, and may be diagnosed incidentally. (39)

There would also need to be a consistent system to review those who were found to have MGUS. Establishing a program that monitors those with MGUS for progression to myeloma as well as addressing all monitoring and management of potential complications is likely to be costly. Any established monitoring program would need the involvement of several secondary care specialties to provide the assessments and investigations that may be needed, for instance access to DEXA scans for assessment of osteoporosis, (181) to facilities to allow bone marrow biopsy in those with possible progression to myeloma, (8) and to expert clinical assessment. This group of older adults often have multiple comorbidities that add extra complexity,(182) and expert clinical assessment would be needed to ensure that alternative underlying causes for any complication are investigated as needed. This would require the establishment of considerable infrastructure on a national basis, as well as collaboration between many different specialist teams, and between primary and secondary care.(177) To justify this investment, clear guidance on appropriate evidence-based patient pathways for the management of complications would be needed. As mentioned, the financial impact of MGUS has not yet been clearly established, therefore it is difficult to balance the cost of a program for screening & monitoring against potential healthcare savings.

1.3 Hypothesis and aims

As the issue of diagnostic delay in plasma cell dyscrasias has several underlying causes, it will need several different combined approaches to address the issue fully.

1.3.1 Hypothesis

Diagnostic delay occurs at several points in the pathway to diagnosis of multiple myeloma. Those patients with longer pathways have more severe disease, and patients diagnosed through emergency presentations may have experienced longer pathways to diagnosis. Through assessment of patients who have previously been diagnosed with myeloma, areas where delay occurs can be identified to allow targeted interventions to reduce delay.

Strategies to improve early diagnosis of myeloma could be aimed at identification before symptoms develop. This may be through the identification of abnormal blood test results before symptoms develop, or through detection and monitoring of MGUS.

1.3.2 Aims

The aims of this thesis can be divided into three areas:

- To assess pathways to diagnosis in myeloma
    - To outline the pathways to diagnosis taken by patients with myeloma
    - To assess whether those that are referred by their general practitioner to a non-haematology secondary care specialty or that present via acute services experience a longer pathway to diagnosis
    - To describe the symptoms experienced prior to diagnosis in myeloma patients within the UK and assess whether particular symptoms are more likely to be reported in a particular pathway to diagnosis

    - To assess the rates of end organ damage and symptoms at diagnosis in those with previous knowledge of MGUS
- To identify abnormal blood test results that could be used to create algorithms for reflex testing
    - To identify the blood test abnormalities commonly present in those with newly diagnosed myeloma and assess whether they can be detected on blood test results prior to diagnosis
- To identify a cohort with a high prevalence of MGUS
    - To assess the prevalence of MGUS in patients being admitted to hospital as an acute admission
    - To compare the rate of MGUS in acute admissions to previously published population rates, to determine if acute admissions are a high-risk group
    - To assess whether patients who are admitted due to an infection are more likely to have MGUS

1.3.3 Thesis structure

Chapter 3: Pathways to diagnosis and symptom profile during the diagnostic pathway in multiple myeloma – data from the TEAMM trial.

Data from the Tackling Early Morbidity and Mortality in Multiple Myeloma (TEAMM) trial was used to outline the pathways to diagnosis taken by patients with multiple myeloma in the UK, and the symptoms experienced by these patients. Length of pathway intervals were assessed to identify where in the diagnostic pathway delay was occurring, with the aim of identifying where interventions for early diagnosis could be targeted. Symptoms and markers of disease

severity were compared between the pathways, to explore reasons for the higher mortality rate seen in patients diagnosed through acute services.

Chapter 4: The impact of a prior diagnosis of MGUS on pathways to diagnosis & end organ damage in multiple myeloma.

Participants within the TEAMM trial who were diagnosed with MGUS before the development of myeloma were identified, and their symptoms and rates of end organ damage were compared to those without prior knowledge of MGUS. This aimed to address whether prior knowledge of MGUS led to lower levels of complications at diagnosis of myeloma, as this would suggest that increased identification of MGUS may be beneficial.

Chapter 5: Identification of abnormal blood test results prior to diagnosis in those with multiple myeloma.

Data from a local cohort of patients diagnosed with multiple myeloma was used to identify abnormalities that were present on routine blood tests at and prior to diagnosis, to identify blood test abnormalities that were present for some time prior to diagnosis which could be built into an algorithm for automated or reflex testing, to identify patients with myeloma before the development of more easily recognisable symptoms.

Chapter 6: The prevalence of Monoclonal Gammopathy of Undetermined Significance in Acute Hospital Admissions.

Chapter 6 discusses the results of a study conducted in the acute medicine department at University Hospitals Birmingham, which investigated the prevalence of paraproteinaemia in patients admitted to hospital, to identify whether this was a population with a higher rate of MGUS, where future strategies aimed at identification of MGUS could be targeted.

2 GENERAL METHODS

2.1 Patient cohorts

For this research patients were recruited from the following cohorts:

1. Tackling Early Morbidity and Mortality in Multiple Myeloma – the TEAMM trial
2. Patients diagnosed with myeloma at University Hospitals Birmingham
3. Patients diagnosed with autoimmune hepatitis at University Hospitals Birmingham
4. Prevalence of MGUS in Acute Hospital Admissions Study

2.1.1 Tackling Early Morbidity and Mortality in Multiple Myeloma – the TEAMM trial

Chapters 3 and 4 of this thesis use data obtained from the TEAMM trial.

TEAMM was a randomised controlled trial of supportive care with prophylactic antibiotics. Patients with newly diagnosed multiple myeloma were recruited from 93 hospitals within the UK through the myeloma trials network.

Those in the treatment arm received levofloxacin for 12 weeks compared to placebo.

2.1.1.1 Approvals & funding

The study had ethical approval from the West Midlands – Coventry and Warwickshire Research Ethics Committee (reference 11/WM/0220). The sponsors were University of Birmingham and University of Warwick. The study was funded by the NIHR HTA Programme.

No further ethical approval was needed for the analyses performed in this thesis. No patient identifiable data from the TEAMM trial was accessed during the course of this analysis. Results discussed in this thesis were presented back to the trial oversight committee and at the investigators meeting.

2.1.1.2 Outcomes

The primary outcome was the number of febrile episodes from randomisation up to 12 weeks.

Secondary outcomes were:

- Mortality
- Carriage of healthcare associated infection, including:
    - methicillin-resistant Staphylococcus aureus (MRSA)
    - Clostridium difficile
    - extended-spectrum beta-lactamases (ESBL)
- Number of days in hospital from randomisation to 12 weeks
- Number of days in hospital on anti-infective treatment
- Number of clinically documented episodes of infection

2.1.1.3 Inclusion & exclusion criteria

Inclusion criteria:

- Aged 21 years or over
- Able to provide written consent to participate in the trial
- Within 14 days of starting anti-myeloma therapy for newly diagnosed multiple myeloma (either 14 days before treatment initiation or 14 days after)

Exclusion criteria:

- Patients who were not planned to undergo active treatment for their myeloma
- Those who had previously received anti-myeloma therapy (excluding local radiotherapy or bisphosphonates)
- Patients with a mandatory requirement for antibiotic prophylaxis

- Patients with contraindications to levofloxacin, including:
    - allergy to levofloxacin or quinolones
    - previous tendon disorder due to fluoroquinolone use
    - the use of other antibiotic prophylaxis (excluding Pneumocystis prophylaxis)
    - the use of amiodarone, arsenic trioxide, or antiepileptics
- Women of childbearing age who were not using appropriate methods of contraception to prevent pregnancy, or women who were breastfeeding
- Active concurrent other malignancy, or other malignancy within the previous 5 years, except:
    - Treated carcinoma in situ of the cervix or breast
    - Surgically removed squamous or basal cell carcinoma of the skin
    - Incidental histological finding or prostate cancer, stage T1a or T1b only

2.1.1.4 Involvement

TEAMM was run by the Warwick Clinical Trials Unit (CTU), with the Principal Investigator Professor Mark Drayson and Lead for the trial at Warwick Clinical Trials Unit Professor Janet Dunn. The original study design had been conceived through discussion of a group of haematologists. All data collection was performed by local site teams, and data queries by Warwick CTU.

My involvement in TEAMM was in analysis of the diagnostic pathway and symptom data which is discussed in this thesis. My role included data cleaning, creation of a separate database of the diagnostic pathway and symptom data, and subsequent analysis of this data.

Diagnostic pathways and symptom data were reviewed in collaboration with Dr Stella Bowcock, lead haematologist for the TEAMM trial, and Professor Mark Drayson, principal

investigator for TEAMM. Statistical analyses were performed in collaboration with Dr Gulnaz Iqbal, statistician for TEAMM at Warwick Clinical Trials Unit.

2.1.1.5 Recruitment dates

Recruitment took place between 2012 and 2016.

2.1.1.6 Data collected at recruitment

To help provide further information to address the problem of early mortality, participants in the trial provided extra information regarding how they were diagnosed, including where they were seen prior to reaching their diagnosis, and about the symptoms they had experienced from their myeloma.

At their initial study visit, prior to randomisation, a case report form was completed for each participant. Data was collected on basic demographic and staging information, including:

- Age
- Gender
- Ethnicity
- Performance status at diagnosis and 6 months prior to diagnosis
- Presence of bone disease at diagnosis
- Blood test results at diagnosis, including both full blood count (FBC) and selected biochemistry results
- Components of the ISS score at diagnosis

2.1.2 Patients diagnosed with myeloma at University Hospitals Birmingham

Data from patients diagnosed with multiple myeloma at University Hospitals Birmingham (UHB) is included in Chapter 5.

UHB is a tertiary care centre that offers a dedicated haematology service, with both inpatient and outpatient services, including stem cell transplantation.

2.1.2.1 Approvals

Local approval was obtained for service evaluation via the Clinical Audit Registration and Management System (registration number CARMS-13633). NHS Research Ethics Committee (REC) approval was not needed as this was determined to be a clinical audit.

No patient identifiable data from this cohort is included in this thesis.

2.1.2.2 Inclusion & exclusion criteria

Inclusion:

- Patients diagnosed with active multiple myeloma at UHB
- Aged over 18 years

Exclusion:

- Patients diagnosed with active multiple myeloma at another centre and referred to UHB for further management, after treatment was initiated in another centre
- Patients with smouldering multiple myeloma (SMM) or monoclonal gammopathy of undetermined significance (MGUS) without progression to active multiple myeloma
- Patients with no evidence of multiple myeloma documented on UHB electronic systems

2.1.2.3 Involvement

Initial identification of patients was performed by the Health Informatics department at UHB. Retrospective data was collected for electronic systems by myself. No contact with the patients was required.

2.1.2.4 Patient identification

No local database of those diagnosed with multiple myeloma is available. Patients with myeloma were therefore identified based on clinical coding on UHB electronic systems, which are described in Table 2.1. Data was obtained for all patients where a coded diagnosis of myeloma had been recorded since 2007, until the data was obtained on 21st July 2017. Patients were identified using ICD code (ICD 10 – CM C90 Multiple Myeloma), recorded on either the PAS (Patient Administration System) or the Somerset Cancer Register.

2.1.2.5 Data collected

Date of diagnosis was determined using the European Network of Cancer Registries (ENCR) criteria. In order of priority, this is:

1) date of first histological confirmation
2) date of cancer-related hospital admission
3) date of first cancer-related outpatient consultation
4) date of diagnosis
5) date of death.

Where available, the date of histological confirmation was used as date of diagnosis.

Demographic data collected were:

- Age at diagnosis
- Gender
- Ethnicity
- Deprivation decile calculated using post code

Blood test results were obtained for each patient, up to and including the date of diagnosis. Those included were:

- Full blood count, including haemoglobin, total white cell count (WCC), levels of neutrophils, lymphocytes, basophils, monocytes and eosinophils, mean corpuscular volume (MCV), reticulocyte count, and platelet count, haematocrit
- Urea and electrolytes, including urea, creatinine, sodium, and potassium
- Liver function tests, including ALT, AST, alkaline phosphatase, and albumin
- Bone profile, including albumin, calcium and total protein
- C reactive protein (CRP)
- Immunoglobulin levels (IgG, IgA and IgM)
- Serum free light chain levels (kappa and lambda)

2.1.3 Patients diagnosed with autoimmune hepatitis at University Hospitals Birmingham

Data from patients with autoimmune hepatitis managed at University Hospitals Birmingham are included in Chapter 5.

This cohort was chosen for comparison of blood test results, as patients may have multiple immunoglobulin and liver function measurements in a short period of time as both are

currently used to assess response to immunosuppression. Although patients with autoimmune hepatitis may have elevated IgG levels, they do not have a paraprotein related to their disease. (183)

2.1.3.1 Approvals

NHS Research Ethics Committee (REC) approval was not needed as this was determined to be a clinical audit. Local approval was obtained for service evaluation via the Clinical Audit Registration and Management System (registration number CARMS-12368).

No patient identifiable data from this cohort is included in this thesis.

2.1.3.2 Inclusion & exclusion criteria

Inclusion criteria:

- Diagnosed with autoimmune hepatitis
- Aged 18 years old or over

Exclusion criteria:

- No paired blood test results for liver function tests and immunoglobulins available on UHB electronic record of pathology test results

2.1.3.3 Involvement

Initial identification of patients was performed by the Health Informatics department at UHB. Retrospective data was collected for electronic systems by myself. No contact with the patients was required.

2.1.3.4 Patient identification

Patients were identified based on clinical coding for autoimmune hepatitis on electronic patient records.

2.1.3.5 Data collected

Data were collected on all available blood tests results for these patients with a measurement of total protein, albumin and immunoglobulin levels on the same blood sample.

2.1.4 Prevalence of MGUS in Acute Hospital Admissions Study

Chapter 6 discusses participants recruited to the study Prevalence of MGUS in Acute Hospital Admissions.

This study took place on the Clinical Decisions Unit (CDU), at University Hospitals Birmingham (UHB). This includes a 68-bed medical admissions unit, where patients initially stay during an acute admission, and the Acute Medicine Clinic (AMC), where patients may be reviewed initially if their predicted length of stay is less than 12 hours, before being admitted to hospital or discharged home. Both areas receive patients who have been referred via Accident and Emergency (A&E) or by their general practitioner (GP) as well as smaller numbers referred through other routes, for instance from outpatient clinic attendance.

2.1.4.1 Approvals & funding

Ethical approval was given by the West Midlands - Coventry and Warwickshire NHS Research Ethics Committee on 1st August 2016 (reference 16/WM/0279). This ethical approval was updated on 28th October 2016 and 2nd November 2017 following substantial amendments to alter the methods and inclusion criteria respectively.

The October 2016 amendment altered the protocol to allow collection of 6ml of blood from each participant purely for use in the study. The original ethical approval had been obtained

on the basis of performing the tests required for the study on surplus sample taken for clinical care.

The November 2017 amendment altered the inclusion criteria to allow recruitment of participants who did not have capacity to provide consent, if assent was provided by a personal consultee.

Local approval was given by the UHB Research & Development department, reference RRK5862.

Sponsorship was provided by the University of Birmingham.

The study was funded by the Clinical Immunology Service at the University of Birmingham. A grant of £10,000 was received from Experimental Cancer Medicine Centre (ECMC) Birmingham.

2.1.4.2 Recruitment

Patients who met the inclusion criteria for the study were identified by the clinical team, who highlighted them as potential participants. They were then provided with a written participant information sheet. Participants who had capacity to consent to take part provided written consent for participation in the study. From November 2017, for participants who did not have capacity to provide consent, assent was sought from a personal consultee.

2.1.4.3 Inclusion and exclusion criteria

November 2016 to November 2017:

Inclusion criteria:

- Aged 18 year or over
- Admitted to hospital as an acute medical admission
- Able to provide written informed consent

Exclusion criteria:

- Unable to provide written informed consent

November 2017 onwards:

Inclusion criteria:

- Aged 18 years or over
- Admitted to hospital as an acute medical admission

Exclusion criteria:

- Unable to provide written consent **and** unable to attain assent from a personal consultee

2.1.4.4 Recruitment dates

Recruitment took place over 16 months, from 21st November 2016 to 21st March 2018.

2.1.4.5 Involvement

The principal investigator for the study 'Prevalence of MGUS in Acute Hospital Admissions' was Dr Alex Richter, with co-investigators Prof Mark Drayson and Dr Elizabeth Sapey. Protocol

creation and ethical, HRA and local research approval applications were performed with input from myself and all three investigators.

Participant recruitment and sample collection was performed by myself, with assistance of clinical staff on the Clinical Decisions Unit at UHB.

Sample processing and assays were performed by the Clinical Immunology Service at University of Birmingham, including Sian Faustini, research fellow.

2.2 Definitions of multiple myeloma, smouldering myeloma and MGUS

For the 'Prevalence of MGUS in Acute Admissions' study, the diagnostic criteria used to assess abnormal results were the diagnostic criteria specified by the International Myeloma Working Group (IMWG), a division of the International Myeloma Foundation.(13) These criteria are shown in Figure 1.1.

For patients identified through UHB clinical systems as having multiple myeloma, these patients' details were not compared to the IMWG diagnostic criteria as part of this thesis. A documented diagnosis of multiple myeloma in clinical records was taken to represent local clinical assessment as meeting the relevant diagnostic criteria.

For patients recruited to the TEAMM trial, the diagnostic criteria used for symptomatic multiple myeloma were based on the BCSH and UKMF Guidelines on the Management and Diagnosis of Multiple Myeloma September 2010,(184) and were:

- 'M protein' in serum and/or urine
- Bone marrow (clonal) plasma cells or biopsy proven plasmacytoma
- Myeloma-related organ or tissue impairment (including bone lesions)

As all participants in TEAMM were started on anti-myeloma therapy, they were all assessed by the local clinical team as having symptomatic multiple myeloma.

2.3 Definitions of end organ damage in myeloma

Throughout this thesis, the presence of 'CRAB' features is used as a marker of end organ damage in myeloma. These abnormalities (hypercalcaemia, renal impairment, anaemia and bone disease) are assessed using the criteria specified by the IMWG criteria for myeloma diagnosis,(13) shown in Table 1.1.

2.4 Normal/reference ranges

Where blood test results for patients diagnosed with multiple myeloma at UHB, or for patients at UHB recruited through the 'Prevalence of MGUS in Acute Hospital Admissions' study are compared to a normal or reference range, the ranges used are those specified by UHB for biochemistry or haematology tests, and those specified by the CIS at the University of Birmingham for immunology tests, as these are the laboratories that processed the samples. These reference ranges are shown in Appendix 1.

Where an uncorrected calcium result was available, this was used to calculate corrected calcium. The equation used for this was: [calcium] + (40 – [albumin] x 0.02).(185) The albumin result used to perform this correction was obtained from the same sample.

2.5 Programs used & electronic systems

Statistical analyses for all chapters were performed using SPSS (IBM SPSS Statistics 25, USA).

Data for all chapters was stored and accessed using Microsoft Excel and Microsoft Access (USA).

For data from the TEAMM trial, data was accessed from the trial database by members of the trial management group, stored at Warwick Clinical Trials Unit. This data was exported into Excel for further use.

For patients diagnosed with myeloma at UHB (Chapter 5) and participants recruiting to the Prevalence of MGUS in Acute Hospital Admissions study (Chapter 6), data were accessed through the electronic systems used by UHB, shown in Table 2.1.

Name of System	Description of system	Designed by
Clinical Portal	Access to clinical letters, referrals, imaging reports, pathology reports, laboratory reports, dates of hospital attendance	UHB
Prescribing Information and Communications System (PICS)	Electronic clinical system with details of admissions and attendances; coding of admission reason and source of referral; prescriptions and medication charts; blood test results; inpatient patient location and discharge letters	Birmingham Systems, UHB
Telepath Laboratory Information Management System	Electronic laboratory system used by the Clinical Immunology Service, where the results of all tests performed by the CIS are available	Computer Sciences Corporation (CSC)

Table 2.1: Electronic systems used to access patient records.
Systems used to access electronic patient records for two cohorts of patients within this thesis: 1) patients diagnosed with multiple myeloma at University Hospitals Birmingham; 2) patients recruited to the study 'Prevalence of MGUS in Acute Hospital Admissions'.

2.6 Statistical considerations

All statistical analyses were performed using SPSS statistics.

A p value of <0.05 is used to signify statistical significance throughout.

The distribution of each continuous variable was assessed for normality, initially using visual inspection of histograms and Q-Q plots, calculation of z score for skewness and kurtosis, and by Shapiro-Wilk's test and Kolmogorov-Smirnov's test for normality.

When summarising continuous variables, mean and standard deviation are used for those variables that are normally distributed; median and interquartile range (IQR) are reported for variables that are not normally distributed.

2.6.1 Group differences

For continuous data that was not normally distributed, Kruskal-Wallis test or Mann-Whitney U test was used to analyse differences between groups. Within this thesis there is no continuous dependent variable where the data is normally distributed, therefore only non-parametric tests were used.

The Kruskal-Wallis test was used to analyse continuous or ordinal data where more than two groups were present for the independent variable. Where the Kruskal-Wallis test was performed, a post hoc analysis was performed using Dunn's (1964) procedure with Bonferroni correction for multiple comparisons to determine differences between two groups.

The Mann-Whitney U test was used to analyse continuous or ordinal data where there were two groups for the independent variable.

Chi square test was used for comparison of dichotomous variables between groups.

Chi square test for homogeneity was used to assess dichotomous dependent variables between multiple groups. Where this test was performed, comparisons were made between each group of the independent variable by pairwise comparison using the z-test of two proportions, with Bonferroni correction for multiple comparisons.

A Chi square goodness-of-fit test was used in Chapter 3 to compare type of presenting symptom by diagnostic pathway taken by participants, and in Chapter 6 for comparison of rates in the study population to expected rates based on previous research.

The Chi square test of independence was used in Chapter 4 to assess for association between prior knowledge of MGUS and the pathway to diagnosis.

2.6.2 Comparison between time points

Chapter 5 includes data on the difference in blood test results over time, comparing results at three time points. For this analysis, only participants with data for all three time points were included. This data was analysed using a one-way repeated measures ANOVA. When the one-way repeated measures ANOVA was used, sphericity was assessed using Mauchly's test of sphericity. If the assumption of sphericity was not met, as signified by a statistically significant result of Mauchly's test, then a Greenhouse-Geisser correction was applied to correct the result of the one-way repeated measures ANOVA.

2.6.3 Correlation

Analysis of correlation between two variables is discussed in Chapter 5. The distribution of both continuous variables was assessed for normality by visual inspection of histograms and by Shapiro-Wilk test. This showed that the distributions of both variables did not follow a normal distribution, but were right skewed. As the results were not normally distributed, Spearman's rank-order correlation was used to test for correlation.

One of the variables assessed in this way (immunoglobulin levels) contained results from two laboratories. 209 out of 218 immunoglobulin results were from the Clinical Immunology Service at University of Birmingham, 9 samples were from the Biochemistry laboratory at UHB. To ensure that the inclusion of results from two different laboratories did not affect correlation between results, the analyses were run again after removing the results from Biochemistry.

2.6.4 Power calculation

For chapter 3 and 4, no power calculation was performed regarding the sample size needed for the analysis performed in this thesis, as the sample size of TEAMM had been determined by the primary outcomes of the study, rather than the supplemental analyses discussed here.

Chapter 6 discusses a pilot study to assess the prevalence of MGUS with a defined population. A sample size of 670 participants was needed in order to detect a rate of MGUS of 5% (in comparison to an expected rate of 3%) with 80% power and 5% level of significance.

3 PATHWAYS TO DIAGNOSIS AND SYMPTOM PROFILE DURING THE DIAGNOSTIC PATHWAY IN MULTIPLE MYELOMA – DATA FROM THE TEAMM TRIAL

3.1 Introduction

Current evidence suggests that diagnostic delay in myeloma is associated with poorer patient outcomes (34, 41) but although this is recognised, there is little published data about current pathways to diagnosis and where potential opportunities for earlier diagnosis were missed, leading to diagnostic delay. Specifically, this chapter will explore:

- The diagnostic pathways taken by patients with myeloma
- The length of pathway of patients diagnosed via acute services compared to those diagnosed from primary care referral to haematology services, as those diagnosed in acute services have a higher mortality (27)
- The impact of referral to non-haematology secondary care services on the length of diagnostic pathway and on stage of disease
- The range of symptoms reported by patients with myeloma, and whether these symptoms relate to the diagnostic pathway

As discussed in the introduction, patients with multiple myeloma experience diagnostic delay, with a long pathway prior to diagnosis.(38) Patients with myeloma who present through acute pathways have a higher mortality,(27) and higher rates of end organ damage at diagnosis. (186) A possible explanation is longer diagnostic pathways in patients diagnosed via acute services, as longer delays are associated with higher rates of end organ damage at

diagnosis.(34, 41) This chapter aims to address whether those diagnosed via acute services do experience a longer delay in diagnosis.

Research into other cancers has shown that the length of different intervals within the diagnostic pathway can be associated with the stage of disease at diagnosis.(187) Identifying within which interval delay occurs would support interventions to reduce this delay.

In myeloma, the most common routes or pathways to diagnosis are GP outpatient referral and emergency presentation.(27) However, previous research has shown that patients are often referred to haematology from other specialties.(36) It is important to explore the impact that referral to other secondary care specialties has on the length of diagnostic pathway and diagnostic intervals.

Due to the non-specific nature of the symptoms, and the frequent involvement of other physiological systems such as bone disease or renal impairment,(186) it is predictable that some patients will be referred to secondary care specialties other than haematology. Little research has been undertaken to determine which patients are being diagnosed via this non-haematology secondary care pathway, in order to identify whether particular patient groups or presentations are being misdirected. It is important to assess whether patients who have been diagnosed via these pathways experience a longer diagnostic interval, higher rates of complications or more advanced disease at diagnosis.

3.2 Hypotheses

This chapter will explore the following hypothesis:

The non-specific symptoms associated with myeloma lead to differing pathways to diagnosis depending on the symptom burden. Diagnosis through direct referral to haematology services is associated with shorter pathways and lower complication rates at diagnosis.

3.3 Aims

This hypothesis will be tested using the following aims:

- To outline the pathways to diagnosis taken by patients with myeloma
- To assess whether those that are referred by their general practitioner to a non-haematology secondary care specialty experience a longer pathway to diagnosis
- To assess whether those patients that present via acute services have a longer pathway to diagnosis
- To describe the symptoms experienced prior to diagnosis in myeloma patients within the UK
- To assess whether particular symptoms clusters are more likely to be reported by patients in a particular pathway

3.4 Methods

3.4.1 The Tackling Early Morbidity and Mortality in Multiple Myeloma Trial

Patient information was collected from the TEAMM (Tackling Early Morbidity and Mortality in Multiple Myeloma) trial, which has been described in Chapter 2, Section 2.1.1.

3.4.2 Additional data collected at trial recruitment to assess diagnostic pathways

Supplemental questions were included in the TEAMM study at baseline to assess healthcare consultations and symptoms prior to diagnosis.

These questions were:

1. When did the patient first notice bodily changes and/or symptoms that they attribute to the myeloma? (please note down incidental findings on laboratory tests also)
   (This question included 4 lines for recording symptoms, plus a space for date of onset for each of the four lines)
2. When did the patient first visit a doctor or nurse at their local general practice about any of these symptoms or bodily changes?
3. How many times did the patient consult a doctor or nurse at their local general practice about any of these symptoms or bodily changes before they were referred (or diagnosed, if no GP referral)?
4. When did the patient first visit the hospital (includes A&E)?
5. Which hospital department was the patient first seen in (includes A&E)?
6. When did the patient first see a haematologist about any of these symptoms?

The answers to these questions were used to categorise the pathway that patients took to reach their diagnosis, and to assess the range of symptoms.

3.4.3 Pathways to diagnosis

The potential pathways taken by patients to reach their diagnosis is shown in Figure 3.1. Participants were categorised into three pathways to diagnosis:

1. 'acute' – diagnosis via acute services such as emergency admissions or A&E
2. 'direct' to haematology – referred from primary care GP to haematology
3. 'other secondary care' – seen by a secondary care specialty other than haematology prior to haematology review, but no documented contact with acute services

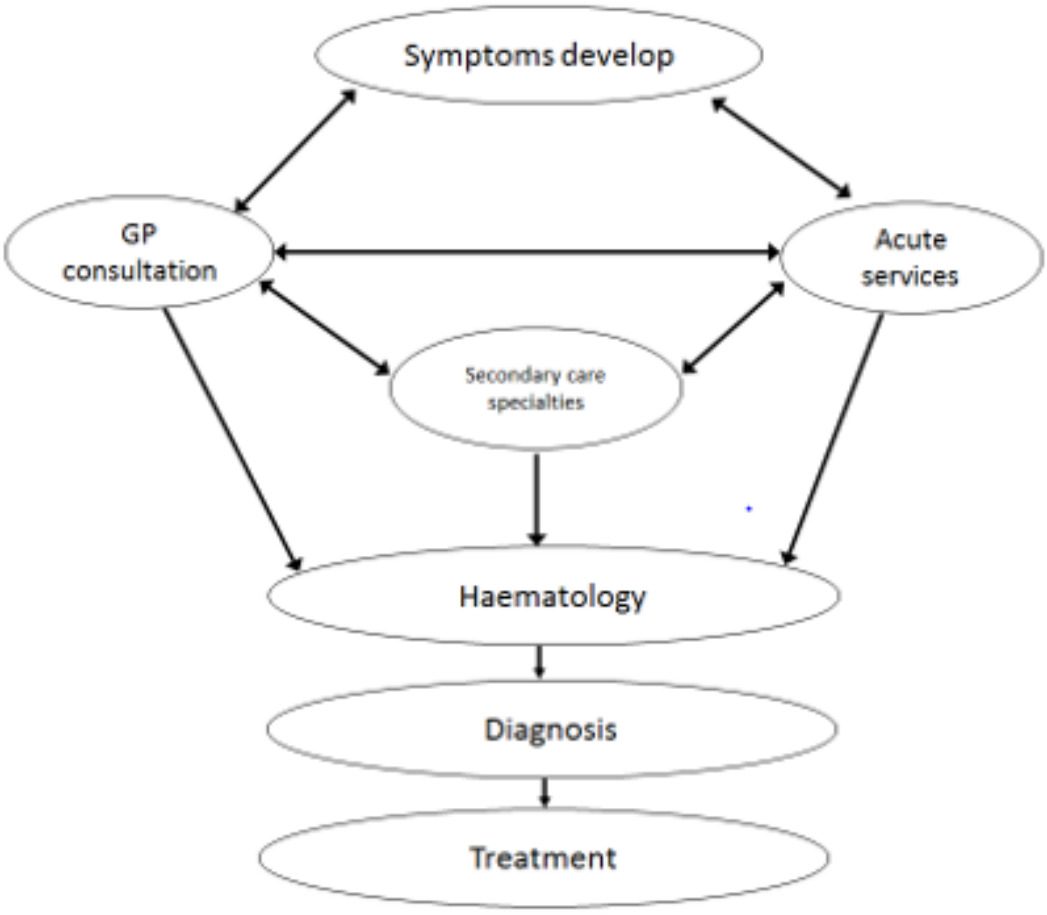


Figure 3.1 Possible pathway steps taken by patients during diagnostic pathway, from initial symptom onset to diagnosis and treatment.
Arrows show direction of travel & referral.

The pathway was categorised based on the department documented as the hospital department where the patient was first seen.

Entries from 'first hospital department seen in' were reviewed to remove variability in the terms used. As this was free text, there was variation in the way this information was recorded. Entries reflecting different naming conventions for the same department were grouped, for example 'ED', 'emergency department', 'A&E' and 'accident and emergency'. Terms reflecting an acute medical admission were grouped together, including 'AMU', 'EAU', 'emergency assessment unit', and 'acute medical unit'. Terms referring to medical or surgical specialties were grouped under commonly used umbrella terms, for example 'trauma', 'orthopaedics' and 'trauma and orthopaedics' were grouped.

3.4.3.1 Acute pathway

The acute pathway included those initially seen in Accident and Emergency, Acute Medicine/Medical Admissions Units, or Surgical Admissions Units. Those where documented symptoms included phrases such as 'admitted acutely' or 'emergency admission' were also included in the 'acute' pathway. Participants recording a GP consultation prior to or on the same day as their attendance at acute services were classified as an 'acute pathway' diagnosis, in keeping with the method used in Public Health England's Routes to Diagnosis.

3.4.3.2 Direct pathway

For participants not diagnosed via the acute pathway, those reporting haematology as first secondary care contact formed the 'direct' pathway.

3.4.3.3 Other secondary care

For participants who weren't diagnosed via the acute or direct pathways, the first department attended was reviewed and compared to the date of haematology review and date of GP

consultation, if available. If adequate information was provided to determine which secondary care specialty they had been reviewed by, they were allocated to the 'other secondary care' pathway.

Two clinicians (CA and SB) separately allocated participants into the three pathways. For participants where there was initial disagreement on the pathway taken, the information was reviewed and discussed with a third clinician.

3.4.4 Markers of severity: CRAB features & staging

Several factors were identified as markers of severity of disease, which could be used to compare participants diagnosed via the three pathways. These included performance status, International Staging System (ISS) score and the presence of end organ damage (CRAB features).

3.4.4.1 Performance status

The performance status was recorded using the Eastern Cooperative Oncology Group (ECOG) performance status scale.(188)

3.4.4.2 ISS stage

The stage of disease was recorded using the International Staging System for multiple myeloma, which was calculated for each participant based on the entry of each component of the ISS into the case report form (CRF) at study recruitment. (14)

3.4.4.3 CRAB features of end organ damage

The presence of end organ damage was assessed based on the presence of CRAB features (hypercalcaemia, renal impairment, anaemia and bone disease) as described in Section 2.3.

On review of free text symptoms, if one of the reported symptoms was fracture then this was also included.

3.4.5 Intervals

Several intervals were determined from the dates provided. Commonly used intervals are shown in Figure 1.2.

The patient interval was determined by comparison of date of onset of earliest symptom and date of earliest healthcare consultation (in either primary or secondary care).

The diagnostic interval was determined by comparison of date of first healthcare consultation and date of haematology consultation.

As date of diagnosis was not provided, the date of first haematology consultation was used as a surrogate marker.

All dates were collected from patient recall.

3.4.6 Symptoms

Symptoms were documented as free text entries for each participant. Entries were reviewed and grouped together to remove variability in how symptoms were recorded, for instance 'back pain', 'spinal pain', and 'pain in back' were grouped together as 'back pain'. These symptoms were then grouped together into broader categories of similar symptoms.

Broader symptom categories were created to allow identification of trends of symptoms. This categorisation system was reviewed by five clinicians to ensure they accurately reflected the symptoms represented. Where there was disagreement on how to group symptoms, then the symptoms were not grouped together. The categories used were in keeping with categories

used in previous studies, to allow for comparison. Categorisation of symptoms is shown in Table 3.1.

Where more than one symptom was documented within one free text box, the individual symptoms were recorded with the associated start date reported by the participant. The same symptom reported multiple times was only counted once. Data was not collected on end dates of symptoms, and no specific data was collected on changes in symptom severity, therefore it was assumed that all symptoms continued from the given date of onset.

Where participants reported monoclonal gammopathy of undetermined significance (MGUS) or smouldering multiple myeloma (SMM) in free text, this was noted separately and not included in symptom counts. Positive diagnostic test results, e.g. abnormal serum free light chains, were noted separately as a diagnostic test rather than a symptom.

If the patient reported that myeloma was found during investigation or monitoring for another condition, e.g. 'found during…', and no other symptoms were recorded, this was recorded as an incidental finding of myeloma. Similarly, if participants documented that they were asymptomatic or words to that effect e.g. 'no symptoms' then this was also recorded as an incidental finding.

3.4.6.1 Comparison of symptoms to intervals

Symptoms were separated by comparing date of symptom onset to dates of consultation. Presenting symptoms were those that were present before first healthcare consultation. If there was no start date given for a symptom, it was not included in analysis of presenting symptoms. For each symptom category, the proportion of participants with these symptoms presenting through each pathway was calculated and compared.

Abnormal blood results – non-specific B12 deficiency Thrombocytopenia High PSA Low albumin Low total protein Neutropenia Unspecified abnormal blood result Raised ferritin Thrombocytosis	**Gastrointestinal (GI) symptoms** Abdominal pain Altered bowel habit Constipation Diarrhoea Dyspepsia Dysphagia Nausea Unspecified 'GI symptoms' Vomiting GI bleeding	**Other pain symptoms** Limb pain (arm) Chest pain (including rib pain) Face pain Foot pain General pain Limb pain (groin) Hand pain Limb pain (hip) Joint pain Joint pain (knee) Limb pain (leg) Limb pain Radicular pain Limb pain (shoulder)	**Systemic symptoms** Anorexia Fatigue Generally unwell Reduced exercise tolerance Low mood Sweats (including night sweats Weight gain Weight loss Falls Collapse/dizziness
Abnormal blood results – myeloma related Raised ESR Raised total protein Hypercalcaemia	**Infection** Cellulitis Lower respiratory infection 'recurrent' site not specified Upper respiratory infection UTI 'Viral' Fever		
Anaemia		**Renal** AKI AKI on CKD CKD	**Other symptoms** Atrial fibrillation Limb swelling Hypertension Itching Mouth ulcers/mucositis Pallor Palpitations Rash/skin problems Restless legs
Back pain Including neck pain			
Bleeding or thrombosis Bruising Epistaxis Gum bleeding Haematuria Haemoptysis PE or DVT	**Abnormal lumps** Chest swelling Clavicle lump Head lump Lower back lump Neck lump Unspecified lump	**Respiratory symptoms** Cough Hoarse voice Shortness of breath Abnormal chest x-ray	
Bone disease Fracture Lytic lesion(s) Plasmacytoma	**Neurological symptoms** Symptoms of spinal cord compression Carpal tunnel Confusion Headache Visual disturbance	**Urological symptoms** Nocturia Reduced urine output Urgency Urinary frequency Bladder outflow problems	

Table 3.1 : Categorisation of symptoms reported by participants within the TEAMM trial.
The categories used are shown in bold, with the individual symptoms included in each category below the broad category heading used to group them.
PE = pulmonary embolism; DVT = deep vein thrombosis; AKI = acute kidney injury; CKD = chronic kidney disease; ESR = erythrocyte sedimentation rate; GI = gastrointestinal; PSA = prostate specific antigen.

3.5 Results

3.5.1 Participant characteristics

In total, 977 participants were included. The demographic details for all participants are shown in Table 3.2.

Age	**Male**	**White British ethnicity**	**eGFR >50ml/min**	**ISS Stage 3**	**Planned high dose therapy**	**ECOG PS 0-2**	**Bone disease at presentation**
Median: 67 years *IQR:* 60-75 *Range*: 28-98	63%	87.5%	76%	30.5%	54%	93%	74%

Table 3.2: Demographics and participant characteristics for TEAMM trial participants.
Data shown for the 977 participants in the TEAMM trial. IQR for eGFR is not reported here, as eGFR was recorded categorically. IQR: interquartile range. ISS: International Staging System. ECOG PS: Eastern Cooperative Oncology Group (ECOG) performance status. Bone disease at presentation defined by radiological evidence of bone disease.

3.5.2 Pathway to diagnosis

Diagnostic pathways were available in 915 participants. The remaining patients had not recorded enough information to determine their diagnostic pathway.

From the 915 participants, 51% (468 participants) were diagnosed via presentation to their GP and then referral to haematology (termed here as the 'direct' pathway). 29% (269 participants) were diagnosed via acute services (termed the 'acute' pathway) and 20% (178 participants) were seen by a secondary care specialty other than haematology after being seen in primary care (termed 'other secondary care' pathway).

Table 3.3 shows the age, gender and ethnicity of those presenting via each pathway. There was no significant difference in the age of the patients presenting via each pathway (Kruskal-Wallis test $X^2(2)=5.927$, p=0.052). There was variation in the gender split for the pathways, with a higher proportion being female in the direct pathway compared to the acute pathway (Chi square, p=0.016). There was no significant difference between the proportion of female

participants in the ‘other secondary care’ pathway compared to either of the other pathways. There was a higher proportion of participants from ethnic backgrounds other than white British in the acute pathway compared with the direct pathway (Chi square, p=0.023).

Table 3.4 shows the range of secondary care specialties who saw participants in the ‘other secondary care’ pathway. The most common specialties were Trauma and Orthopaedics, Gastroenterology and GI/colorectal surgery and respiratory medicine.

	Acute pathway (n=269)	Direct pathway (n=468)	Other secondary care pathway (n=168)
Age (years) Median *IQR*	 67 *58-74*	 68 *61-75*	 66 *58-73*
Gender Male, n (%)	 181 (67.3%)	 271 (57.9%)	 119 (66.9%)
Ethnicity White British, n (%)	 224 (83.2%)	 419 (89.7%)	 260 (89.9%)

Table 3.3: Age and gender of participants seen via each pathway.
Data available for age and gender for all participants within each pathway. Median and interquartile range shown for age in years. Significant difference demonstrated between proportion of male participants in the direct pathway vs acute and other secondary care pathways (Chi square, p = 0.016), and in the proportion of patients who were not white British in the acute pathway vs acute pathway (Chi square, p=0.023)

Secondary care specialty	Number of participants	% of those in other secondary care pathway (n=178)	% overall (n=915)
Orthopaedics	35	19.7%	3.8%
Gastroenterology	25	14%	2.7%
Respiratory	21	11.8%	2.3%
Renal medicine	19	10.7%	2.1%
Oncology	16	9%	1.7%
Rheumatology	9	5.1%	1%
Urology	9	5.1%	1%
General medicine	8	4.5%	0.9%
Neurology & neurosurgery	7	3.9%	0.8%
Cardiology	6	3.4%	0.7%
ENT	5	2.8%	0.5%
GI surgery	4	2.2%	0.4%
Geriatrics	3	1.7%	0.3%
Endocrinology	3	1.7%	0.3%
General surgery	3	1.7%	0.3%
Cardiothoracic surgery	1	0.6%	0.1%
Dermatology	1	0.6%	0.1%
Gynaecology	1	0.6%	0.1%
Ophthalmology	1	0.6%	0.1%
Pain clinic	1	0.6%	0.1%

Table 3.4: Secondary care specialties where participants were seen in 'other secondary care' pathway
Table shows the number of participants reporting this specialty as first hospital department contact, the percentage of those in the 'other secondary care' pathway seeing this specialty (out of 178 participants), and the percentage of participants overall reporting seeing this specialty (of the 915 participants where pathway to diagnosis could be determined. ENT: Ear, Nose and Throat surgery; GI: gastrointestinal.

3.5.3 Markers of severity and end organ damage

Data available on end organ damage is shown in Table 3.5. At diagnosis, 10.2% of patients did not have end organ damage as defined by IMWG CRAB features. Bone disease was the most common end organ damage present at diagnosis, affecting 71% of participants. Lytic lesions were the most common form of bone disease reported, affecting 69.4% of those with bone disease and 48.7% of participants overall. The next most common bone complication was fracture, affecting 52.6% of those with bone disease, and 36.9% of participants overall.

	Overall		**Acute**		**Direct**		**Other secondary care**	
Hypercalcaemia	5.9%	45/763	8.1%	19/235	5.1%	18/354	3.9%	5/129
Renal impairment	11%	86/785	18.8%	45/239	4.9%	18/367	11.4%	15/132
Anaemia	51.1%	403/788	62.9%	151/240	43.4%	159/366	50.4%	67/133
Bone disease	71%	686/966	82.6%	219/265	65.3%	311/476	66.9%	119/178

Table 3.5: The number of participants reporting CRAB features at diagnosis.
Shown for all those with data available, and for those diagnosed via each pathway with data available for individual CRAB features. Percentage of participants with each feature recorded, with the number of those reporting the feature and with data available shown for each feature & pathway.

Comparing the pathways, there was no significant difference in the proportion of patients with hypercalcaemia (Chi square, $X^2(2)=3.421$, $p=0.181$). There was a higher rate of renal impairment in those with presenting via acute or 'other secondary care' pathways compared with those presenting through the direct pathway (Chi square, $X^2(2)= 29.795$, $p <0.001$). There was also a higher rate of anaemia in the acute pathway participants compared with the direct pathway (Chi square, $X^2(2)=22.024$, $p <0.001$), but no difference in the rate of anaemia in those seen in 'other secondary care' compared to either the acute pathway or the direct pathway. A higher proportion of those diagnosed via the acute pathway had bone disease compared to the direct pathway or the 'other secondary care' pathway (Chi square,

$X^2(2)=23.438$, $p<0.001$). There was no difference between the proportion of participants with bone disease comparing the direct and 'other secondary care' pathway.

The number of CRAB features reported per participant presenting via each pathway is shown in Table 3.6. Comparing by pathway to diagnosis, patients presenting via acute pathways were more likely to have two or more CRAB features present at diagnosis (Chi square, acute vs direct & acute vs 'other secondary care', $p<0.0001$).

Performance status and ISS by pathway to diagnosis are shown in Table 3.7. Those attending via acute pathways were more likely to have a poor performance status, and worse ISS, than those in the direct pathway or 'other secondary care' pathway (Chi square, $p<0.0001$).

	Overall		**Acute**		**Direct**		**Other secondary care**	
No CRAB features	10.2%	77/755	3.1%	7/229	14.5%	51/352	10.1%	13/129
One CRAB feature	49.7%	375/755	38.4%	88/229	55.4%	195/352	55.8%	72/129
Two CRAB features	31.9%	241/755	43.7%	100/229	25.6%	90/352	27.1%	35/129
Three CRAB features	6.9%	52/755	12.7%	29/229	3.7%	13/352	6.2%	8/129
Four CRAB features	1.3%	10/755	2.2%	5/229	0.9%	3/352	0.8%	1/129

Table 3.6: Number of CRAB features reported per participant, by route.
Shown as a percentage of those with data available for each all four CRAB features (hypercalcaemia, renal impairment, anaemia, bone disease), for all participants and by pathway. Number of those with data available is also shown.

		Overall		Acute		Direct		Other secondary care	
ECOG Performance status	0-2	93%	836/899	86.8%	231/266	96.3%	439/456	93.8%	166/177
	3-4	7%	63/899	13.2%	35/266	3.7%	17/456	6.2%	11/177
CRAB features present	0	10.2%	77/755	3.1%	7/229	14.5%	51/352	10.1%	13/129
	1	49.7%	375/755	38.4%	88/229	55.4%	195/352	55.8%	72/129
	≥2	40.1%	303/755	58.5%	134/229	30.1%	106/352	34.1%	44/129
ISS	1	26.6%	206/775	19%	42/221	29.8%	117/393	29.2%	47/161
	2	44%	341/775	39.4%	87/221	49.1%	193/393	37.9%	61/161
	3	29.4%	228/775	41.6%	92/221	21.1%	83/393	32.9%	53/161

Table 3.7: Markers of severity of disease by pathway to diagnosis.
ECOG (Eastern Cooperative Oncology Group) performance status, grouped into 0-2 and 3-4. Number of CRAB (hypercalcaemia, renal impairment, anaemia, bone disease) features of end organ damage shown, grouped into no features, one feature and 2 or more features. ISS = International Staging System score. Percentage, number per category, and number with data available shown for each marker of severity by pathway to diagnosis.

3.5.4 Diagnostic intervals

The length of time from symptom onset to presentation and diagnosis is shown in Table 3.8. Time from first consultation to haematology consultation is also shown.

The median number of days from symptom onset to haematology review was 70 days. Patients who were diagnosed via the 'direct' pathway had the same median number of days from initial symptom onset to haematology review as those patients diagnosed via the 'acute' pathway. Those who were diagnosed via the 'other secondary care' pathway had a significantly longer pathway than either the direct or acute pathways, with a median of 120 days from initial symptom onset to haematology review (Kruskal-Wallis test, $p<0.0001$).

Overall, the median patient interval, from symptom onset to first consultation, was 3 days (IQR 0-54). There was no significant difference in the reported patient interval between the different pathways to diagnosis (median 0 days acute pathway vs 6 days direct pathway vs 8 days 'other secondary care' pathway, Kruskal-Wallis, $p=0.065$).

The median diagnostic interval, from first consultation to diagnosis, was 42 days. There was a significant difference in the length of the diagnostic interval between different pathways. Those diagnosed through 'other secondary care' services had a longer diagnostic interval than those diagnosed via the acute pathway or the direct pathway (median 35 days acute pathway & 33 days direct pathway vs 102 days 'other secondary care' pathway, Kruskal-Wallis, 'other secondary care' compared to acute and 'other secondary care' compared to direct, $p < 0.0001$).

To assess intra-hospital delay by pathway, the time from first consultation in secondary care to haematology review was assessed. Comparing the number of days from initial hospital contact to haematology review, those who were diagnosed via 'other secondary care' waited longer than those diagnosed via the 'acute' pathway (median 30 days vs 9 days, Kruskal-Wallis test, 'other secondary care' vs acute, $p<0.0001$). Despite this, in those diagnosed via the acute pathway 25% of patients experienced an intra-hospital interval from first hospital contact to haematology consultation of 30 days or more.

	Overall	Acute	Direct route	Other secondary care
Total interval: Days from 1st symptom to haematology review	70 (29-174) (N=870)	59 (19-138) (N=265)	59 (25-161) (N=430)	120 (69-268) (N=175)
Patient interval: Days from 1st symptom to first consultation	3 (0-54) (N=732)	0 (0-37) (N=239)	6 (0-59) (N=352)	8 (0-71) (N=141)
Diagnostic interval: Days from first consultation to haematology review	42 (15-113) (N=803)	35 (8-100) (N=265)	33 (13-88) (N=384)	102 (47-181) (N=155)
Intra-hospital interval: Days from 1st hospital visit to haematology review	N/A	9 (2-30) (N=262)	N/A	30 (9-60) (N=173)

Table 3.8: Length of pathway intervals.
Shown in days – median number of days, with IQR in brackets. Intra-hospital interval is not displayed here for total participants or direct pathway as this is not applicable to the direct pathway.
Kruskal-Wallis test: p value <0.0001 for total interval comparing 'other secondary care' vs direct & acute pathways; p 0.065 comparing patient interval direct vs acute vs 'other secondary care'; p<0.0001 comparing diagnostic interval for 'other secondary care' vs acute and direct pathways; p<0.0001 comparing intra-hospital interval for acute pathway vs 'other secondary care' pathway

3.5.5 GP attendances prior to acute attendance

Figure 3.2 shows the number of recalled and self-reported GP consultations per participant.

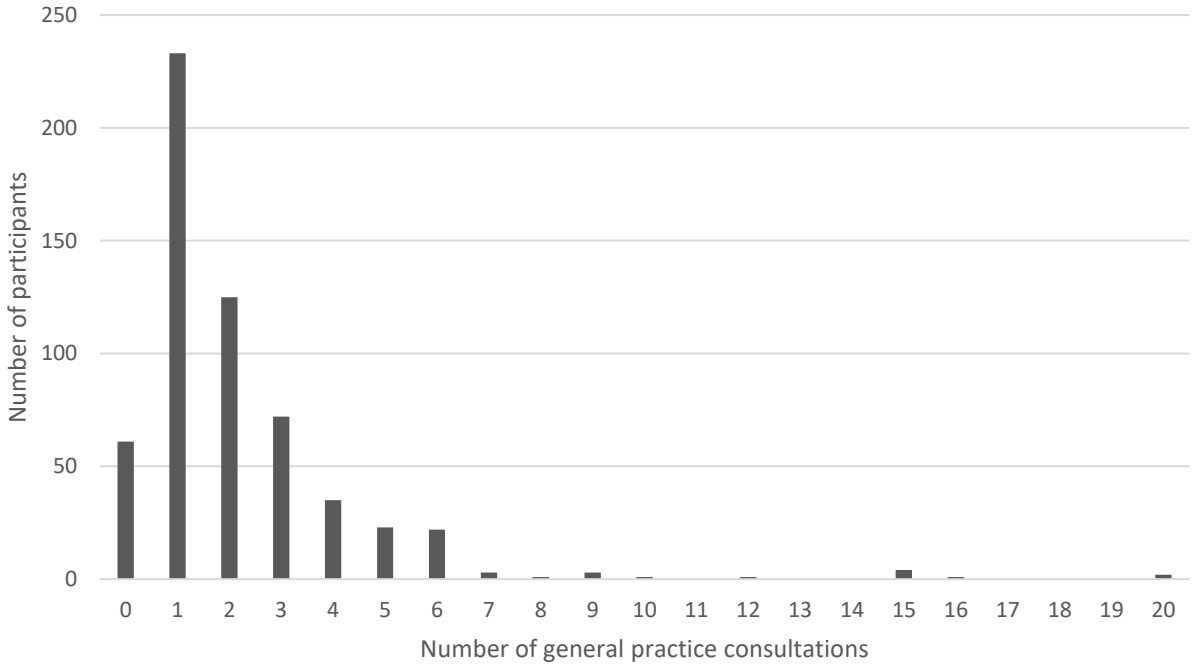


Figure 3.2: Histogram of number of general practice consultations reported by participants.
587 participants recorded data for number of general practice (GP) consultations. The reported number of consultations ranged from 0 to 20.

Of those that were diagnosed via the acute pathway, 72.5% (195) had seen their GP prior to consulting acute services, or on the same day. The median length of time from GP to acute presentation was 18 days (IQR 0-78 days). 25.6% of acute pathway patients who saw their GP did so for the first time on the same day as attending acute services. The length of time from initial consultation to presentation in acute services is shown in Figure 3.3. As shown in Table 3.9, there was no difference in age distribution, gender or ethnicity between patients who did not see GP before acute services and those who did see their GP prior to acute services. There was also no difference in the number of CRAB features (Mann-Whitney U test, p=0.258), ECOG performance status (Mann-Whitney U test, p=0.317) or ISS score (Mann-Whitney U test p=0.972) between these two groups.

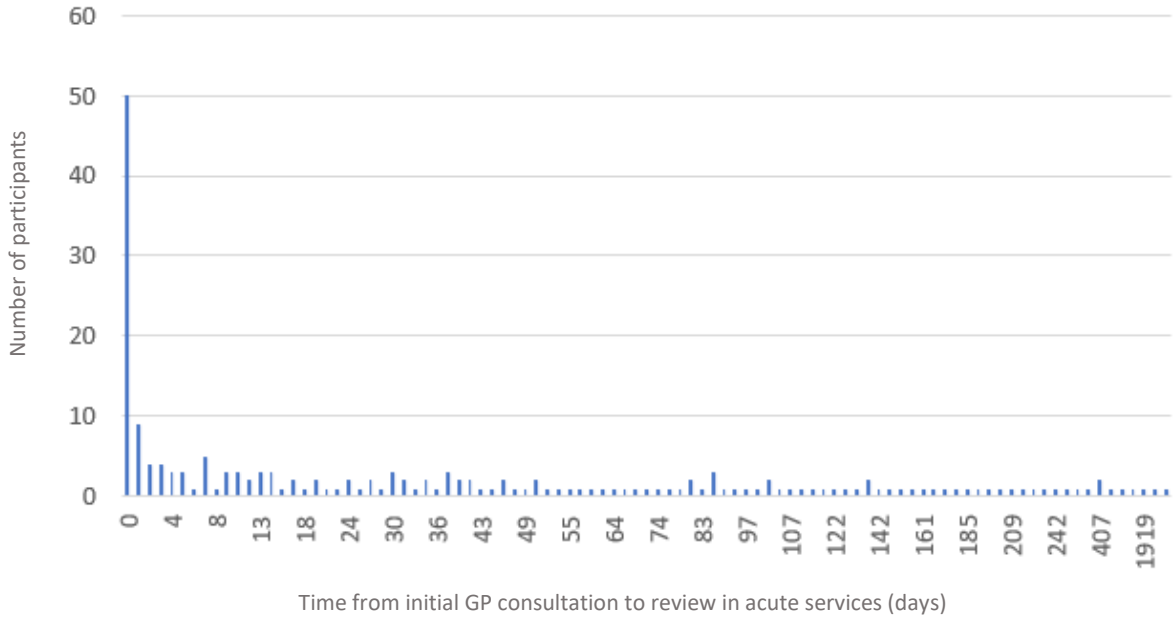


Figure 3.3: Time from initial GP consultation to acute services in participants diagnosed via acute pathway
For those 195 participants diagnosed via the acute pathway who had seen their GP prior to acute consultation, time from initial GP consultation to presentation in acute services (days). Note- x axis is not linear.

	Didn't see GP before acute services (n=74)	**Saw GP prior to acute services** (n=195)
Age (years) Median *IQR*	 68 *60-78*	 67 *57-74*
Gender Male, n (%)	 49 (66.2%)	 132 (67.7%)
Ethnicity White British, n (%)	 59 (79.7%)	 165 (84.6%)

Table 3.9: Age, gender and ethnicity of those presenting through acute services who did or did not consult GP prior to acute services.
For the 269 participants diagnosed through acute services, demographic details for those who did and did not report seeing their GP prior to acute services. No significant differences seen between the two groups (Age: Mann-Whitney U, p=0.08; Gender: Chi square, p=0.818; Ethnicity: Chi square, p=0.338)

3.5.6 Patient reported symptoms

Of the 977 total participants, 767 (78.5%) reported symptoms with a date of onset prior to first healthcare consultation, therefore classified here as 'presenting symptoms'. In total, 1217 individual presenting symptoms were reported by these 767 participants. Three hundred and nine patients reported more than one symptom at initial presentation. The median number of symptoms at initial presentation was 1, with a range from 0 to 6, as shown in in Figure 3.4.

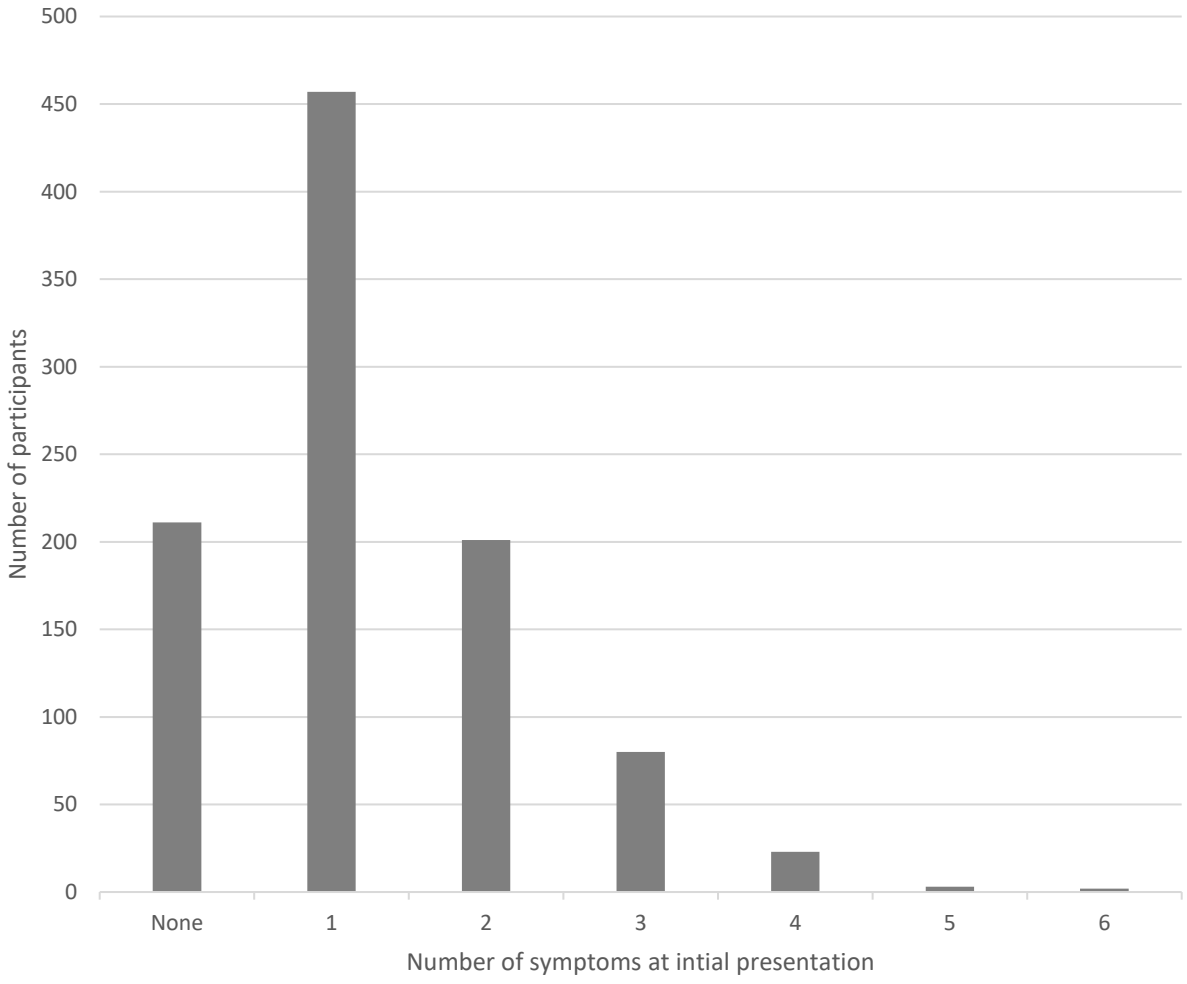


Figure 3.4: Histogram of number of symptoms reported with a start date prior to initial presentation. Of the 977 total participants, the number of symptoms that were recorded per participant with a start date prior to initial consultation. 210 participants reported no symptoms that started prior to initial consultation, however this includes participants who reported diagnoses of pre-cursor disease, diagnostic investigations or symptoms without associated dates.

A breakdown of those that did not document presenting symptoms is shown in Figure 3.5. Thirty-two participants (3.3% of all participants) specified that their diagnosis was an incidental finding. Twenty-five participants reported a diagnosis of MGUS or SMM and did not provide any information regarding other symptoms - participants with MGUS/SMM will be discussed further in Chapter 4. Symptoms beginning after initial consultation are reported in Section 3.5.8.

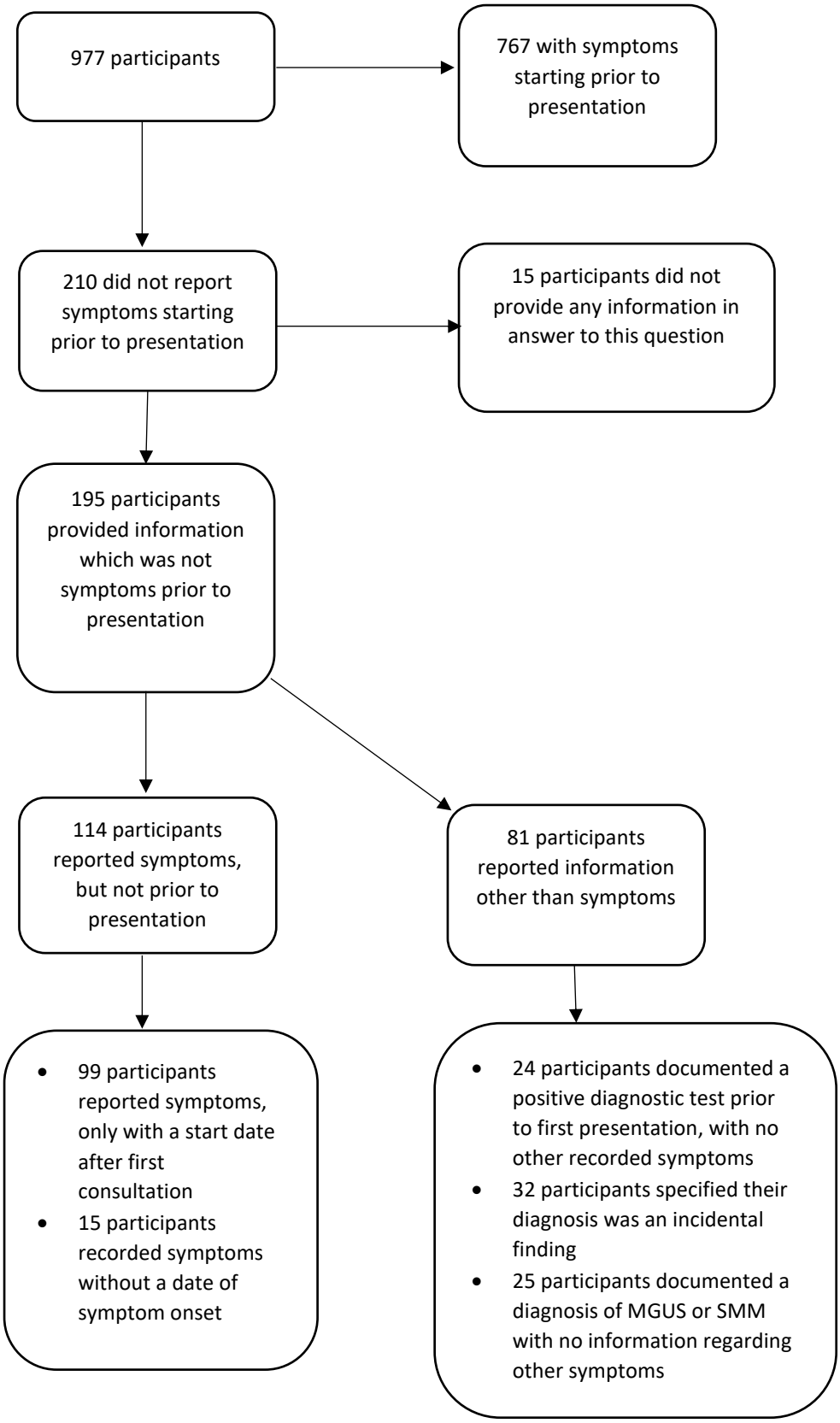


Figure 3.5: Diagram outlining participants who did not provide symptoms prior to presentation.
This refers to data recorded by participants in answer to 'When did the patient first notice bodily changes and/or symptoms that they attribute to the myeloma?'. Some of the 114 participants reporting symptoms after initial start date and the 767 participants reporting symptoms prior to presentation also reported diagnostic tests, or diagnoses of pre-cursor disease. MGUS: monoclonal gammopathy of undetermined significance; SMM: smouldering multiple myeloma.

Comparing by pathway to diagnosis, there was a higher proportion of participants who did not report symptoms at presentation in the direct pathway than in the acute or 'other secondary care' pathways (direct: 120 participants (25.6%) vs acute: 35 participants (13%) and 'other secondary care': 14 participants (8.3%), Chi square p <0.001). There was no significant difference between the proportion of participants who reported no symptoms in the acute pathway and 'other secondary care' pathway.

3.5.7 Presenting symptoms

The presenting symptoms are shown in Table 3.10. There were 125 different symptoms reported at presentation by participants, after exclusion of diagnostic test results, MGUS or SMM diagnoses, or incidental findings. The most common individual symptom was back pain, affecting 39.3% of those who reported symptoms and 30.8% of participants overall.

51 symptoms were reported at presentation by a single participant. These included symptoms such as low mood, weight gain, jaundice, itching and palpitations.

These reported symptoms were combined into categories. The detailed symptoms included in each category are showed in Table 3.1. The number of participants reporting a symptom in these categories at presentation is shown in Table 3.11.

3.5.8 All symptoms reported prior to diagnosis

All symptoms reported by the participants, irrespective of start date, are shown in Table 3.12 to outline the range of symptoms experienced by the time patients received their diagnosis.

Looking specifically at 'bone pain', 34 of the reported symptoms specified bone pain or bony pain.

Many patients reported symptoms that started after initial presentation. Symptoms starting after initial consultation were reported by 277 participants.

Symptoms that started between primary care consultation and consultation in acute services are shown in Table 3.13. Symptoms that started between review in acute services and haematology review, or between primary care and haematology review for the 'direct' and 'other secondary care' pathway, are shown in Table 3.14.

Some participants reported symptoms that started after the date of first haematology consultation. These represent symptoms that developed after haematology review but before recruitment to the study. These symptoms, shown in Table 3.15, demonstrate that some patients' symptoms are still increasing during specialist investigation and around treatment initiation.

Presenting symptom	Number of participants	Presenting symptom	Number of participants
Unspecified back pain	245	Carpal tunnel	2
Fatigue	121	Fracture arm	2
Chest pain	80	Unilateral knee swelling	2
Weight loss	71	Hoarse voice	2
Unspecified anaemia	65	Acute lower back pain	1
General pain	59	Buttock & lower back pain	1
Shortness of breath	49	Neck stiffness	1
Lower back pain	40	Neck & lower back pain	1
Hip pain	40	Low mood	1
Shoulder pain	26	Weight gain	1
Abdominal pain	26	Radicular pain	1
Leg pain	19	Face pain	1
Hypercalcaemia	18	Foot pain	1
Lower respiratory tract infection	17	Hand pain	1
Anorexia	16	Limb pain	1
Generally unwell	14	Normocytic anaemia	1
Spinal cord compression symptoms	13	Abnormal Chest x-ray	1
Night sweats	12	Hoarse voice	2
Unspecified renal problem	12	Jaundice	1
Cough	11	Unspecified gastrointestinal symptom	1
Headache	10	Cellulitis	1
Nausea	10	Tooth infection	1
Vomiting	10	Upper respiratory tract infection	1
Limb swelling	8	Viral infection	1
Epistaxis	8	Fracture shoulder	1
Collapse/dizziness	7	Fracture thumb	1
Reduced exercise tolerance	7	B12 deficiency	1
Raised total protein	7	High PSA	1
Abnormal blood results (not specified)	7	Hyperkalaemia	1
Acute kidney injury	7	Hypernatraemia	1
Neck pain	6	Leukopenia	1
Recurrent unspecified infection	6	Low albumin	1
Recurrent lower respiratory tract infection	6	Low total protein	1
Fracture (not specified)	6	Pancytopenia	1
Arm pain	5	Raised ferritin	1
Joint pain	5	Thrombocytopaenia	1
Constipation	5	Thrombocytosis	1
Visual disturbance	5	Chronic kidney disease	1
Upper back pain	4	Proteinuria	1
Knee pain	4	Atrial fibrillation	1
Groin pain	4	Dry skin	1
Recurrent urinary tract infection	4	Hypertension	1
Raised Erythrocyte sedimentation rate	4	Itching	1
Fracture vertebrae	4	Mucositis	1
Lytic lesions	4	Pallor	1
Falls	3	Palpitations	1
Macrocytic anaemia	3	Rash (unspecified)	1
Fever	3	Rash (vasculitic)	1
Confusion	3	Gum bleeding	1
Fracture humerus	3	Haemoptysis	1
Fracture rib	3	Pulmonary embolism	1
Neutropenia	3	Chest plasmacytoma	1
Bruising	3	Chest swelling	1
Haematuria	3	Clavicle lump	1
Urinary frequency	3	Head lump	1
Buttock pain	2	Lower back lump	1
Generally unwell	2	Neck lump	1
Sweats	2	Neck swelling	1
Altered bowel habit	2	Unspecified lump	1
Diarrhoea	2	Nocturia	1
Dyspepsia	2	Reduced urine output	1
Gastrointestinal bleeding	2	Urgency	1
Urinary tract infection	2		

Table 3.10: Presenting symptoms reported in the TEAMM trial.
Shows the number of participants who reported each symptom prior to the date of first consultation/healthcare contact.

Symptom categories	Total number of presenting symptoms in this category	Number of participants reporting a symptom in this category
Back pain	301	301
Other pain *(excluding back pain)*	247	234
Systemic symptoms	257	207
Anaemia	68	68
Respiratory symptoms	63	59
Gastrointestinal symptoms	61	53
Infection	42	42
Neurological symptoms	33	32
Abnormal blood results (suggestive of myeloma)	29	29
Other abnormal blood results	21	21
Bone disease & fracture	23	23
Renal problems	21	21
Other symptoms	19	19
Bleeding/thrombosis	17	16
Lumps & bumps	8	8
Urological symptoms	6	6

Table 3.11: Categories of presenting symptoms for TEAMM participants
The first results column shows the number of symptoms starting before first healthcare contact belonging to each category. The second results column shows the number of participants who reported a presenting symptom in the symptom category. Participants could report more than one symptom in a symptom category.

Of the 113 participants who reported anaemia as a symptom at any point in the pathway, 86 had a haemoglobin result available. 56 (65.1%) met the IMWG criteria for anaemia, 30 (34.9%) did not. Of the 46 participants who reported renal symptoms at any point in the pathway, 39 had a creatinine result available. 18 (46.2%) met the IMWG criteria for renal impairment, 21 (53.8%) did not. Of the 34 participants who reported hypercalcaemia as a symptom, 28 had a calcium result available. 8 (28.6%) met the IMWG criteria for hypercalcaemia, 20 (71.4%) did not.

Symptom categories	Times a symptom was reported in this category	Number of participants reporting a symptom in this category
Back pain	364	364
Other pain (excluding back pain)	325	298
Systemic symptoms	335	267
Anaemia	113	113
Gastrointestinal symptoms	86	74
Respiratory symptoms	78	74
Infection	59	54
Neurological symptoms	54	53
Abnormal blood results suggestive of myeloma	51	51
Renal	46	46
Other abnormal blood results	32	32
Bone disease	45	42
Bleeding/thrombosis	25	24
Other symptoms	23	23
Abnormal lump	12	12
Urological symptoms	8	8

Table 3.12: Categories of symptoms reported by TEAMM participants, at any point in diagnostic pathway.
881 participants reported symptoms. Participants could report symptoms in more than one category, and more than one symptom in each category. First column shows the number of times that a symptom in the category was recorded. Second column shows the number of participants that reported at least one symptom in each category.

Symptom categories	Number of symptoms reported in this category	Number of participants with a new symptom
Systemic symptoms	19	16
Other pain	14	13
Back pain	11	11
Gastrointestinal symptoms	10	9
Neurological symptoms	6	6
Abnormal blood test results suggestive of myeloma	5	5
Bone disease	4	4
Renal	4	4
Bleeding/thrombosis	3	3
Infection	3	2
Respiratory symptoms	3	3
Anaemia	2	2
Abnormal lumps	1	1
Urological symptoms	1	1

Table 3.13: Categories of symptoms starting between GP consultation and consultation in acute services.
For the 195 participants diagnosed via the acute pathway with a prior GP consultation, symptoms reported with a start date between date of GP consultation and date of consultation in acute services. The number of symptoms meeting this criterion, reported in each category is shown. No symptoms in 'other abnormal blood test results' met this criterion.

Symptom categories	Number of symptoms reported in this category	Number of participants reporting a symptom in this category
Other pain	45	39
Systemic symptoms	31	26
Back pain	28	28
Anaemia	22	22
Abnormal blood test results suggestive of myeloma	16	16
Renal	15	15
Bone disease	11	10
Gastrointestinal symptoms	10	8
Neurological symptoms	10	10
Respiratory symptoms	10	10
Other abnormal blood test results	9	9
Infection	9	9
Bleeding/thrombosis	3	3
Other symptoms	2	2
Abnormal lumps	1	1
Urological symptoms	1	1

Table 3.14: Symptoms with an onset while awaiting haematology review.
For 881 participants who recorded symptoms at any point within the pathway. The number of symptoms per category that were reported as starting after review in acute services (for 'acute' participants) or after GP review (for 'direct' or 'other secondary care' participants) but before the date of haematology review

Symptom categories	Number of symptoms reported in this category	Number of participants reporting a symptom in this category
Systemic symptoms	21	17
Back pain	20	20
Anaemia	17	17
Other pain	15	14
Bone disease	5	5
Gastrointestinal symptoms	4	3
Infection	4	4
Neurological symptoms	3	3
Renal	3	3
Bleeding/thrombosis	2	2
Respiratory symptoms	2	2
Abnormal blood tests suggestive of myeloma	1	1
Other abnormal blood tests	1	1
Other symptoms	1	1

Table 3.15: Symptoms which started after haematology review.
For participants diagnosed via any pathway, of the 881 participants who reported symptoms at any point within the pathway. Symptoms with a reported start date after that of haematology review. Number of symptoms per category recorded.

3.5.9 Number of symptoms per participant by pathway

The number of symptoms reported per participant at presentation for each of the three pathways to diagnosis was compared. There was a significant difference in the number of symptoms per participant between the pathways (Kruskal-Wallis, $\chi^2(2) = 13.477$, p 0.001). There was a significant difference between the direct pathway compared with the acute pathway, with a higher number of symptoms in the acute pathway (pairwise comparison, p=0.006) and between the direct pathway compared with the 'other secondary care' pathway, with a higher number of symptoms in the 'other secondary care' pathway (pairwise comparison, p=0.012). There was no difference between the number of presenting symptoms per participant when comparing the acute pathway with the 'other secondary care' pathway.

Comparing the number of symptoms reported by each participant by the time of recruitment to the trial (the total number of symptoms reported), there were ongoing differences between the pathways, with a significant difference between the number of symptoms per participant (Kruskal-Wallis, $\chi^2(2)=25.176$, p <0.005). The total number of symptoms per participant was significantly different when comparing the direct pathway and the acute pathway, with a higher number of symptoms in the acute pathway (pairwise comparison, p <0.001), and when comparing the direct pathway with the 'other secondary care' pathway, with a higher number of symptoms in the 'other secondary care' pathway (pairwise comparison, p=0.006). There was no difference in the number of symptoms per participant between the acute pathway and the 'other secondary care' pathway.

3.5.10 Symptoms by pathway to diagnosis

The number of symptoms reported in each category by the pathway that patients took to reach their diagnosis is shown in Table 3.16.

There was some variation in the proportion of patients reporting some symptom categories who were diagnosed via each pathway. While most symptom categories were distributed across the three pathways in a way that was not significantly different to that expected, there were two categories (with enough participants to allow comparison) where there was a significant difference. The proportion of patients with neurological symptoms diagnosed via acute services was higher than expected, with a statistically significant difference (percentage with neurological symptoms via each pathway compared to overall participants via each pathway, Chi square, p= 0.012). There was also a significant difference in patients presenting with bone disease, with a higher proportion presenting through acute services (percentage with bone disease via each pathway compared to overall participants via each pathway, Chi square p= 0.013).

Detailed symptoms for those participants presenting through 'other secondary care' are shown in Table 3.17, with symptoms grouped by secondary care specialty of first presentation.

Symptom category *Total*	**Acute** *29.4%*	**Direct** *51.1%*	**Other secondary care** *19.5%*
Back pain (n=292)	32.9%	49.3%	17.8%
Systemic symptoms (n=195)	27.7%	48.7%	23.6%
Other pain (excluding back pain) (n=223)	29.1%	48%	22.9%
Anaemia (n=64)	25%	59.4%	15.6%
Respiratory symptoms (n=58)	27.6%	44.8%	27.6%
Gastrointestinal symptoms (n=52)	44.2%	38.5%	17.3%
Infection (n=41)	39%	41.5%	19.5%
Neurological symptoms* (n=33)	43.8%	25%	31.3%
Abnormal blood results, suggestive of myeloma (n=29)	41.4%	58.6%	0%
Bone disease* (n=23)	56.5%	26.1%	17.4%
Other abnormal blood results (n=20)	15%	75%	10%
Renal (n=20)	40%	15%	45%
Other symptoms (n=17)	35.3%	35.3%	29.4%
Bleeding/thrombosis (n=15)	26.7%	53.3%	20%
Abnormal lump (n=8)	12.5%	62.5%	25%
Urological symptoms (n=6)	50%	16.7%	33.3%

Table 3.16: The pathway taken by participants with each category of symptoms.
Of those with an identifiable pathway, the percentage of participants diagnosed via each pathway is shown below the column headings, for comparison.
For each symptom category, only those with a symptom in that category, and for whom a pathway to diagnosis could be determined are included. For each symptom category, the percentage of participant reporting this symptom who were diagnosed via each pathway is shown.
*Categories where the percentage diagnosed via each pathway was significantly different from that expected are marked with *.*

Orthopaedics (35 participants)	N
Back pain	18
Unspecified pain	3
Hip pain	3
Spinal cord compression symptoms	2
Arm pain	2
Shoulder pain	2
Bone disease	1
Carpal tunnel syndrome	1
Chest pain	1
Foot pain	1
Leg pain	1
Fatigue	1
Weight loss	1
Gastroenterology (25 participants)	**N**
Anaemia	6
Weight loss	6
Back pain	5
Shortness of breath	5
Fatigue	4
Abdominal pain	3
Anorexia	3
Chest pain	2
Unspecified pain	2
Altered bowel habit	1
Night sweats	1
Diarrhoea	1
Nausea	1
Hoarseness	1
Renal	1
Cough	1
Pain clinic (1 participant)	**N**
Back pain	1

Respiratory (21 participants)	N
Chest pain	7
Back pain	5
Fatigue	3
Weight loss	3
Bone disease	2
Recurrent LRTI	2
Unspecified pain	2
Constipation	1
LRTI	1
Recurrent infection	1
Spinal cord compression symptoms	1
Anaemia	1
Hip pain	1
Falls	1
Shortness of breath	1
Renal medicine (19 participants)	**N**
Back pain	7
Renal	7
Fatigue	3
Weight loss	2
Night sweats	1
Urinary frequency	1
Shoulder pain	1
Shortness of breath	1
Generally unwell	1
Endocrinology (3 participants)	**N**
Headache	1
Limb swelling	1
Collapse/dizziness	1
Fatigue	1

Oncology (16 participants)	N
Back pain	6
Hip pain	4
Chest pain	2
Leg pain	2
Shoulder pain	2
Fatigue	2
Jaundice	1
LRTI	1
Unspecified pain	1
Leucopenia	1
Renal	1
Cough	1
Night sweats	1
Weight loss	1
Rheumatology (9 participants)	**N**
Back pain	3
Chest pain	2
Epistaxis	1
Bone disease	1
Limb swelling	1
Rash (vasculitic)	1
Fatigue	1
Sweats	1
Neurology & neurosurgery (7 participants)	**N**
Back pain	1
Recurrent infection	1
Night sweats	1
Unspecified pain	1
Leg pain	1
Fatigue	1

Urology (9 participants)	N
Unspecified pain	2
Fatigue	2
Back pain	1
Haematuria	1
Abdominal pain	1
Recurrent UTI	1
Groin pain	1
Hip pain	1
Shoulder pain	1
Night sweats	1
Weight loss	1
Urgency	1
General medicine (8 participants)	**N**
Fatigue	4
Shortness of breath	2
Chest pain	2
Unspecified pain	1
Cough	1
Back pain	1
Headache	1
Night sweats	1
Weight loss	1
ENT (5 participants)	**N**
Back pain	2
Hoarse voice	1
Shortness of breath	1
Clavicle lump	1
Spinal cord compression symptoms	1
Chest pain	1
Face pain	1

Cardiology (6 participants)	N
Shortness of breath	3
Fatigue	3
Anaemia	1
Spinal cord compression symptoms	1
Palpitations	1
Chest pain	1
GI surgery (4 participants)	**N**
Back pain	2
Weight loss	2
Thrombocytosis	1
Anaemia	1
Abdominal pain	1
Carpal tunnel	1
Fatigue	1
Geriatrics (3 participants)	**N**
Epistaxis	1
Unspecified pain	1
Shortness of breath	1
Fatigue	1
Weight loss	1
General surgery (3 participants)	**N**
Anaemia	1
LRTI	1
Gynaecology (1 participant)	**N**
Fatigue	1
Cardiothoracic surgery (1 participant)	**N**
Chest plasmacytoma	1
Dermatology (1 participant)	**N**
Hand pain	1
Unilateral knee swelling	1
Ophthalmology (1 participant)	**N**
Visual disturbance	1

<u>Table 3.17:</u> Presenting symptoms in those attending 'other secondary care' specialties.
N= number of participants reporting each symptom.
LRTI = lower respiratory tract infection; UTI = urinary tract infection; GI = gastrointestinal; ENT = Ear, Nose and Throat surgery.

3.6 Discussion

3.6.1 Summary of results

The key findings demonstrated in this chapter are:

- Diagnostic pathway:
    - Most patients were diagnosed by direct referral from primary care to haematology (51%), with 29% diagnosed via acute services and 20% seeing a non-haematology secondary care specialty
    - Many different secondary care specialties were involved in the diagnostic pathway, including medical and surgical specialties
    - Comparing the different pathways to diagnosis, there was no difference in the length of the patient interval
- Pathway intervals:
    - The total length of the diagnostic pathway was the same for those seen in acute services and those referred from primary care to haematology, but longer for those seen in non-haematology secondary care services
    - Those seen in non-haematology secondary care specialties had a prolonged interval between seeing a specialty and haematology consultation
- Participants diagnosed via acute services:
    - Those presenting through acute services were more likely to have renal impairment, anaemia and bone disease
    - Despite not having a longer diagnostic pathway, those patients diagnosed through acute services were more likely to have two or more markers of end organ damage, to have a poor performance status, and to have worse ISS score, indicating poorer prognosis, at diagnosis

    - A quarter of patients seen in acute services had over a one-month interval from seeing acute services to haematology consultation
    - Most patients seen in acute services had previously been seen in primary care
- Patient symptoms:
    - Patients experienced a wide range of symptoms
    - The most common symptoms were back pain, other pain (excluding back pain) and systemic symptoms
    - Patients often did not report their pain symptoms as 'bone pain'
- How symptoms relate to the diagnostic pathway:
    - Many patients develop further symptom during the diagnostic pathway, increasing their symptom burden
    - Those seen in acute services or in non-haematology secondary care reported more symptoms
    - Those patients with neurological symptoms or bone disease were more likely to be diagnosed via acute services

3.6.2 The TEAMM cohort

The cohort of participants included in TEAMM differs from the general cohort of patients diagnosed with multiple myeloma nationally. In participants recruited to TEAMM, the median age of participants was 67 years, with an interquartile range from 60 to 75 years, demonstrating that this was a relatively young group of patients compared to the age distribution of patients nationally, where the median age at diagnosis is over 70 years old. (189)

The participants had a relatively good performance status, with only 7% having an ECOG performance status 3 or lower. While this may be partly due to the inclusion criteria which specified that patients must be planned for active treatment, this may also reflect the requirements of the study procedures for TEAMM, where participants committed to several activities such as completion of patient diaries, as well as several nasal swabs and stool cultures over a 4-month period.

These differences should be considered when reviewing the results, as this cohort may be a younger, healthier population than the average patient diagnosed with myeloma.

In the results discussed here, markers of end organ damage, performance status and ISS stage at diagnosis have been used to judge severity. Other common outcome measures such as survival have not been assessed for several reasons. Follow-up data is only available for the TEAMM cohort for 12 months so far, and the survival in the TEAMM cohort is relatively good compared to the expected survival of myeloma populations in general, leading to a relatively low mortality rate. As the mortality rate is low, this limits comparisons in survival data comparing subgroups of the cohort, for instance by pathway, due to the small number of events. When comparing survival to total interval, this could be affected by lead time bias. This bias is removed by using a severity marker that is measured at the time of diagnosis.

3.6.3 Diagnostic pathway

As expected, the majority of participants were diagnosed through the 'direct' pathway, first consulting their GP and then seeing haematology as their first point of contact within secondary care. This is the pathway to diagnosis that most services are based around in the NHS, with the expectation that the majority of patients initially present to their GP with new health concerns and then are referred to the appropriate specialty if needed.

The proportion presenting via acute services in the TEAMM cohort was lower than the national rate of emergency presentation (29% vs 34%). This may be related to the differences in the TEAMM population compared to the general myeloma population discussed above. Previous research has suggested that emergency presentation in other malignancies is more likely in older patients – the younger age range of the TEAMM population may explain the lower than expected percentage diagnosed via acute services.

Twenty percent of participants reported seeing a non-haematology secondary care specialty as their first point of hospital contact. It is not surprising that many patients were seen by Trauma and Orthopaedics, as patients present with bone disease; similarly, presentation via renal medicine may be expected from myeloma-related renal disease. As these specialties see patients with common complications of myeloma, it may be that they have a higher index of suspicion than other specialties, and are more likely to request testing for myeloma. The wide range of specialties involved in these patients highlights that education to improve recognition of myeloma needs to involve many secondary care specialties as well as primary care.

There were 67 participants in this trial where the diagnostic pathway could not be determined. This may reflect the phrasing of the questions asked at recruitment. The question '*Which hospital department was the patient first seen in (includes A&E)?*' was answered by some patients with departments such as 'outpatients' or 'nuclear medicine', or with a general hospital name rather than a department.

There was also an element of ambiguity when assessing which secondary care specialties were involved. Participants reporting 'oncology/haematology' as the first hospital department they were seen in were recorded as following the 'direct' pathway if the date of

first consultation with a haematologist matched the date of first hospital consultation. Participants may have been seen by haematology in a department signposted as oncology due to the common practice of co-locating haematology and oncology outpatient and inpatient services (190) for example in Macmillan centres.(191) If oncology without further comment was reported as the first department seen, or date of first hospital consultation and first haematology consultation differed, then this was counted as initial assessment by oncology. While this may exclude some patients seen by haematologists within a combined haematology/oncology location from the 'direct' pathway, it was important not to discount that some patients may have been referred to oncology by their GP, and to prevent missing data caused by variations in local practice.

3.6.3.1 Pathway intervals

The patient interval reported in this cohort was short, at a median of only 3 days. This is shorter than the patient interval reported in previous studies, with a patient interval of 13.5 days reported by Lyratzopoulos et al (62) and 31 days reported by Howell et al (38). The overall length of pathway reported here is also shorter that that reported in previous studies, for example the study by Neal et al that reported a median time to diagnosis of 156 days,(66) and Howell et al who found a median time to diagnosis of 163 days (38).

While this difference may be due to difference in the study populations, there are other potential sources of bias. This study used patient reported dates of symptom onset to calculate pathway intervals. This may introduce bias as retrospective recollection of dates introduces recall bias. Leiva et al (2017) demonstrated that intervals calculated using patient reported dates of symptom onset have poor correlation to intervals calculated for the same patients using either primary or secondary care data.(192) As intervals calculated from

different data sources are likely to vary, it is therefore important to compare wherever possible between studies that have used methodology involving similar data sources. Howell et al collected patient reported data, (38) however Lyratzopoulos used primary care records.(62)

When comparing the intervals reported here to those from previous research, the intervals discussed here for total pathway and diagnostic interval will be shorter, as date of first haematology review was used as a surrogate for date of diagnosis. Recommended definitions for date of diagnosis use the date of biopsy that confirmed histological diagnosis.(47) For myeloma, this will occur after initial specialist review. The decision to use date of haematology review rather than date of randomisation was made there was a 28-day flexibility (14 days pre- and post- treatment initiation) that was allowed in the recruitment process that means a precise date of treatment initiation could not be assumed for the participants. As haematology consultation was used rather than histological diagnosis, the intervals calculated here are therefore likely to be an underestimate of the true diagnostic interval and total interval. While this may affect comparison to previous studies, there is no reason to expect a significant variation between the pathways in this analysis (direct vs acute vs 'other secondary care'), therefore comparisons between the pathways remain valid.

There were significant differences in the overall pathway length, with those diagnosed via non-haematology secondary specialities experiencing a longer pathway compared to those diagnosed via direct or acute pathways. The diagnostic interval was significantly longer in participants diagnosed via this pathway compared with the others.

This seems to be largely related to intra-hospital delay. When comparing those diagnosed via acute services with those diagnosed via other secondary care specialties, those seeing other secondary care specialties had a significantly longer intra-hospital delay. Potential reasons for this difference include system factors such as referral pathways.

In the National Health Service, delays may be caused by referral back into primary care from secondary care,(193, 194) which adds the time taken to hand back to primary care and the time to refer back from primary care in to haematology. This may be affected by local agreements and arrangements regarding specialty referral that relate largely to local funding arrangements.(193, 194) Even if referral is made within secondary care as a referral between departments, delay can still be added at this point. Although acute services may still also experience delay in this stage, they may be able to arrange rapid inpatient review.(195)

3.6.4 Participants diagnosed via acute services

Those diagnosed via acute services had higher rates of renal impairment, of anaemia, and of bone disease at diagnosis. End organ damage at diagnosis was assessed using documented disease present at recruitment. The main disadvantage of using this data is that participants may have been treated prior to recruitment features of acute kidney injury, hypercalcaemia or severe anaemia. This method may therefore underestimate the presence of CRAB features at diagnosis. When comparing the number of participants who reported anaemia, renal disease or hypercalcaemia as a symptom to the presence of these features in their blood test results at diagnosis, many participants did not meet the diagnostic criteria for the symptoms reported. This might reflect those participants that had had anaemia, renal impairment or hypercalcaemia treated before recruitment into the trial. Also, some participants may have

had test results outside if the normal range, but not meeting the IMWG criteria for end organ damage.

Participants diagnosed via the acute pathway had more CRAB features, but also had a worse performance status, and a poorer ISS score, which reflects poorer prognosis.(14) These findings together reflect that patients diagnosed via this pathway are a more unwell subgroup of patients than those diagnosed via the other pathways. Comparing overall pathway length, these patients had worse disease, but did not have a longer overall pathway to diagnosis. This suggests that in this group, higher rates of end organ damage and poorer prognosis are not necessarily reflecting longer pathways to diagnosis, but are a result of more aggressive disease.

Although the intra-hospital delay was shorter for those presenting via acute services, 25% of participants were still waiting >30 days from consulting acute services to haematology review. Given that these patients had a poorer performance status, higher rate of end organ damage and worse stage of disease, it should be easier to recognise these patients as having myeloma.

Most patients diagnosed via acute services had seen their GP previously. This can likely be split into two groups – those who initially consulted primary care but then developed further symptoms or another trigger that prompted them to consult acute services, and those that were sent by their GP to acute services. In the UK, for emergency admissions overall, 21% are referred from their GP. (196) In this study, a quarter of participants diagnosed through the acute pathway saw their GP the same day as they saw acute services – these participants are likely those who were referred by primary care directly to acute services. This group of patients were likely reviewed by their general practitioner and recognised as acutely unwell, requiring urgent assessment and treatment.

Overall, there was a high proportion of missing data regarding the number of GP consultations per participant, with no data recorded for 390 out of 977 participants. On assessment of the data that was recorded, there were a high proportion of patients who reported that they had only had one consultation. These results were discussed with a wider group, including the PI of the TEAMM trial, and representatives from haematology and primary care. It was felt that this was unlikely to reflect the true picture of primary care consultation. Previous research has already demonstrated that patients with myeloma have multiple GP attendances, as shown by Lyratzopoulos et al.(59) Identifying a haematological problem generally requires blood tests, which require two GP consultations (one to request the test and one to review the result). A more accurate way to collect this data may be through primary care records, rather than research using patient reported data where there may have been recall errors.

3.6.5 Symptoms

Symptoms were reported by the majority of participants within this study and were wide ranging. The wide range of symptoms demonstrates why there can be difficulty in diagnosis.

As expected, back pain was a frequently reported symptom, both starting prior to first presentation, and developing after initial consultation. Although fatigue was the next most common individual symptom, back pain was more than twice as commonly reported. Some of the individual symptoms reported by participants were related and clearly reflected the same underlying process, for instance fracture in different bones.

Looking at the symptoms grouped into categories, pain other than back pain was the second most common category of presenting symptom. Although this was frequently localised to an area of the body, the majority of patients did not record ‘bone pain’ specifically. This is

consistent with previous studies that have found pain to be a common presenting symptom.(37, 39)

Systemic symptoms were also common. This was expected based on previous research by Howell et al and Forbes et al that reported systemic symptoms in 52.5% and 47% respectively.(37, 39) The high proportion of participants reporting systemic symptoms as a presenting feature demonstrates the non-specific nature of some of the symptoms that patients experience. Fatigue, for example, is a common complaint in primary care, with 5-7% of patients attending primary care reporting tiredness as a symptom.(197) The positive predictive value of fatigue in primary care for myeloma is too low for it be used as a predictor of disease. (86)

Lyratzopoulos suggested that the likelihood of multiple GP consultations before diagnosis is related to difficulty of diagnosis in certain malignancies.(198) In myeloma, this wide range of non-specific presenting symptoms, and the low positive predictive value of the symptoms that are widely known, such as back pain, likely contributes to the multiple consultations reported by patients.

Din et al demonstrated that patients with several malignancies, including breast, colorectal, oesophageal and pancreatic, there was an increased diagnostic interval when patients reported symptoms that weren't in the NICE guidelines compared with those symptoms that were included.(199)

The current NICE guidance for investigation of suspected malignancy highlights 'bone pain' as a feature to prompt investigation.(40) Whether pain symptoms are recognised as 'bone pain' is difficult to assess. In this cohort, relatively few participants recorded 'bone pain', but often

specified pain related to a body part. Current NICE guidelines do not mention systemic symptoms as a prompt to investigation.

A substantial proportion of those who didn't report symptoms at initial presentation reported symptoms that started at a later date. It is important to recognise that although these patients may have initially been asymptomatic, they are not asymptomatic when they start their treatment or even by the time they receive their diagnosis. Many of the patients who were symptomatic when they initially presented also developed further symptoms. This adds further evidence to the importance of reducing the diagnostic delay in myeloma – not only may it offer advantages in stage of disease at diagnosis and complications, but also in reducing the symptom burden for this group of patients.

Patients diagnosed via the acute pathway and 'other secondary care' pathway reported a higher number of symptoms. Although there are differences in the number of presenting symptoms reported by participants in each pathway, these appear to be largely due to the number of patients in each group who did not report symptoms. Although this may be related in part to errors with patient recall, previous research has suggested that a proportion of patients are asymptomatic at identification, for instance those picked up from abnormal blood test results during investigation or monitoring of another condition. (38) Those patients identified through an incidental finding may be more likely to be referred directly from primary care to haematology. It would be expected that very few asymptomatic patients would be diagnosed via acute services, except in cases of severe derangement of blood test results that may require urgent treatment e.g. renal failure or hypercalcaemia.

There was some difference in the type of symptoms reported by the participants diagnosed via each pathway. If the nature of presenting symptoms did not impact the pathway taken by

patients, then those with any category of symptom would be diagnosed via all three pathways in similar proportions to the overall proportion diagnosed via each pathway, i.e. around 50% of participants with back pain would be diagnosed via the 'direct' pathway as around 50% overall take this pathway. This assumption was assessed for the most common symptom categories, although the categories where small numbers reported symptoms could not be assessed due to the low numbers involved. This showed that neurological symptoms and bone disease symptoms were more likely to be seen via the acute pathway.

In myeloma, a proportion of patients present with complications of the disease that can develop rapidly, without preceding symptoms, and require emergency treatment. It is unavoidable that these patients are diagnosed as an emergency if they have not had prior symptoms, as there would not have been an opportunity for earlier recognition. This may explain the higher proportion of patients with neurological symptoms, which includes spinal cord compression, and bone disease/fracture symptoms presenting through acute services demonstrated here, as these patients may experience a sudden event that causes severe and distressing symptoms, and necessitates urgent investigation and management.

Summary: Patients with multiple myeloma present through varied diagnostic pathways, and have wide ranging symptoms. There is often significant end organ damage present at diagnosis, particularly in those who present through acute pathways who may have more rapidly progressing disease. Strategies are needed to identify these patients earlier, before end organ damage develops. Once strategy may be to identify patients with monoclonal gammopathy of undetermined significance, before progression to multiple myeloma.

4 THE IMPACT OF A PRIOR DIAGNOSIS OF MGUS ON PATHWAYS TO DIAGNOSIS & END ORGAN DAMAGE IN MULTIPLE MYELOMA

4.1 Introduction

In the last chapter, patients presenting to acute services had a greater burden of complications, and patients presenting through non-haematology secondary care services had a long wait preceding their diagnosis. Myeloma is preceded by monoclonal gammopathy of undetermined significance (MGUS), which can be detected on blood tests for years prior to diagnosis.(88) Previous studies have suggested that patients under follow-up for MGUS or other plasma cell disorders prior to the diagnosis of symptomatic multiple myeloma are less likely to have complications at the time of diagnosis.(117) This is important as the frequently occurring complications can cause significant morbidity for patients. Common complications present at diagnosis include long bone fractures, infections requiring hospitalisation, or renal failure requiring dialysis.(35) If these complications could be prevented, the symptom burden for patients, healthcare costs and hospital use could be reduced for this group.

The recognition of progression to symptomatic multiple myeloma in patients with MGUS is via two pathways- through planned monitoring in patients without reported symptoms, or by investigation of new symptoms developing in a patient with known MGUS.(162)

After initial progression from MGUS or smouldering multiple myeloma (SMM) to active multiple myeloma, patients may still be asymptomatic. As shown in the previous chapter, some patients with active multiple myeloma do not have symptoms when the disease is initially identified. Many patients with MGUS will be identified by rising paraprotein levels on routine monitoring.(162) This may allow early detection of the rising paraprotein, before symptoms and complications develop. If a high proportion are diagnosed in this way, then a

high proportion of those with preceding knowledge of MGUS will be asymptomatic at myeloma diagnosis, and have less end organ damage.

Patients may also be identified when new symptoms develop. When patients are diagnosed with MGUS, the risk of transformation to myeloma should be explained to the patient, and as part of this discussion the common symptoms of myeloma that should prompt them to see their GP should be explained.(7) This should allow them to seek help promptly at the first sign of symptoms. If this system is effective, then patients with MGUS should present earlier in the course of their symptoms, allowing earlier identification of malignant transformation.

Patients with MGUS may therefore have fewer symptoms at presentation, as well as fewer complications, but it is unclear if their diagnostic pathways might differ from patients with established myeloma.

4.1.1 Hypotheses

- Patients with known MGUS have been identified as at risk of progression and undergo monitoring, therefore they are more likely to be referred by their general practitioner (GP) to haematology, and less likely to be diagnosed via acute services.
- In patients with MGUS or smouldering multiple myeloma, progression to myeloma is often detected through monitoring, and so they will have: 1) less end organ damage present at diagnosis, and 2) fewer symptoms.

4.1.2 Aims

- Identify patients within the Tackling Morbidity and Mortality in Multiple Myeloma (TEAMM) trial cohort who had preceding knowledge of MGUS or SMM
- Outline the pathways to diagnosis taken by the TEAMM MGUS patients, including the number who were diagnosed via acute services
- Compare the rates of end organ damage at diagnosis in those with known MGUS to those without known MGUS
- Assess the range of symptoms reported by the TEAMM MGUS patients to determine if they experienced fewer symptoms

4.2 Methods

4.2.1 Identification of patients with MGUS from the TEAMM trial

The TEAMM cohort has been described previously in Chapter 3, Section 3.4.1 and Chapter 2, Section 2.1.1.

Although questions were included on how participants reached the point of diagnosis, no specific question was asked regarding any previous diagnosis of MGUS.

Two strategies were used to identify those participants who were known to have MGUS prior to their myeloma diagnosis.

Firstly, the free-text entries in answer to *'When did the patient first notice bodily changes and/or symptoms that they attribute to the myeloma? (please note down incidental findings on laboratory tests also)'* were reviewed. Participants who reported MGUS or monoclonal gammopathy, or who reported a diagnostic test result consistent with MGUS rather than

myeloma, were classified as having known MGUS. Similarly, participants reporting smouldering multiple myeloma as a free text symptom were included in this group.

Secondly, the time from first haematology review to randomisation was reviewed. Randomisation was used as a surrogate for date of treatment initiation and therefore diagnosis, as the trial entry required them to be within 14 days of starting antimyeloma treatment (without any previous treatment). Those with a time delay of over 6 months from first haematology review to trial randomisation were identified.

These participants are grouped together here as those 'with prior knowledge of MGUS'.

The classification of patients as those with or without prior knowledge of MGUS was reviewed by myself and a consultant haematologist, SB.

4.2.2 Pathways to diagnosis

Pathways were analysed in the same way as described in Section 3.4.3. Pathway intervals are not reported in this chapter – this is discussed further in this chapter's discussion (Section 4.4).

4.2.3 End organ damage at diagnosis

End organ damage was assessed using the CRAB (hypercalcaemia, renal disease, anaemia, bone disease) features as defined by the International Myeloma Working Group criteria and described in Section 2.3.

4.2.4 Performance status and ISS stage

Performance status and ISS stage at diagnosis were assessed using the scales described in Section 3.4.4.1 and Section 3.4.4.2.

4.2.5 Symptoms

Symptoms were grouped and classified as described in Section 3.4.6. The symptoms reported in the chapter are symptoms reported by participants with prior knowledge of MGUS with a start date for the symptom occurring at any point in the diagnostic pathway. When comparing these symptoms to those without known MGUS, the symptoms start at any point within the diagnostic pathway.

4.2.6 Statistics

The statistical methods used in this chapter have been discussed in Section 2.6.

4.3 Results

4.3.1 Demographics

Of the 977 participants, 149 were identified as likely having known MGUS prior to diagnosis (15.3% of participants).

Age, gender and ethnicity of those with known MGUS is shown in Table 4.1. The age distribution of those with prior knowledge of MGUS was significantly different to that of those without prior knowledge of MGUS (Mann-Whitney U test, p=0.004), with a higher median age in those with prior knowledge of MGUS (70 years median compared to 67 years median). A lower proportion of those with known MGUS were male (Chi square, p=0.025).

	Known MGUS (n=149)	**Not known MGUS** (n=828)
Age, median (IQR)	70 (63-78)	67 (59-74)
Gender Male, n (%)	81 (54.4%)	530 (64%)
Ethnicity White British, n (%)	132 (88.6%)	723 (87.6%)

Table 4.1: Demographics of those with and without known monoclonal gammopathy of undetermined significance (MGUS) in the TEAMM trial.
Of all 977 participants in TEAMM, 149 were classified as 'known MGUS', 828 were not classified as known MGUS. Age shown in years, median and interquartile range. Significant difference found in age distribution (Mann-Whitney U, p 0.004). Gender – percentage of participants in each category who were male is shown, significantly lower proportion of male participants in those with known MGUS (Chi square, p=0.025). No significant difference in the proportion of participants who were White British comparing those with known MGUS to those without known MGUS (Chi square, 0.743). Percentages shown to 1 decimal place.

4.3.2 Pathway to diagnosis

The pathway to diagnosis could be determined for 141 (94.6%) participants with known MGUS, and for 774 (93.5%) participants who were not known to have MGUS. This is shown in Table 4.2.

74.5% of participants with known MGUS were diagnosed via the direct pathway, from GP to haematology. The acute pathway (diagnosis involving acute services) was the least frequent pathway in those with prior knowledge of MGUS (14 participants, 9.4% of those with known MGUS). There was a significant association between whether a participant was known to have MGUS, and the pathway to diagnosis ($\chi^2(2) = 51.905$, $p < 0.0005$). Those with prior knowledge of MGUS were more likely to be diagnosed via direct referral from GP to haematology, while those without prior knowledge of MGUS were more likely to have been diagnosed via acute services.

	Acute		Direct		Other secondary care		Unknown	
Known MGUS	9.4%	14/149	74.5%	111/149	10.74%	16/149	5.37%	8/149
Not known MGUS	30.8%	255/828	43.12%	357/828	19.57%	162/828	6.52%	54/828

Table 4.2: Pathway to diagnosis for those with and without known MGUS.
Percentage of those with or without known MGUS who were diagnosed via each route, with numbers also shown. Pathway was classified as unknown if the pathway could not be determined from the information provided.

4.3.3 End organ damage at diagnosis

The percentage of participants with each feature of end organ damage at diagnosis is shown in Table 4.3. As with the trial cohort as a whole, bone disease was the most common feature of end organ damage, affecting 55% of those with known MGUS, while hypercalcaemia was the least common CRAB feature, affecting 1.72%. Each CRAB feature was present in a significantly lower percentage of those with known MGUS than those without prior knowledge of MGUS.

The number of CRAB features reported per participant in the two groups is shown in Figure 4.1 and Table 4.4. Comparing the number of CRAB features reported per participant in those with prior knowledge of MGUS to those without prior knowledge of MGUS, there was a significant difference in the number of CRAB features per participant, with lower numbers of CRAB features reported for those with known MGUS (Mann-Whitney U test, $p<0.0005$).

There were no participants with prior knowledge of MGUS who reported the presence of 3 or more CRAB features at diagnosis.

There was a statistically significant association between known MGUS and the absence of CRAB features at diagnosis ($\chi^2(1)=41.598$, $p<0.0005$).

	Overall		Known MGUS		Not known MGUS		Chi square p value
Hypercalcaemia	5.9%	45/763	1.72%	2/116	6.65%	43/647	0.038
Renal impairment	11%	86/785	4.17%	5/120	12.18%	81/665	0.01
Anaemia	51.1%	403/788	36.67%	44/120	53.74%	359/668	0.001
Bone disease	71%	686/966	55%	82/149	73.9%	604/817	<0.0005

Table 4.3: The presence of CRAB features in those with and without known MGUS.
For each CRAB feature, the percentage shown is the percentage of those with the feature out of those with data available. The number of those with a positive finding and with data available is also shown.
All p values shown are for Chi square comparison of % with and without CRAB feature in 'Known MGUS' vs 'Not known MGUS'

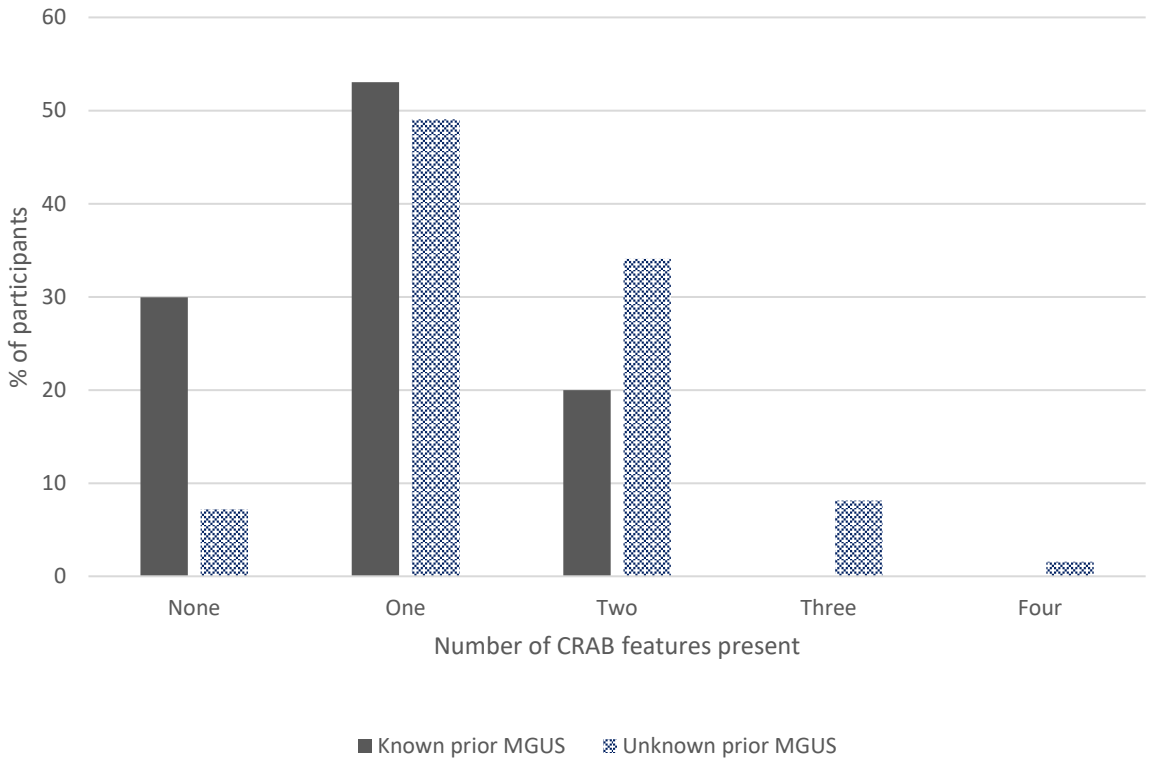


Figure 4.1: Number of CRAB features per participant.
All participants included had data available for all CRAB features – 115 participants with known MGUS, 640 participants without known MGUS. The number of CRAB features reported by percentage of participants per group is shown.

Number of CRAB features	Known MGUS		Not known MGUS	
None	27%	31/115	7.2%	46/640
One	53%	61/115	49%	314/640
Two	20%	23/115	34.1%	218/640
Three	0%	0/115	8.1%	52/640
Four	0%	0/115	1.6%	10/640

Table 4.4: Number of CRAB features per participant.
Data for participants with data available for all four CRAB features – 115 participants with known MGUS, 640 participants without known MGUS. CRAB features (Hypercalcaemia, renal impairment, anaemia, bone disease) as defined by International Myeloma Working Group criteria.

4.3.4 Performance status and ISS stage

The performance status of the participants with and without known MGUS is shown in Table 4.5, as is the ISS stage.

There was a significant difference in the performance status of participants in the two groups with worse performance status in those without known MGUS (Kruskal-Wallis, p <0.0005). There was a higher proportion of participants with a performance status of 0 in those with known MGUS than those without known MGUS (Chi square, p=0.005).

There was also a significant difference in the ISS stage of participants in the two groups, with a worse ISS stage in those without known MGUS (Kruskal-Wallis, p=0.001).

	Known MGUS		**Not known MGUS**	
Performance status				
0	45.5%	65/143	33.4%	272/814
1	42.7%	61/143	41.3%	336/814
2	11.2%	16/143	17.2%	140/814
3	0.7%	1/143	7.2%	59/814
4	0	0	0.9%	7/814
ISS				
1	32%	39/122	25.4%	177/698
2	51.6%	63/122	41.5%	290/698
3	16.4%	20/122	33.1%	231/698

Table 4.5: Performance status and ISS stage of those with and without known MGUS.
Of the 149 participants with known MGUS, 143 had data available for performance status & 122 for ISS stage. Of the 828 participants without known MGUS, 814 had data available for performance status & 698 for ISS stage.
ECOG performance status; International Staging System (ISS) staging score.

4.3.5 Symptoms

The symptoms reported by participants with MGUS are shown in Table 4.6 and 4.7. These tables show the symptoms that were reported by participants with prior knowledge of MGUS, with a start date anywhere in the diagnostic pathway, including those occurring after initial haematology consultation.

The most common symptom categories were pain symptoms (excluding back pain), anaemia, systemic symptoms, and back pain. The most common individual symptoms were anaemia and back pain, each reported by 30 participants.

A comparison between symptoms reported in each category in those with known MGUS and those without known MGUS is shown in Table 4.8.

As with the cohort as a whole, many participants with prior knowledge of MGUS reported multiple symptoms.

The total number of symptoms that each participant reported was compared. Figure 4.2 shows the percentage of participants with and without prior knowledge of MGUS who reported multiple symptoms. The number of symptoms reported per participants by those without prior knowledge of MGUS was significantly higher than in those with known MGUS (Mann-Whitney U, $p<0.0005$).

Symptom category	**Number of symptoms reported in this category**	**Percentage of participants reporting symptoms in this category**	
Other pain	38	25.5%	38/149
Back pain	30	20.1%	30/149
Anaemia	30	20.1%	30/149
Systemic symptoms	30	18.1%	27/149
Other abnormal blood results	13	8.7%	13/149
Neurological symptoms	9	6%	9/149
Infection	9	4.7%	7/149
Abnormal blood tests (suggestive of multiple myeloma)	7	4.7%	7/149
Respiratory symptoms	6	3.4%	5/149
Gastrointestinal symptoms	6	3.4%	5/149
Bone disease	5	3.4%	5/149
Renal symptoms	5	3.4%	5/149
Bleeding	3	2%	3/149
Abnormal lumps	3	2%	3/149
Other symptoms	3	2%	3/149

Table 4.6: Number of symptoms reported per category by those with known MGUS.
Columns contain the number of symptoms reported in each category, and the percentage of participants with known MGUS reporting a symptom in each category. Participants could report more than one symptom per category.

Symptoms	Number of participants reporting this symptom
Anaemia	30
Back pain	30
Fatigue	16
General pain	11
Chest pain	9
Hip pain	6
Weight loss	6
Unspecified abnormal blood results	6
Spinal cord compression symptoms	5
Renal disease	5
Leg pain	4
Raised Erythrocyte sedimentation rate	4
Recurrent Lower respiratory tract infection	3
Headache	3
Shoulder pain	3
Generally unwell	3
Cough	3
Recurrent urinary tract infection	2
Lower respiratory tract infection	2
Joint pain	2
Night sweats	2
Lytic lesions	2
Epistaxis	2
Neutropenia	2
Hypogammaglobulinaemia	2
Hypercalcaemia	2
Altered bowel habit	2
Abdominal pain	2
Collapse/dizziness	1
Sweats	1
Anorexia	1
Respiratory symptoms (unspecified)	1
Shortness of breath	1
Hoarseness	1
Knee pain	1
Hand pain	1
Foot pain	1
Itching	1
Unilateral knee swelling	1
Limb swelling	1
Confusion	1
Lymphadenopathy	1
Neck swelling	1
Neck lump	1
Upper respiratory tract infection	1
Recurrent infection	1
Unspecified bone disease	1
Plasmacytoma	1
Fractured vertebrae	1
Gum bleeding	1
Thrombocytosis	1
Thrombocytopenia	1
Pancytopenia	1
Raised total protein	1
Constipation	1
Dyspepsia	1

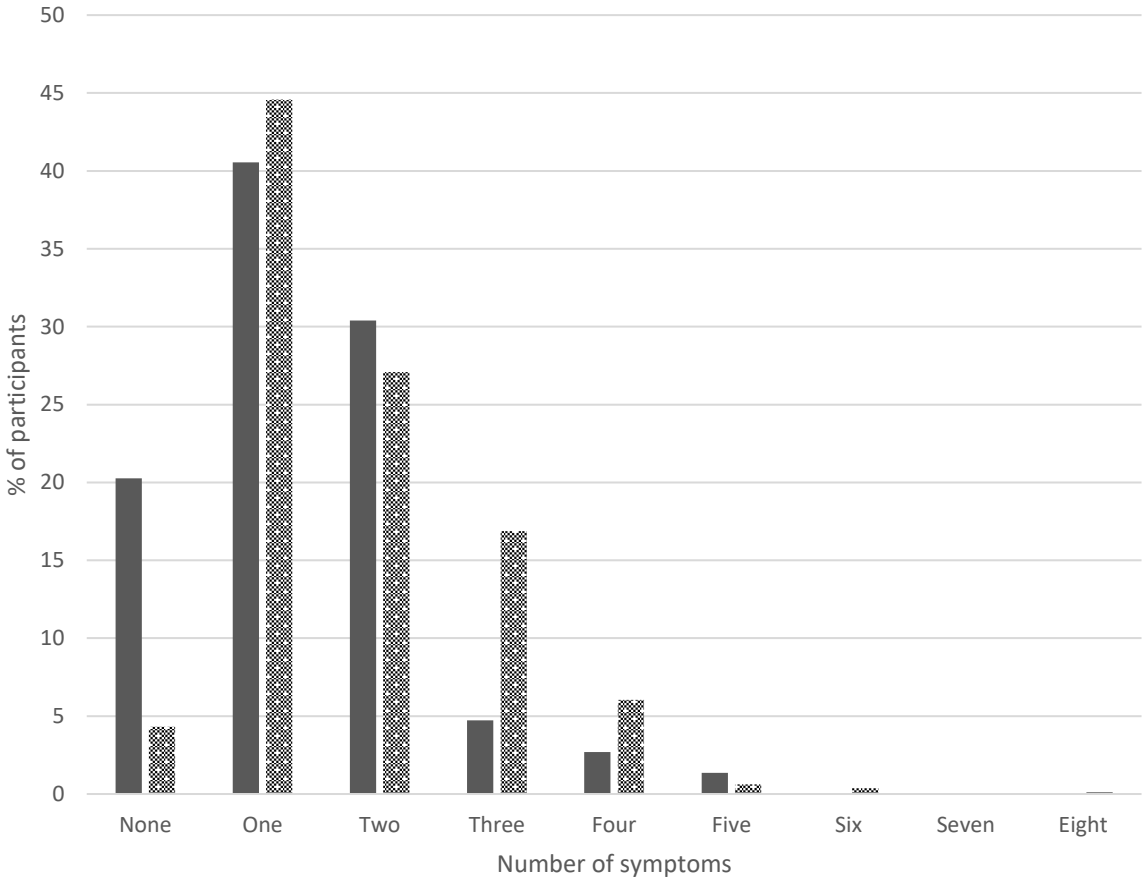
Table 4.7: Specific symptoms reported by participants with known MGUS.
Of the 149 participants with known MGUS, the number of participants who reported each symptom.

Symptom category	Percentage of participants reporting symptoms in each category				Chi square p value
	Known MGUS		Without known MGUS		
Other pain	25.5%	38/149	31.4%	260/828	0.15
Back pain	20.1%	30/149	40.3%	334/828	<0.0005
Anaemia	20.1%	30/149	10%	83/828	<0.0005
Systemic symptoms	18.1%	27/149	28.6%	237/828	0.008
Other abnormal blood results	8.7%	13/149	2.3%	19/828	<0.0005
Neurological symptoms	6%	9/149	5.3%	44/828	0.719
Infection	4.7%	7/149	5.7%	47/828	0.63
Abnormal blood tests (suggestive of multiple myeloma)	4.7%	7/149	5.3%	44/828	0.756
Respiratory symptoms	3.4%	5/149	8.3%	69/828	0.035
Gastrointestinal symptoms	3.4%	5/149	8.3%	69/828	0.035
Bone disease	3.4%	5/149	4.5%	37/828	0.538
Renal symptoms	3.4%	5/149	5%	41/828	0.397
Bleeding	2%	3/149	2.5%	21/828	0.704*
Abnormal lumps	2%	3/149	1.1%	9/828	0.345*
Other symptoms	2%	3/149	2.4%	20/828	0.766*
Urological symptoms	0		1%	8/828	n/a

Table 4.8: Comparison of symptoms reported by those with and without known MGUS

For each symptom category, the percentage of participants reporting a symptom in that category is shown, with a symptom start date at any point in the diagnostic pathway. Data is also shown for the number of participants with a symptom in each category, and the number with data available. Chi square comparison between the percentage of participants reporting symptoms in those with known MGUS and those without known MGUS is shown.

**expected cell counts <5 in Chi square, therefore comparisons limited.*



<u>Figure 4.2:</u> Number of symptoms reported per participant.
The percentage of participants who reported each number of symptoms.
Data available from 148 participants with known MGUS, and from 812 participants without known MGUS.

4.4 Discussion

The key findings demonstrated in this chapter are:

- Participants with prior knowledge of MGUS were less likely to be diagnosed via acute services and more likely to be diagnosed via direct referral from primary care to haematology than those without prior knowledge of MGUS
- Those with prior knowledge of MGUS had less features of end organ damage at diagnosis
- Those with prior knowledge of MGUS had a better performance status & ISS stage
- Those with prior knowledge of MGUS had less symptoms starting before treatment initiation

Those with prior knowledge of MGUS were more likely to be diagnosed via pathways involving only their GP and haematology, and less likely to be diagnosed via acute services. This is expected, as monitoring patients with MGUS should identify transformation to symptomatic multiple myeloma. Ideally, all patients with MGUS who progressed to myeloma would be diagnosed through routine monitoring, or through the identification of symptoms indicating progression in primary care. This is important, as we know that diagnosis via acute services is associated with higher mortality.(27) If identification and monitoring of MGUS leads to prompt identification of progression and to patients avoiding acute admissions, then this may impact morbidity and mortality. Although most participants with known MGUS in this study were diagnosed via primary care pathways, 9.4% were still diagnosed via acute services. This may reflect patients who have rapid development of symptoms requiring emergency intervention, or patients where monitoring has not been frequent enough to detect progression to active myeloma.

In this cohort, those who had prior knowledge of MGUS had fewer features of end organ damage per participant, as defined by the CRAB criteria, than those who did not have a prior diagnosis. This is consistent with previous research that has found decreased complication rates at diagnosis in those under follow-up for plasma cell disorders. Go et al demonstrated that those under follow-up for MGUS prior to myeloma diagnosis were more likely to have no complications at diagnosis,(117) consistent with the results demonstrated here. Previous research showing this benefit has not been performed on a UK population and so this research is novel in our community. This reduction in end organ damage is important as the complications of active myeloma related to end organ damage are associated with morbidity and implicated in early mortality.(200) If identification and monitoring of MGUS improves end organ damage at diagnosis of myeloma, then this supports strategies to identify and appropriately monitor MGUS.

There were some differences in the type of symptoms reported by participants with known MGUS compared to those who without a prior diagnosis of MGUS. There was a lower percentage of participants reporting the common symptoms of back pain and systemic symptoms. Although participants with prior knowledge of MGUS had a lower rate of anaemia based on their blood test results at diagnosis, it was reported by participants as a presenting symptom in a higher percentage of those with prior knowledge of MGUS than those without. This increased reporting of anaemia as a symptom may reflect an altered appreciation of symptoms by patients and clinicians in those being monitored for MGUS. In those under follow-up for MGUS, clinicians may be watching for the development of anaemia as a trigger to further investigation for progression, therefore increasing the proportion of patients where this was recognised as the main presenting feature.

Overall, the number of symptoms reported was lower in those with prior knowledge of MGUS, suggesting that monitoring of MGUS may also reduce the burden of symptoms experienced by patients with myeloma.

Although it is not possible to tell the level of monitoring of MGUS that these participants were receiving from the data collected in TEAMM, the expectation would be that these participants were risk-stratified and then received monitoring at regular intervals, with frequency determined based on their risk of progression.(7) Despite this, some of these participants developed significant symptoms. These included symptoms that can cause significant morbidity, including spinal cord compression. Although those with prior knowledge of MGUS reported fewer symptoms, some of these participants still reported up to five symptoms occurring before they started treatment. This highlights that despite identification and monitoring of MGUS, these are still a group of patients who experience significant symptoms. It is therefore important they receive adequate monitoring and clear communication and explanation of the symptoms that may signify progression to active myeloma.

Although this data demonstrates a clear difference between those with and without known MGUS, there were limitations in the method of identifying those participants with known MGUS that limit the reliability of the results. Participants recruited to TEAMM were not asked regarding previous diagnoses of MGUS or SMM, therefore other methods of identification were used.

As well as those who documented a free text entry regarding MGUS, those with over 6 months from haematology review to randomisation were classed as ‘known MGUS’. Although some patients may have experienced delay between haematology review and treatment initiation

due to logistics or due to diagnostic uncertainty, on discussion with haematologists from three centres it was felt that delay due to these reasons should not exceed 6 months. The disadvantage of this method is that not all of these participants will have had MGUS. Participants with prior smouldering multiple myeloma may also have more than 6 months between initial haematology consultation and treatment initiation, and will have had regular monitoring of their disease, in a manner similar to those with MGUS. There may also have been participants with other haematological disorders who developed myeloma after haematology review for other conditions. Unfortunately, from the data collected in TEAMM it is not possible to identify which participants fall into this group, as a detailed past medical history was not collected. Participants being monitored in primary care for MGUS who were only referred to haematology once they progressed to myeloma may have also been missed by this method. As participants in both categories may have been misclassified, we cannot be certain that the results shown here fully capture the overall picture in those who develop active myeloma from known MGUS. Similarly, it was not possible to differentiate between MGUS and SMM, and it is possible that there are differences between these groups. If future research studies utilise the same design as TEAMM to capture data regarding diagnostic pathways, then additional data collection regarding previous diagnoses of MGUS and SMM will allow more in-depth evaluation of these patients, to confirm the findings of this study.

Detailed analysis of the pathway intervals is not provided in this chapter, as there was variability in the way participants with MGUS reported their pathways to diagnosis and dates of consultation. This likely reflects that the questions were not designed to account for alternative pathways that MGUS patients may take. For example, some participants reported the date of initial GP consultation simultaneous with the date of initial MGUS diagnosis, whereas other participants reported the date of MGUS diagnosis in date of initial symptom

onset and a later date of GP consultation related to development of symptomatic multiple myeloma. Again, if data was collected this way in further studies, the questions could be amended and clarified to obtain this detailed data.

Summary: These findings highlight the importance of MGUS identification. They suggest that a prior diagnosis of MGUS is associated with less end organ damage at diagnosis of myeloma and better performance status, and with fewer symptoms experienced by the patient.

Currently, population-based screening for MGUS or for myeloma itself is not recommended, therefore identification relies on testing based on clinical suspicion. To identify patients earlier, there are two possible approaches – either identification of myeloma at an earlier stage, for instance through automated processes to recognise abnormal blood test results, or through identification of a population with a high risk of MGUS, where screening could be targeted.

5 IDENTIFICATION OF ABNORMAL BLOOD TEST RESULTS PRIOR TO DIAGNOSIS IN THOSE WITH MULTIPLE MYELOMA

5.1 Introduction

Previous research has suggested that the abnormalities present on blood tests at the time of diagnosis of myeloma may have been present for some time and could be used to reduce diagnostic delay.(84) Identification of abnormalities could be used to prompt earlier testing for myeloma, either as part of an automated system or via feedback to clinicians to suggest further investigations.(67)

Recent research has suggested that haemoglobin begins to fall in the three years prior to a diagnosis of myeloma, with changes also occurring in erythrocyte sedimentation rate (ESR) and plasma viscosity over the two years prior to diagnosis. Some markers, such as renal failure or hypercalcaemia, are likely to be later events.(201)

Previous strategies to prompt reflex testing for paraproteinaemia have included globulin or total protein levels.(80) Although the globulin level is not routinely reported as part of liver function tests,(82) it can be calculated as the difference between the serum albumin and total protein levels.(202) An understanding of how calculated globulin relates to immunoglobulin levels in individuals without myeloma is needed to allow interpretation of results. There are many other conditions that cause abnormalities in immunoglobulin levels where calculated globulin may be a useful marker of disease, such as autoimmune hepatitis,(183) and strategies for testing calculated globulin need to recognise that abnormalities may be seen in other conditions.

To identify blood test results that could be used to signify myeloma, it is important to characterise the range of abnormalities that are present at diagnosis. This allows the

identification of common features, as well as highlighting the proportion of patients who would not be identified by using some common features such as renal failure or hypercalcaemia. Previous blood test results for the same patients can then be reviewed to assess how long these abnormalities have been present.

5.2 Hypothesis

Patients with myeloma have detectable abnormalities for a period of time prior to diagnosis that could prompt earlier testing if identified. Test results prior to diagnosis from patients with known myeloma could be used to construct automated methods of earlier testing.

5.3 Aims

- To identify a local cohort of patients who received a new diagnosis of multiple myeloma within the past ten years and determine how many of these patients had blood test results available preceding their diagnosis
- To identify what abnormalities are commonly present in those with newly diagnosed myeloma
- To assess whether abnormalities can be detected on blood test results prior to diagnosis
- To demonstrate a correlation between calculated globulin as determined from routine blood test results and serum immunoglobulin levels, in patients with and without myeloma

5.4 Methods

5.4.1 Identifying a local cohort

As discussed in Chapter 2 Section 2.1.2, a cohort of patients who were diagnosed with multiple myeloma at University Hospitals Birmingham (UHB) were identified.

Inclusion criteria:

- Patients diagnosed with active multiple myeloma at UHB
- Aged over 18 years

Exclusion criteria:

- Patients diagnosed with active multiple myeloma at another centre and referred to UHB for further management, after treatment was initiated in another centre
- Patients with smouldering multiple myeloma (SMM) or monoclonal gammopathy of undetermined significance (MGUS) without progression to active multiple myeloma
- Patients with no evidence of multiple myeloma documented on UHB electronic patient record systems

Blood test results were obtained for these patients, as described in Section 2.1.2.5.

5.4.2 Blood test results at diagnosis

To assess blood test abnormalities at diagnosis, the most recent result for each test for each patient was extracted. For those diagnosed prior to 2012, AST was selected as the transaminase component of the LFTs; from 2012 onwards, ALT was used. Results that were more than 14 days from the date of diagnosis were excluded, as they may not accurately reflect abnormalities at diagnosis.

5.4.3 Blood test results prior to diagnosis

To allow comparison with previous research by Koshiaris et al,(201) test results were grouped in 90 day intervals, working backwards from the date of diagnosis. Five years of blood tests results were included. For each test, a mean level was calculated for each 90-day date range.

Markers assessed were:

- Haemoglobin (g/L)
    - Haemoglobin in men and in women
- Mean corpuscular volume (MCV) (fL)
- Haematocrit
- Corrected calcium (mmol/L)
- C-reactive protein (CRP) (mg/L)
- Creatinine (µmol/L)
- Serum albumin (g/L)
- Serum total protein (g/L)

For each result, change over time was analysed for patients with a result available for all of three selected time periods: close to diagnosis (0-89 days), one year before (360-449 days) and two years before (720-809 days). These results were analysed using one-way repeated measures ANOVA, as discussed in Section 2.6.2.

5.4.4 Calculated globulin

To confirm the correlation between calculated globulin (CG) and serum immunoglobulin levels, two cohorts were investigated:

1) a cohort of patients without known multiple myeloma
2) patients identified as having multiple myeloma diagnosed at UHB

5.4.4.1 Patients without myeloma

Patients with autoimmune hepatitis managed at University Hospitals Birmingham were identified based on clinical coding for autoimmune hepatitis. This cohort was chosen as patients may have multiple immunoglobulin and liver function measurements in a short period of time as both are currently used to assess response to immunosuppression. Although patients with autoimmune hepatitis may have elevated IgG levels, they do not have a paraprotein related to their disease. (183)

Inclusion criteria:

- Diagnosed with autoimmune hepatitis
- Aged 18 years old or over

Exclusion criteria:

- No paired blood test results for liver function tests and immunoglobulins available on UHB electronic record of pathology test results

Local approval was obtained via the Clinical Audit Registration and Management System. NHS Research Ethics Committee approval was not needed.

Data was collected on all available blood test results for these patients with a measurement of total protein, albumin and immunoglobulin levels on the same blood sample. Calculated

globulin was determined for each result by subtracting the albumin level from the total protein level.

Where immunoglobulin levels are measured routinely, levels of IgG, IgA and IgM are reported, and levels of IgE and IgD are not measured. The total level of IgG, IgA and IgM (combined) measured in the sample was compared to the calculated globulin level using Spearman's rank-order correlation.

Outliers were identified by visual inspection of the correlation plots. Clinical notes for outlying patients were reviewed to identify whether potential confounding factors were present.

5.4.4.2 Patients with myeloma

For the patients described in Section 2.1.2, results at and prior to diagnosis were obtained as described in Section 5.4.2. Calculated globulin was determined for each blood test result that featured both albumin and total protein on the same sample. Results within 14 days of date of diagnosis were identified. These results were then compared to immunoglobulin results reported within 24 hours of the CG result. Correlation was assessed using the same method as for those patients without myeloma described above.

5.4.4.3 Calculated globulin prior to diagnosis

Calculated globulin levels for blood test results prior to diagnosis in those patients described in Section 2.1.2.5 were assessed in the same way as other blood test results prior to diagnosis, as described in section 5.4.3.

The percentage of patients with each subtype of myeloma, based on heavy chain component, who had an abnormal calculated globulin at diagnosis was assessed. The lower limit of normal

was placed at 18g/L and the upper limit of normal at 45g/L, based on previous research. (73, 80)

5.5 Results

5.5.1 Identifying a local cohort of myeloma patients

The initial search returned 1319 patients coded as multiple myeloma at University Hospitals Birmingham. After case note review, 287 patients were identified as meeting our inclusion criteria. Reasons for exclusion are shown in Figure 5.1. Many patients were diagnosed at another centre (shown in Table 5.1) or had a haematological condition other than active multiple myeloma (shown in Table 5.2).

Blood test results were obtained for 285 patients out of the 287 patients identified. In total, 57235 results were obtained. After removal of results where a test was not performed or where there was a discrepancy between date of diagnosis and date of test result, 56711 results were available for analysis.

The results available ranged from 0-5777 days prior to diagnosis. The fewest results available for a patient was 10, reflecting 10 components of an FBC from a single sample. The highest number available for one patient was 2535 individual tests, covering a period of 4774 days (13 years) prior to diagnosis.

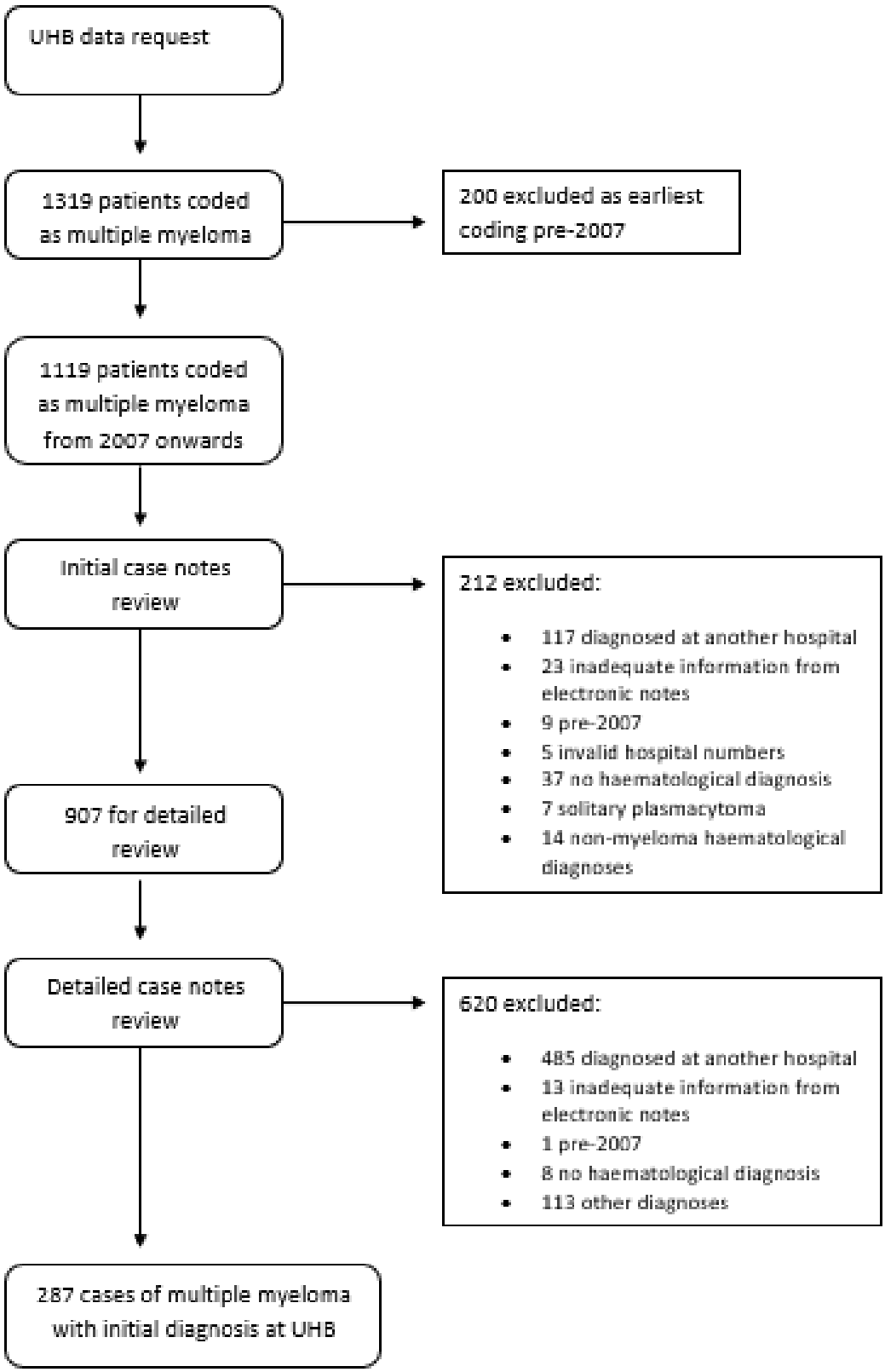


Figure 5.1: Modified consort diagram showing the pathway to identification of patients diagnosed with multiple myeloma at University Hospital Birmingham
UHB= University Hospitals Birmingham. Steps shown in identification of those diagnosed with active multiple myeloma at UHB, for inclusion in study, from those identified on initial data search coded as multiple myeloma (ICD 10 code CM C90 Multiple myeloma)

Local hospitals	
Birmingham Heartlands Hospital	5
Burton	18
City	15
Coventry	3
George Eliot (Nuneaton)	2
Good Hope Hospital	2
Hereford	5
Kidderminster	1
New Cross (Wolverhampton)	73
North Staffordshire	2
Redditch	27
Russell's Hall Hospital (Dudley)	1
Sandwell	39
Shrewsbury	127
Stafford	15
Telford	11
Walsall	10
Warwick	1
Worcester	90
Other UK	
Bath	1
Berkshire	1
Brighton	1
Charing Cross (London)	1
Derby	3
Dorchester	1
Gloucester	1
Leicester	2
Norfolk	1
Portsmouth	1
Preston	2
Reading	1
Royal Marsden (London)	1
Sheffield	1
Surrey	1
Swindon	2
Worthing	1
Overseas	
Australia	1
South Africa	1
Spain	1
New Zealand	1
Private hospital	5
Unknown	7
TOTAL	***485***

Table 5.1: Location of diagnosis for those who received diagnosis at another centre.
For those patients excluded at detailed case note review, the centre where they received their initial diagnosis of active multiple myeloma (before their care was transferred to University Hospitals Birmingham).

Other haematological diagnosis	
Acute lymphoblastic leukaemia	1
Acute myeloid leukaemia	13
Non-Hodgkin lymphoma	8
Chronic lymphocytic leukaemia	2
Chronic myelomonocytic leukaemia	1
Dendritic cell neoplasm	1
Diffuse large B cell lymphoma	2
Familial platelet disorder	1
Leukaemia (unspecified)	1
Lymphoma (unspecified)	4
Mantle cell lymphoma	2
Myelodysplastic syndrome	1
Mycosis fungoides	1
Post-transplant lymphoproliferative	2
Sarcoma	1
T cell lymphoma	1
Plasma cell disorder	
Amyloidosis	14
Gamma heavy chain disease	1
Monoclonal gammopathy of renal significance	1
Monoclonal gammopathy of undetermined significance	11
Multiple plasmacytoma	2
Plasma cell leukaemia	4
Solitary plasmacytoma	17
POEMS syndrome	5
Smouldering multiple myeloma	15
Waldenstrom's macroglobulinemia	1
TOTAL	***113***

Table 5.2: Haematological diagnosis for those who had haematological disease other than active multiple myeloma. Diagnosis of those who were excluded at detailed case note review stage, who had another haematological disease, but did not have active multiple myeloma.
POEMS syndrome = Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal paraprotein, Skin changes.

5.5.1.1 Patient demographics

Demographic details for all 287 patients identified as being diagnosed with active multiple myeloma are shown in Table 5.3. The median age of these patients at diagnosis was 69 years, and 71.6% of patients were of white British ethnic origin.

The subtype of myeloma diagnosed in these patients is shown in Table 5.4. The most common subtype was IgG myeloma (50.8%). The demographics of those diagnosed with each subtype of myeloma are shown in Table 5.5.

	N (%)	
Age at diagnosis		
Median	69	
Interquartile range	59-78	
Range	30-94	
Gender		
Female	138	(48.1%)
Male	149	(51.9%)
Ethnicity		
White British	205	(71.4%)
Black – Caribbean	21	(7.3%)
Indian	11	(3.8%)
Pakistani	10	(3.5%)
White other	10	(3.5%)
White Irish	7	(2.4%)
African	5	(1.7%)
Black – other	4	(1.4%)
Chinese	1	(0.3%)
Other Asian	1	(0.3%)
Mixed – white Asian	1	(0.3%)
Mixed white black Caribbean	1	(0.3%)
Other	8	(2.8%)
Not given	2	(0.7%)
Year of diagnosis		
2007	20	(7.0%)
2008	25	(8.7%)
2009	17	(5.9%)
2010	14	(4.9%)
2011	36	(12.5%)
2012	27	(9.4%)
2013	32	(11.1%)
2014	34	(11.8%)
2015	38	(13.2%)
2016	32	(11.1%)
2017 (Jan-July)	12	(4.2%)
Deprivation decile		
1	72	(25.1%)
2	38	(13.2%)
3	26	(9.1%)
4	23	(8.0%)
5	27	(9.4%)
6	23	(8.0%)
7	29	(10.1%)
8	18	(6.3%)
9	15	(5.2%)
10	15	(5.2%)
unknown	1	(0.3%)

Table 5.3: Demographics of those diagnosed with multiple myeloma
Demographic details for those diagnosed with active multiple myeloma at University Hospitals Birmingham, from 2007 onwards.
Age at diagnosis in years. Deprivation decile calculated using post code.

Type of myeloma	N	%
IgG	146	50.8
IgG kappa	*95*	*33.1*
IgG lambda	*51*	*17.8*
IgA	57	19.9
IgA kappa	*30*	*10.5*
IgA lambda	*27*	*9.4*
IgD	9	3.1
IgD kappa	*2*	*0.7*
IgD lambda	*7*	*2.4*
Biclonal		
IgG & IgA kappa	1	0.3
Light chain	69	24
Kappa light chain	*44*	*15.3*
Lambda light chain	*25*	*8.7*
Unknown or non-secretory	5	1.7

Table 5.4: Subtypes of myeloma diagnosed at University Hospitals Birmingham
Subtype of myeloma in those diagnosed with active multiple myeloma at UHB, grouped by heavy chain and light chain component of the paraprotein identified. Based on findings of histology and/or immunological tests.

	IgG	**IgA**	**IgD**	**Biclonal**	**Light chain**	**Unknown** (including non-secretory)
Age Median (IQR)	71 (61-78)	76 (64-83)	69 (66-78)	57	61 (54-73)	52 (40-63)
Gender (female)	76 (52.1%)	28 (49.1%)	2 (22.2%)	0	29 (42%)	3 (60%)
Ethnicity (White British)	101 (69.2%)	42 (73.7%)	7 (77.8%)	1	52 (75.4%)	2 (40%)

Table 5.5: Demographics for each subtype of myeloma
Basic demographics for each subtype of myeloma, with age in years at diagnosis, gender shown as percentage within subtype who are female, and ethnicity shown as percentage who are white British.
Percentages not given for biclonal myeloma as only one patient in this cohort had biclonal disease.

5.5.2 Blood test results at diagnosis

263 patients (91.6%) had blood test results available from within 14 days prior to diagnosis. A summary of the blood test results closest to date of diagnosis for each participant is shown in Table 5.6. Of those with blood test results available, 94.7% had a full blood count (FBC), 90.9% had a bone profile, 90.1% had liver function tests (LFTs), and 95.1% had urea and

electrolytes (U&Es). The proportion of patients with an abnormal result for each test is shown in Table 5.7.

Blood test	Units	Number of results	Range of results	Median (IQR)		Mean (SD)
Full blood count:						
Haemoglobin	g/L	252	43-160	102	(90-119)	
White cell count	10^9/L	252	1.4-27.1	6.6	(5.2-8.6)	
Platelets	10^9/L	252	18-644	211	(164-281)	
Neutrophils	10^9/L	254	0.6-22.8	4.0	(2.8-5.8)	
Lymphocytes	10^9/L	254	0.1-6.1	1.6	(1.2-2.1)	
Eosinophils	10^9/L	254	0-0.9	0.2	(0.0-0.2)	
Monocytes	10^9/L	254	0.1-3	0.6	(0.4-0.8)	
Basophils	10^9/L	254	0.0-0.2	0.0	(0.0-0.0)	
Mean corpuscular volume	fL	252	65.3-120.6	91.8	(87.5-96.1)	
Haematocrit	L/L	250	0.14-0.45			0.31 (0.06)
Reticulocytes	10^9/L	23	0-114.6	33.1	(23.8-44.4)	
Biochemistry:						
Urea	mmol/L	254	2.8-40	7	(5.2-10.6)	
Creatinine	µmol/L	254	40-977	102	(80-192)	
Sodium	mEq/L	253	120-167	140	(137-142)	
Potassium	mmol/L	250	2.5-5.8			4.3 (0.53)
C-reactive protein	mg/L	221	0-529	6	(<3-22)	
Albumin	g/L	246	16-53	38	(33-42)	
Total protein	g/L	241	36-155	80	(69-93)	
Bilirubin	µmol/L	246	2-26	6	(5-9)	
Alkaline phosphatase *(pre-January 2012)*	IU/L	101	104-656	225	(163-302)	
Alkaline phosphatase *(January 2012 onwards)*	IU/L	150	25-695	85	(62-107)	
ALT *(December 2011 onwards)*	IU/L	145	6-400	18	(13-26)	
AST *(pre-December 2011)*	IU/L	104	7-96	21	(17-29)	
Calcium	mmol/L	249	1.82-3.61	2.35	(2.22-2.48)	
Corrected calcium	mmol/L	242	1.88-3.74	2.4	(2.28-2.53)	

Table 5.6: Blood test results at diagnosis of myeloma.
For the 263 patients with blood test results available within 14 days of diagnosis. Results closest to date of diagnosis included for each patient.
ALT= alanine aminotransferase; AST= aspartate aminotransferase.

Test	Number with results	Above the normal range N (%)		Below the normal range N (%)	
Full blood count:					
Haemoglobin	252	0		204	(81%)
White cell count	252	24	(9.5%)	23	(9.1%)
Platelets	252	9	(3.6%)	41	(16.3%)
Neutrophils	254	32	(12.6%)	21	(8.3%)
Lymphocytes	254	5	(2%)	40	(15.7%)
Eosinophils	254	4	(1.6%)	n/a	
Monocytes	254	46	(18.1%)	8	(3.1%)
Basophils	254	0		0	
Mean corpuscular volume (MCV)	252	39	(15.5%)	8	(3.2%)
Haematocrit	250	0		215	(86%)
Reticulocytes	23	2	(8.7%)	5	(21.7%)
Biochemistry:					
Urea	254	97	(38.2%)	9	(3.5%)
Creatinine	254	113	(44.5%)	4	(1.6%)
Sodium	253	6	(2.4%)	18	(7.1%)
Potassium	250	9	(3.6%)	9	(3.6%)
C-reactive protein	221	91	(41.2%)	n/a	
Albumin	246	1	(0.4%)	74	(30.1%)
Total protein	241	120	(49.8%)	20	(8.3%)
Bilirubin	246	2	(0.8%)	n/a	
Alkaline phosphatase *(pre-January 2012)*	101	16	(15.8%)	0	
Alkaline phosphatase *(January 2012 onwards)*	150	38	(25.3%)	1	(0.7%)
ALT *(December 2011 onwards)*	145	18	(12.4%)	0	
AST *(pre-December 2011)*	104	11	(10.6%)	0	
Calcium	249	35	(14.1%)	25	(10%)
Corrected calcium	242	44	(18.2%)	6	(2.5%)

Table 5.7: Proportion with abnormal test result at diagnosis

Test results within 14 days of diagnosis, latest result for each patient. For each test result, the percentage of patients with a result above or below the normal range.

ALT= alanine aminotransferase; AST= aspartate aminotransferase.

The most common abnormalities were:

- Low haematocrit (86%)
- Low haemoglobin (81%)
- Raised total protein (49.8%)
- Raised creatinine (44.5%)

Comparing the blood tests in groups, 241 patients (96.4%) had an abnormality in at least one component of the FBC, 170 (69.1%) had an abnormality in the bone profile, 128 (51.2%) had an abnormality in LFTs, and 155 (61%) had an abnormality in U&Es.

5.5.2.1 CRAB features at diagnosis

Hypercalcaemia

Hypercalcaemia was seen in 11.2% (27 patients).

Renal insufficiency

Renal insufficiency was found in 26.8% (68 patients).

Anaemia

Anaemia that met the International Myeloma Working Group (IMWG) criteria was found in 54% (136 patients). Sixty-eight patients (27%) had a haemoglobin below the normal range for the local laboratory but did not meet the IMWG criteria for anaemia indicating end organ damage.

In those with a haemoglobin below the normal range, 30 out of 204 (14.7%) had a high MCV and 8 (3.9%) had a low MCV. A normocytic picture was most common, seen in 81.4%.
In those with anaemia as defined by IMWG criteria, 21 (15.4%) had a high MCV and 8 (5.9%) had a low MCV. Again, most patients (78.7%) had a normocytic anaemia.

Haematocrit below the normal range was seen in all patients who met the IMWG criteria for anaemia, and 96.6% of those with a haemoglobin below the lower limit of normal.

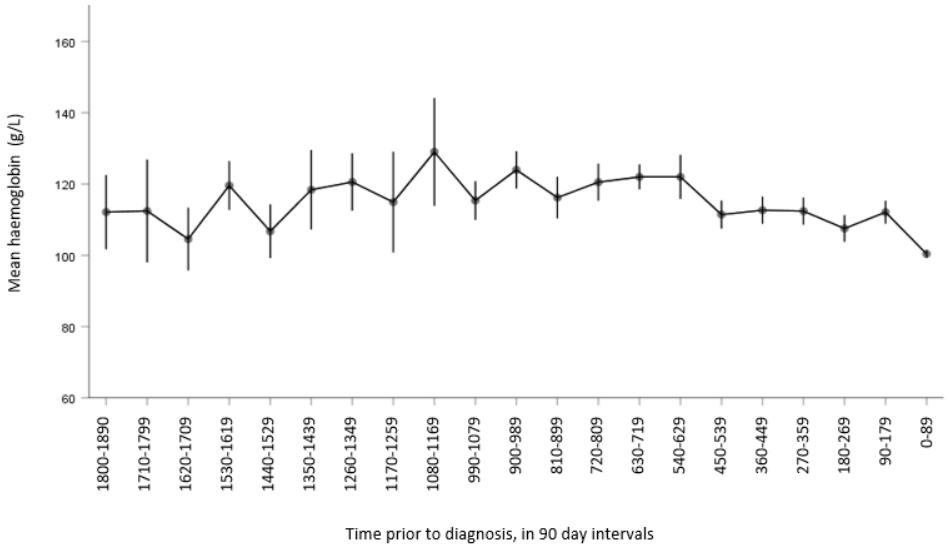
5.5.3 Blood test results prior to diagnosis

5.5.3.1 Routine tests

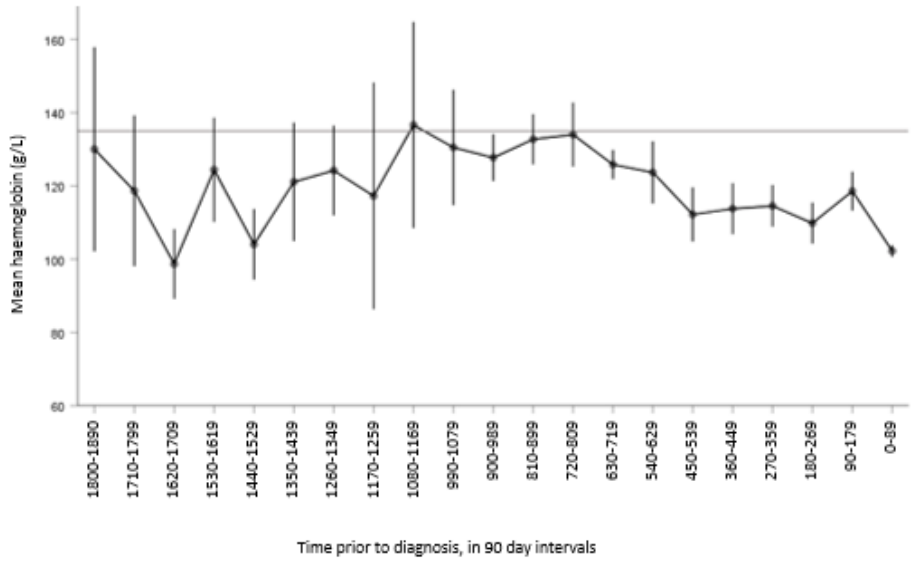
Figure 5.2 shows mean haemoglobin in 90-day intervals prior to diagnosis. Results are shown for all patients, as well as by gender. For each time interval, the 95% confidence interval for the mean is displayed. The results are also shown in Table 5.8 and Table 5.9.

Haemoglobin

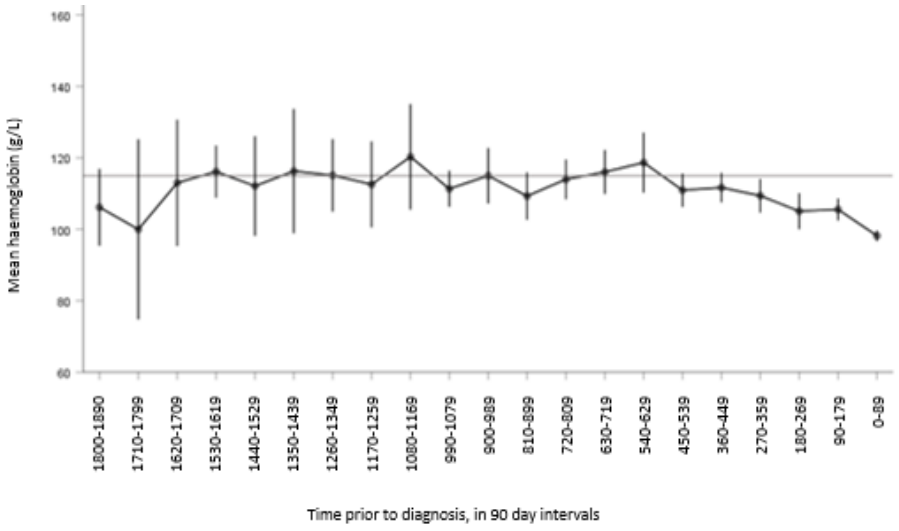
a)



b)



c)



<u>Figure 5.2:</u> Mean haemoglobin prior to diagnosis
Mean haemoglobin (g/L) with 95% confidence intervals, in 90-day intervals prior to diagnosis, for: a) all patients; b) men; c) women. Horizontal line demonstrates lower limit of normal range (135 g/L in men, 115g/L in women).

Interval (days before diagnosis)	Number of results	Mean haemoglobin (g/L)	95% Confidence interval
0-89	1234	100.39	99.27-101.51
90-179	138	112.09	108.51-115.67
180-269	109	107.52	103.77-111.27
270-359	110	112.39	108.55-116.23
360-449	87	112.64	108.8-116.48
450-539	90	111.42	107.47-115.37
540-629	54	122	115.81-128.19
630-719	69	122	118.49-125.51
720-809	58	120.53	115.33-125.73
810-899	51	116.2	110.36-122.04
900-989	34	123.97	118.71-129.23
990-1079	38	115.37	109.93-120.81
1080-1169	15	129	113.86-144.14
1170-1259	14	114.93	100.78-129.08
1260-1349	25	120.56	112.49-128.63
1350-1439	23	118.39	107.21-129.57
1440-1529	27	106.74	99.21-114.27
1530-1619	24	119.58	112.73-126.43
1620-1709	22	104.55	95.74-113.36
1710-1799	9	112.44	98-126.88
1800-1890	24	112.13	101.7-122.56

Table 5.8: Haemoglobin results available prior to diagnosis (all patients)
For all 285 patients at UHB with blood test results available prior to diagnosis. Multiple tests available in each interval for some patients. Haemoglobin measured in g/L. Results shown to 2 decimal places.

	Men			Women		
Interval (days before diagnosis)	**Number of results**	**Mean haemoglobin (g/L)**	**95% Confidence interval**	**Number of results**	**Mean haemoglobin (g/L)**	**95% Confidence interval**
0-89	668	102.25	100.62-103.88	566	98.20	96.73-99.67
90-179	69	118.57	113.25-123.89	69	105.55	102.47-108.63
180-269	56	109.84	104.24-115.44	53	105.08	100.02-110.14
270-359	64	114.55	108.85-120.25	46	109.39	104.66-114.12
360-449	40	113.78	106.81-120.75	47	111.68	107.52-115.84
450-539	34	112.21	104.81-119.61	56	110.95	106.27-115.63
540-629	36	123.67	115.17-132.17	18	118.67	110.28-127.06
630-719	42	125.83	121.86-129.8	27	116.04	109.88-122.20
720-809	19	134.00	125.35-142.75	39	113.97	108.40-119.54
810-899	15	132.73	125.85-139.61	36	109.31	102.64-115.98
900-989	24	127.71	121.3-134.12	10	115.00	107.23-122.77
990-1079	8	130.50	114.74-146.26	30	111.33	106.27-116.39
1080-1169	8	136.63	108.49-164.77	7	120.29	105.52-135.06
1170-1259	7	117.29	86.35-148.23	7	112.57	100.52-124.62
1260-1349	15	124.20	111.94-136.46	10	115.10	104.96-125.24
1350-1439	10	121.10	104.91-137.29	13	116.31	98.90-133.72
1440-1529	18	104.06	94.41-113.71	9	112.11	98.17-126.05
1530-1619	10	124.40	110.17-138.63	14	116.14	108.82-123.46
1620-1709	13	98.69	89.17-108.21	9	113.00	95.34-130.66
1710-1799	6	118.67	98.09-139.25	3	100.00	74.78-125.22
1800-1890	6	130.00	102.12-157.87	18	106.17	95.42-116.92

Table 5.9: Haemoglobin results for men and for women
For all patients with haemoglobin results available. Results split by gender. Shown in 90-day intervals prior to date of diagnosis. Haemoglobin measured in g/L. Results shown to 2 decimal places.

14 patients had a haemoglobin result available within the periods 0-89 days before diagnosis, 360-449 days and 720-809 days before. Analysis of these matched samples showed a significant decrease in haemoglobin over time (one-way repeated measures ANOVA with Greenhouse-Geisser correction, $F=19.981$, $p<0.0005$). There was a significant decrease from 720-809 days to 0-89 days (post-hoc analysis with Bonferroni adjustment, $p<0.0005$), and from 360-449 days to 0-89 days (post-hoc analysis with Bonferroni adjustment, $p=0.007$), but not from 720-809 days to 360-449 days (post-hoc analysis with Bonferroni adjustment, $p=0.098$).

MCV and Haematocrit

Results for MCV are shown in Figure 5.3 and Table 5.10. Results for haematocrit are shown in Figure 5.4 and Table 5.11.

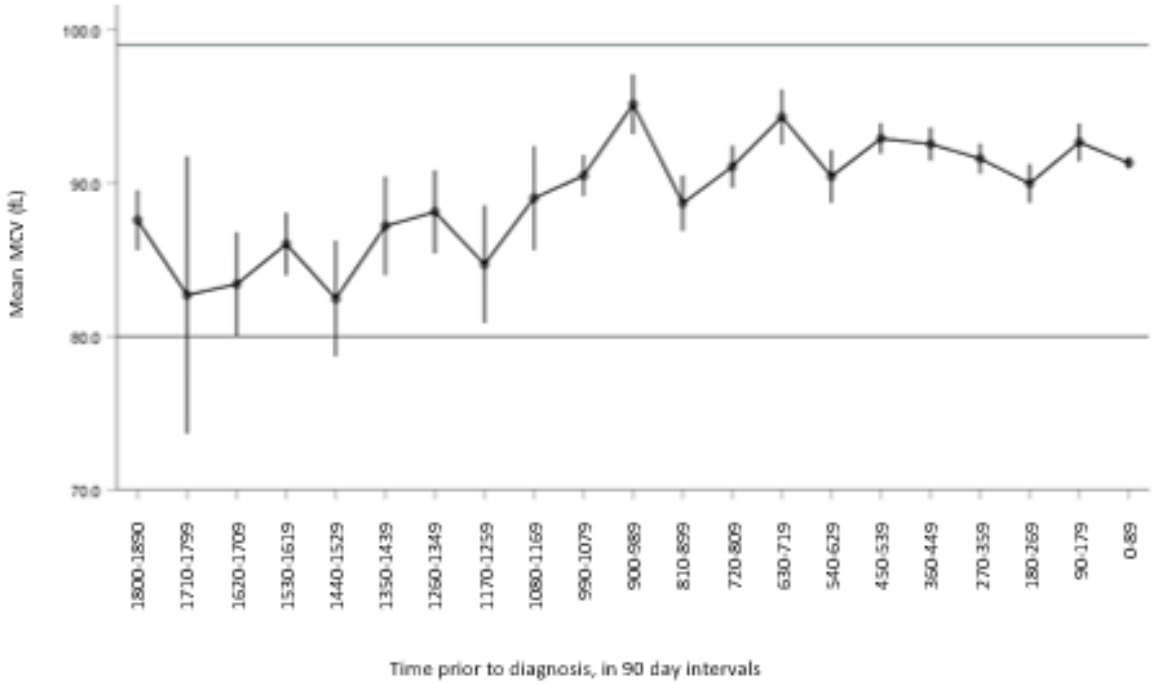


Figure 5.3: Mean MCV prior to diagnosis.
Mean MCV (mean corpuscular volume) in fL, for each 90-day interval prior to date of diagnosis. 95% confidence interval for the mean shown. Horizontal lines demonstrate upper and lower limit of normal (80-99fL).

Interval (days before diagnosis)	Number of results	Mean MCV (fL)	95% Confidence interval
0-89	1219	91.319	90.93-91.70
90-179	137	92.653	91.41-93.89
180-269	108	89.969	88.71-91.23
270-359	110	91.588	90.60-92.58
360-449	87	92.539	91.46-93.62
450-539	89	92.901	91.91-93.90
540-629	53	90.432	88.71-92.16
630-719	69	94.301	92.50-96.10
720-809	57	91.067	89.70-92.44
810-899	51	88.682	86.88-90.49
900-989	34	95.129	93.18-97.08
990-1079	38	90.484	89.14-91.83
1080-1169	15	89.013	85.61-92.41
1170-1259	14	84.700	80.87-88.53
1260-1349	25	88.116	85.41-90.82
1350-1439	23	87.204	83.99-90.42
1440-1529	27	82.463	78.69-86.24
1530-1619	24	86.021	83.97-88.07
1620-1709	22	83.405	80.03-86.79
1710-1799	9	82.700	73.66-91.74
1800-1890	24	87.575	85.62-89.53

Table 5.10: Mean MCV prior to diagnosis.
Mean MCV (mean corpuscular volume) in fL, for each 90-day period prior to date of diagnosis.
Mean shown to 3 decimal places, confidence intervals shown to 2 decimal places.

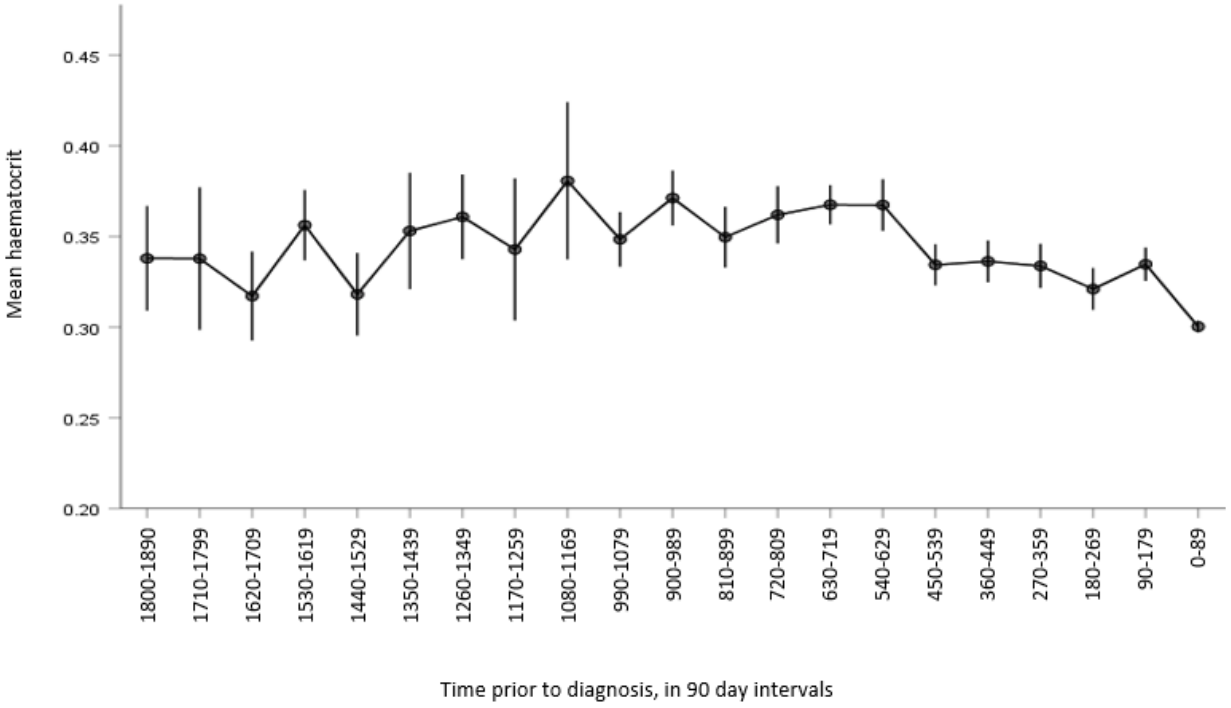


Figure 5.4: Haematocrit prior to diagnosis.
Mean haematocrit for each 90-day interval prior to diagnosis. 95% confidence interval for the mean shown.

Interval (days before diagnosis)	Number of results	Mean haematocrit	95% Confidence interval
0-89	1216	0.3003	0.2969-0.3031
90-179	137	0.3347	0.3258-0.3442
180-269	106	0.3210	0.3094-0.3326
270-359	109	0.3338	0.3216-0.3460
360-449	86	0.3363	0.3248-0.3478
450-539	89	0.3344	0.3230-0.3458
540-629	53	0.3674	0.3531-0.3817
630-719	68	0.3675	0.3566-0.3784
720-809	56	0.3620	0.3461-0.3779
810-899	51	0.3496	0.3328-0.3664
900-989	33	0.3712	0.3561-0.3863
990-1079	38	0.3484	0.3333-0.3635
1080-1169	19	0.3711	0.3348-0.4074
1170-1259	14	0.3429	0.3037-0.3821
1260-1349	24	0.3608	0.3374-0.3842
1350-1439	23	0.3530	0.3209-0.3851
1440-1529	27	0.3181	0.2953-0.3409
1530-1619	24	0.3563	0.3369-0.3757
1620-1709	21	0.3171	0.2926-0.3416
1710-1799	9	0.3378	0.2985-0.3771
1800-1890	24	0.3379	0.3090-0.3668

Table 5.11: Mean haematocrit prior to diagnosis.
Mean and 95% confidence interval for the mean for haematocrit results for each 90-day interval prior to date of diagnosis. Results shown to 4 decimal places (as haematocrit normally reported to two decimal places).

14 patients had an MCV result available within the periods 0-89 days before diagnosis, 360-449 days and 720-809 days before. For these samples, there was no significant change in MCV over time (one-way repeated measures ANOVA, $p=0.811$).

13 patients had a haematocrit result available within the periods 0-89 days before diagnosis, 360-449 days and 720-809 days before. Analysis of these matched samples showed a significant decrease in haematocrit over time (one-way repeated measures ANOVA with Greenhouse-Geisser correction, $F=19.459$, $p<0.0005$). There was a significant decrease from 720-809 days to 0-89 days (post-hoc analysis with Bonferroni adjustment, $p=0.001$), and from 360-449 days to 0-89 days (post-hoc analysis with Bonferroni adjustment, $p=0.006$), but not from 720-809 days to 360-449 days (post-hoc analysis with Bonferroni adjustment, $p=0.302$).

Corrected calcium, CRP and creatinine

Results for corrected calcium are shown in Figure 5.5 and Table 5.12, for CRP in Figure 5.6 and Table 5.13, and for serum creatinine in Figure 5.7 and Table 5.14.

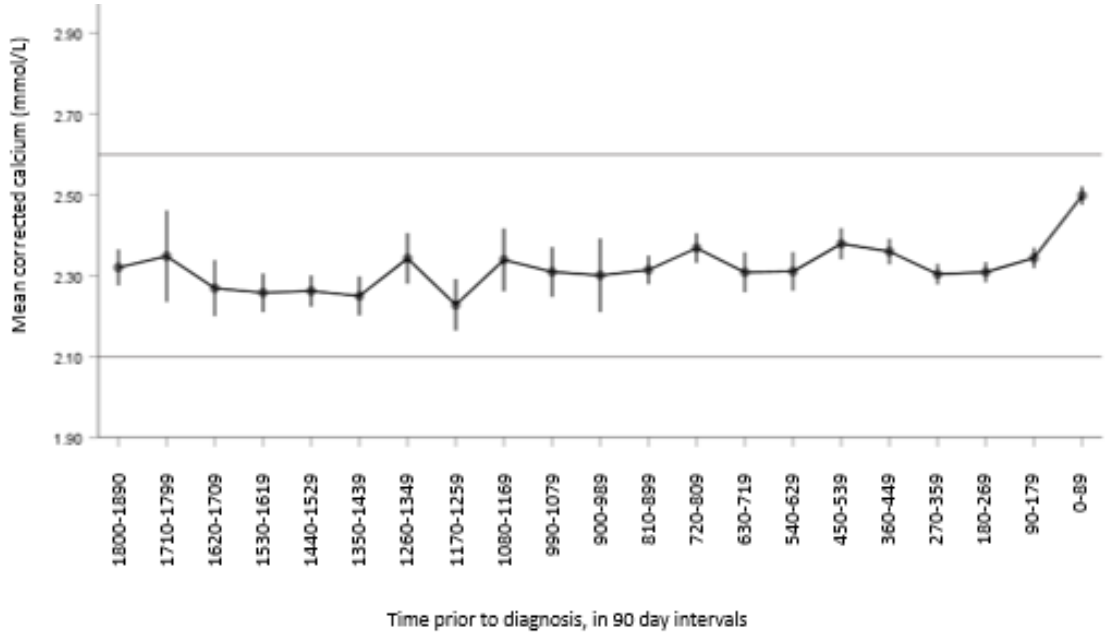


Figure 5.5: Mean corrected calcium prior to diagnosis.
Mean corrected calcium (mmol/L) in 90-day intervals prior to date of diagnosis. 95% confidence intervals shown. Horizontal lines demonstrate upper and lower limit of normal (2.1-2.6mmol/L).

Interval (days before diagnosis)	Number of results	Mean corrected calcium (mmol/L)	95% Confidence interval
0-89	1049	2.4983	2.47-2.52
90-179	101	2.3442	2.32-2.37
180-269	81	2.3089	2.28-2.33
270-359	91	2.3041	2.28-2.33
360-449	66	2.36	2.33-2.39
450-539	55	2.3791	2.34-2.42
540-629	40	2.3107	2.26-2.36
630-719	39	2.3087	2.26-2.36
720-809	43	2.3686	2.33-2.41
810-899	44	2.3145	2.28-2.35
900-989	17	2.3012	2.21-2.39
990-1079	26	2.3096	2.25-2.37
1080-1169	14	2.3393	2.26-2.42
1170-1259	11	2.2282	2.16-2.29
1260-1349	21	2.3429	2.28-2.41
1350-1439	16	2.25	2.2-2.3
1440-1529	21	2.2624	2.22-2.3
1530-1619	15	2.258	2.21-2.31
1620-1709	14	2.2693	2.2-2.34
1710-1799	6	2.3483	2.23-2.46
1800-1890	18	2.3206	2.28-2.37

Table 5.12: Mean corrected calcium prior to diagnosis
Mean corrected calcium (mmol/L) in 90-day intervals prior to diagnosis. 95% confidence interval for the mean shown. Mean to 4 decimal places. Confidence intervals to 2 decimal places.

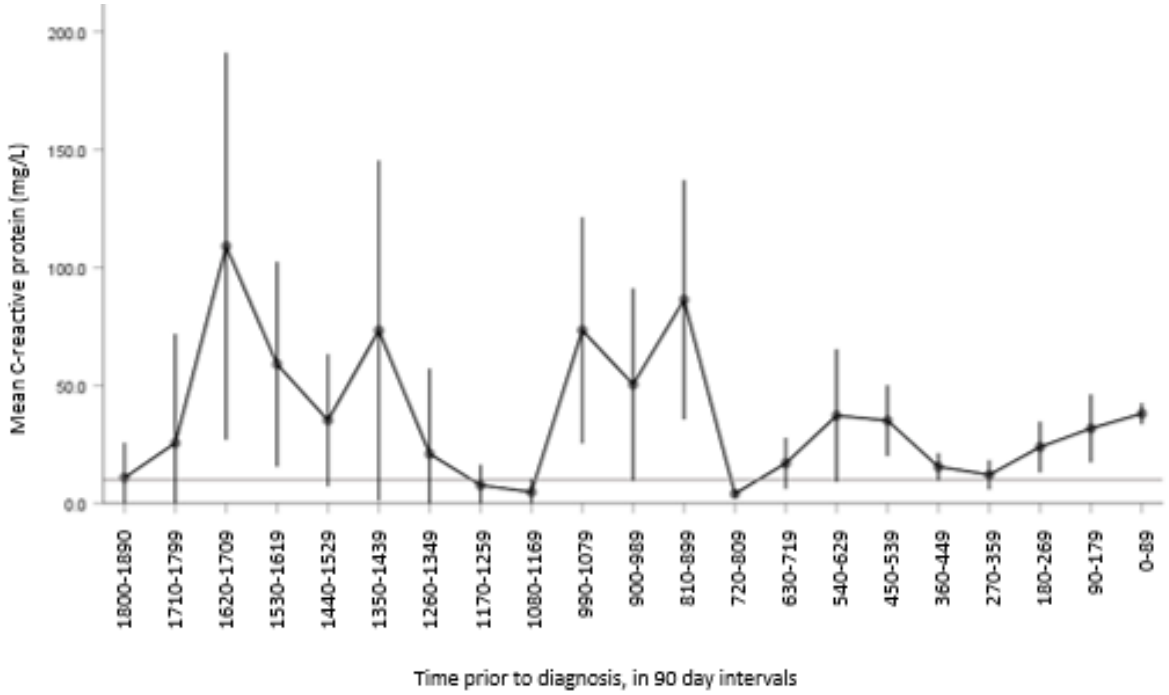


Figure 5.6: Mean CRP prior to diagnosis.
Mean CRP (mg/L) in 90-day intervals prior to the date of diagnosis. 95% confidence intervals shown, where 95% confidence intervals included negative values, this portion of the confidence interval is not shown as CRP cannot have a negative value. Horizontal line denotes upper limit of normal (10mg/L).

Interval (days before diagnosis)	Number of results	Mean CRP (mg/L)	95% Confidence interval
0-89	908	38.046	33.58-42.52
90-179	97	31.774	17.35-46.2
180-269	72	23.894	13.13-34.66
270-359	72	12.09	5-87-18.31
360-449	49	15.5	9.67-21.33
450-539	58	35.1	20.03-50.17
540-629	27	37.222	9.08-65.36
630-719	33	17.003	6.17-27.84
720-809	36	4.061	2.46-5.66
810-899	27	86.326	35.54-137.11
900-989	14	50.429	9.67-91.19
990-1079	18	73.361	25.37-121.35
1080-1169	8	4.75	-1.06 -10.56
1170-1259	3	7.667	-1.06 - 16.39
1260-1349	14	20.964	-15.25 - 57.18
1350-1439	8	73.275	1.13-145.42
1440-1529	15	35.233	7.17-63.29
1530-1619	18	59	15.54-102.46
1620-1709	13	109.038	26.92-191.16
1710-1799	5	25.6	-20.65 - 71.85
1800-1890	11	10.864	-4.07 - 25.8

Table 5.13: Mean CRP prior to diagnosis
Mean CRP (mg/L) shown in 90-day intervals prior to date of diagnosis. 95% confidence intervals for the mean shown. Note some 95% confidence intervals included values less than 0 however CRP cannot be a negative value.

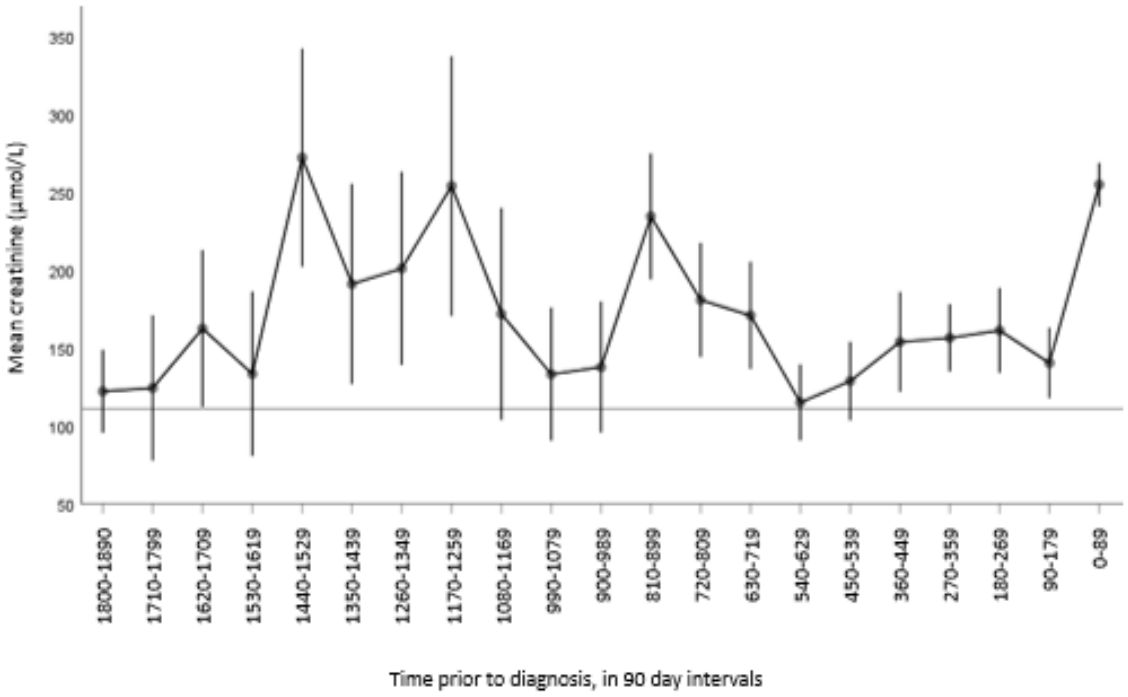


Figure 5.7: Mean creatinine prior to diagnosis
Mean creatinine (µmol/L) in 90-day intervals prior to date of diagnosis, shown with 95% confidence intervals. Horizontal line denoted upper limit of normal (111µmol/L).

Interval (days before diagnosis)	Number of results	Mean creatinine (µmol/L)	95% Confidence interval
0-89	1329	254.81	240.87-268.75
90-179	142	140.49	117.84-163.14
180-269	125	161.34	134.14-188.54
270-359	119	156.54	134.87-178.21
360-449	100	153.93	121.89-185.97
450-539	101	128.85	103.7-154
540-629	57	115.12	90.77-139.47
630-719	71	170.97	136.56-205.38
720-809	68	180.82	144.23-217.41
810-899	65	234.43	193.98-274.88
900-989	34	137.79	95.73-179.85
990-1079	42	133.26	90.61-175.91
1080-1169	20	171.9	103.98-239.82
1170-1259	18	253.89	170.62-337.16
1260-1349	26	201.08	139.12-263.04
1350-1439	23	191.09	126.85-255.33
1440-1529	27	272.02	202.04-342
1530-1619	27	133.52	80.84-186.21
1620-1709	23	162.52	112.24-212.8
1710-1799	18	124.44	77.87-171.01
1800-1890	32	122.25	95.65-148.85

Table 5.14: Mean creatinine prior to diagnosis
Mean creatinine (µmol/L) in 90-day intervals prior to date of diagnosis, 95% confidence interval for the mean. Results shown to 2 decimal places.

8 patients had a corrected calcium result available within the periods 0-89 days before diagnosis, 360-449 days and 720-809 days before. For these samples, there was no statistically significant change in corrected calcium over time (one-way repeated measures ANOVA with Greenhouse-Geisser correction, F=0.656, p= 0.451).

7 patients had a CRP result available within the periods 0-89 days before diagnosis, 360-449 days and 720-809 days before. For these samples, there was no statistically significant change in CRP over time (one-way repeated measures ANOVA with Greenhouse-Geisser correction, F=1.078, p= 0.348).

15 patients had a creatinine result available within the periods 0-89 days before diagnosis, 360-449 days and 720-809 days before. For these samples, there was no statistically significant change in creatinine over time (one-way repeated measures ANOVA with Greenhouse-Geisser correction, F=0.815, p= 0.392).

Albumin and total protein

Results for serum albumin in Figure 5.8 and Table 5.15. Results for serum total protein are shown in Figure 5.9 and Table 5.16.

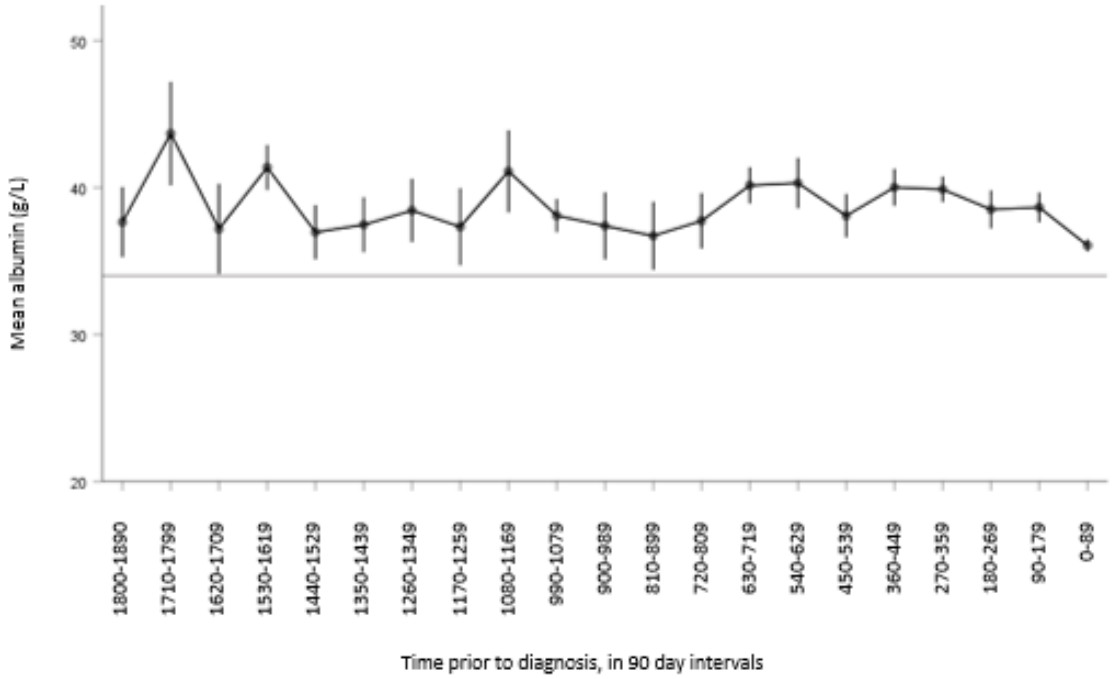


Figure 5.8: Mean serum albumin prior to diagnosis
Mean serum albumin (g/L) for 90-day intervals prior to date of diagnosis, shown with 95% confidence intervals. Horizontal line denotes lower limit of normal (34g/L).

Interval (days before diagnosis)	Number of results	Mean serum albumin (g/L)	95% Confidence interval
0-89	1148	36.06	35.64-36.48
90-179	128	38.65	37.63-39.66
180-269	101	38.51	37.22-39.8
270-359	110	39.88	39.01-40.75
360-449	85	40.01	38.76-41.26
450-539	79	38.09	36.61-39.57
540-629	52	40.31	38.6-42.02
630-719	53	40.15	38.92-41.38
720-809	60	37.73	35.84-39.62
810-899	53	36.72	34.41-39.03
900-989	33	37.39	35.1-39.68
990-1079	32	38.09	36.96-39.22
1080-1169	19	41.11	38.32-43.9
1170-1259	15	37.33	34.71-39.95
1260-1349	25	38.44	36.28-40.6
1350-1439	19	37.47	35.6-39.34
1440-1529	27	36.96	35.12-38.8
1530-1619	19	41.37	39.84-42.9
1620-1709	21	37.19	34.13-40.25
1710-1799	9	43.67	10.1-77.24
1800-1890	20	37.65	35.27-40.03

Table 5.15: Mean serum albumin prior to diagnosis
Mean serum albumin (g/L) in 90-day intervals prior to date of diagnosis. 95% confidence interval for the mean shown. Results to 2 decimal places.

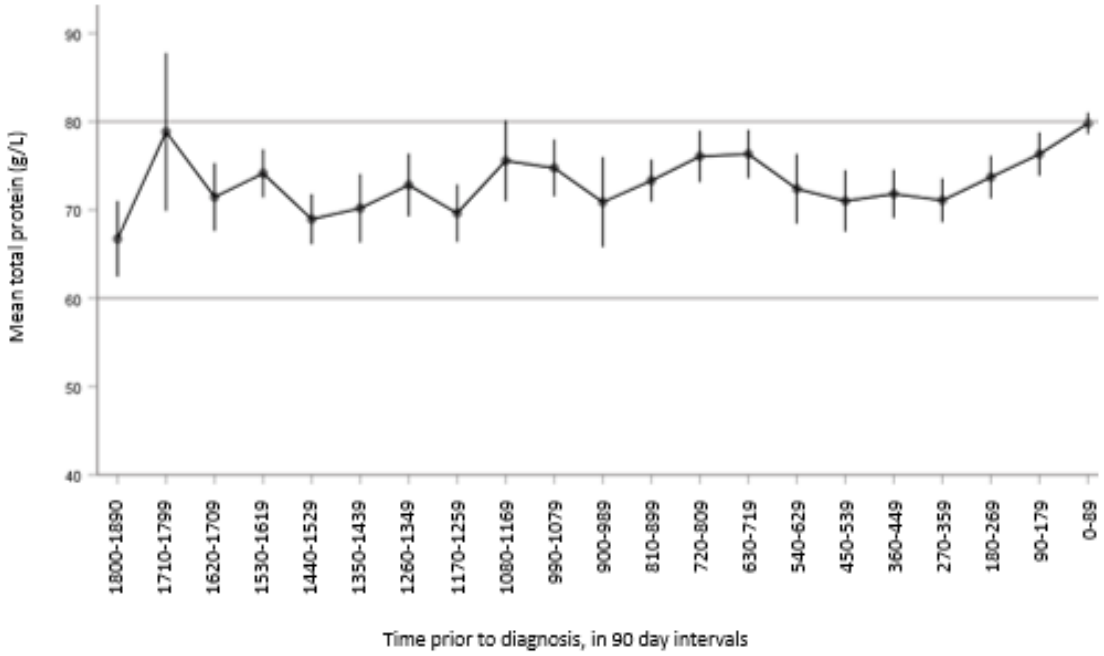


Figure 5.9: Mean serum total protein prior to diagnosis
Mean serum total protein (g/L) in 90-day intervals prior to date of diagnosis, shown with 95% confidence intervals. Horizontal lines denote upper and lower limit of normal range (60-80g/L).

Interval (days before diagnosis)	Number of results	Mean serum total protein (g/L)	95% Confidence interval
0-89	1024	79.8	78.59-81.01
90-179	102	76.32	73.87-78.77
180-269	81	73.72	71.29-76.15
270-359	91	71.09	68.61-73.57
360-449	65	71.82	69.07-74.57
450-539	55	71.02	67.54-74.5
540-629	41	72.39	68.44-76.34
630-719	39	76.33	73.6-79.06
720-809	45	76.07	73.15-78.97
810-899	44	73.32	70.93-75.71
900-989	18	70.89	65.8-75.98
990-1079	28	74.75	71.53-77.97
1080-1169	14	75.57	70.99-80.15
1170-1259	11	69.64	66.39-72.89
1260-1349	22	72.82	69.27-76.37
1350-1439	16	70.19	66.31-74.97
1440-1529	21	68.95	66.12-71.78
1530-1619	15	74.13	71.41-76.85
1620-1709	15	71.47	67.63-75.31
1710-1799	6	78.83	69.89-87.77
1800-1890	18	66.72	62.43-71.01

Table 5.16: Mean serum total protein prior to diagnosis.
Mean serum total protein (g/L) in 90-day intervals prior to date of diagnosis. 95% confidence interval for the mean shown. Results shown to 2 decimal places.

14 patients had a serum albumin result available within the periods 0-89 days before diagnosis, 360-449 days and 720-809 days before. For these samples, there was no statistically significant change in serum albumin over time (one-way repeated measures ANOVA, p= 0.111).

9 patients had a serum total protein result available within the periods 0-89 days before diagnosis, 360-449 days and 720-809 days before. For these samples, there was no statistically significant change in serum total protein over time (one-way repeated measures ANOVA, p= 0.255).

5.5.4 Calculated globulin

5.5.4.1 Patients without myeloma

56 patients with autoimmune hepatitis were identified, with 218 results in total available with concurrent albumin, protein and immunoglobulin measurement. Most results were from January 2015 to October 2016, with one result from 2014, one from 2004 and one from 2002.

Calculated globulin for these samples ranged from 17g/L to 87g/L. Two results were over 80g/L – both were from the same patient, who had HIV as well as autoimmune hepatitis.

The correlation between CG and the sum of IgG, IgM and IgA levels is shown in Figure 5.10. There was a strong positive correlation between CG level and total measured Ig level (Spearman's Rho, $r_S(216)=0.932$, $p<0.0005$).

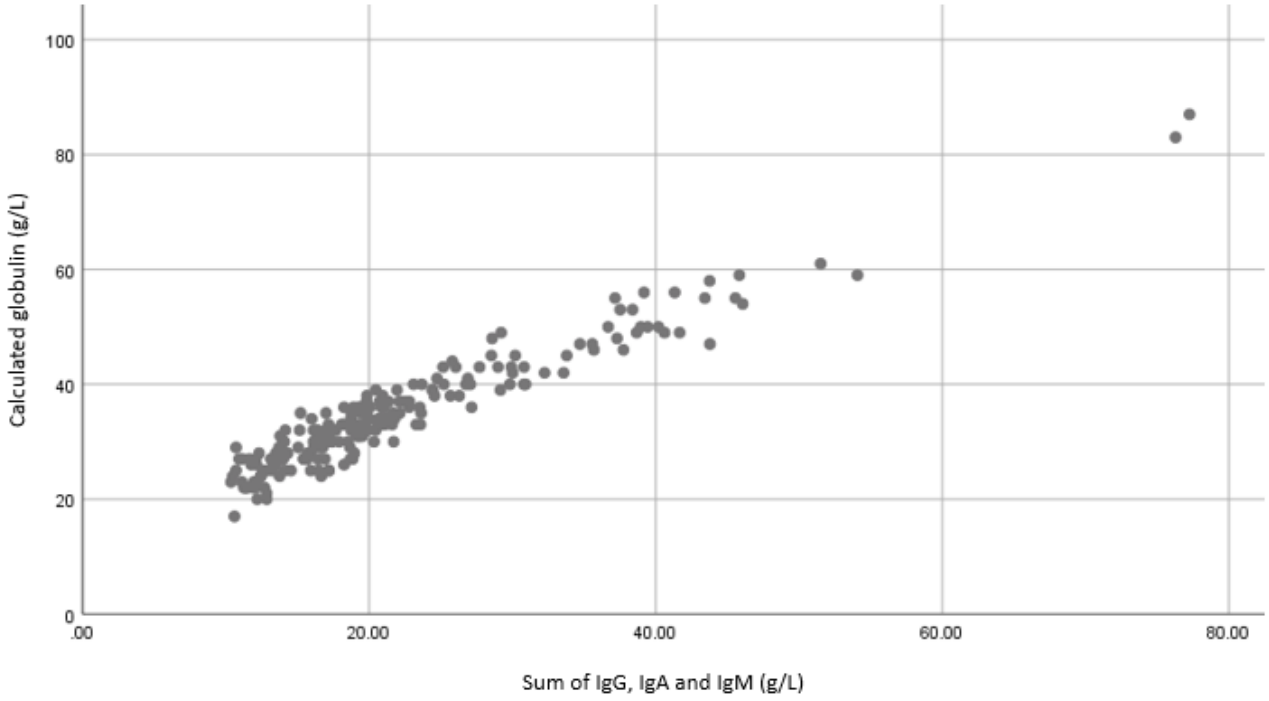


Figure 5.10: Correlation between sum of immunoglobulin classes and calculated globulin.
218 results from 56 patients with autoimmune hepatitis at UHB. Immunoglobulin levels and calculated globulin in g/L.
Spearman's rank-order correlation: $r_s(216)=0.932$, $p<0.0005$

The correlation between calculated globulin and each measured immunoglobulin class is shown in Figures 5.11, 5.12 and 5.13. Comparing calculated globulin level to IgG level, there was a strong positive correlation (Spearman's Rho, $r_s(216)=0.884$, $p<0.0005$). Comparison of IgA levels and CG showed a weak positive correlation (Spearman's Rho, $r_s(216)=0.445$, $p<0.0005$). There was minimal positive correlation between IgM levels and CG (Spearman's Rho, $r_s(216)=0.24$, $p<0.0005$).

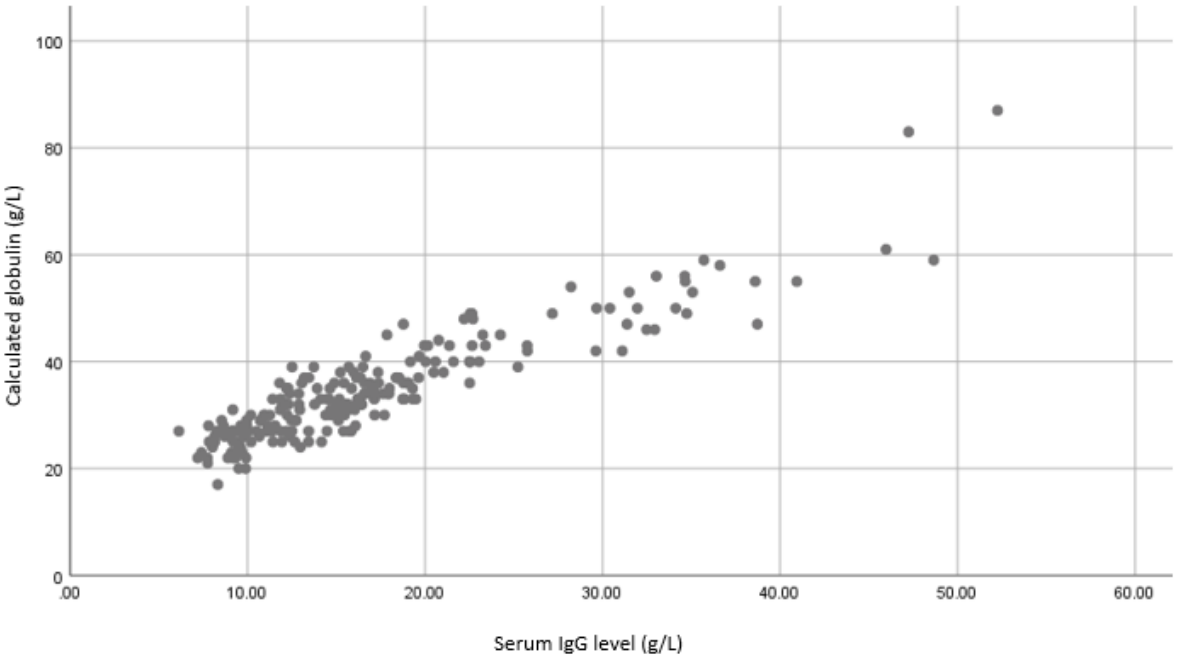


Figure 5.11: Correlation between serum IgG level and calculated globulin.
Serum IgG level and calculated globulin in g/L. 218 results from 56 patients with autoimmune hepatitis at UHB.
Spearman's rank-order correlation: $r_s(216)=0.884$, $p<0.0005$.

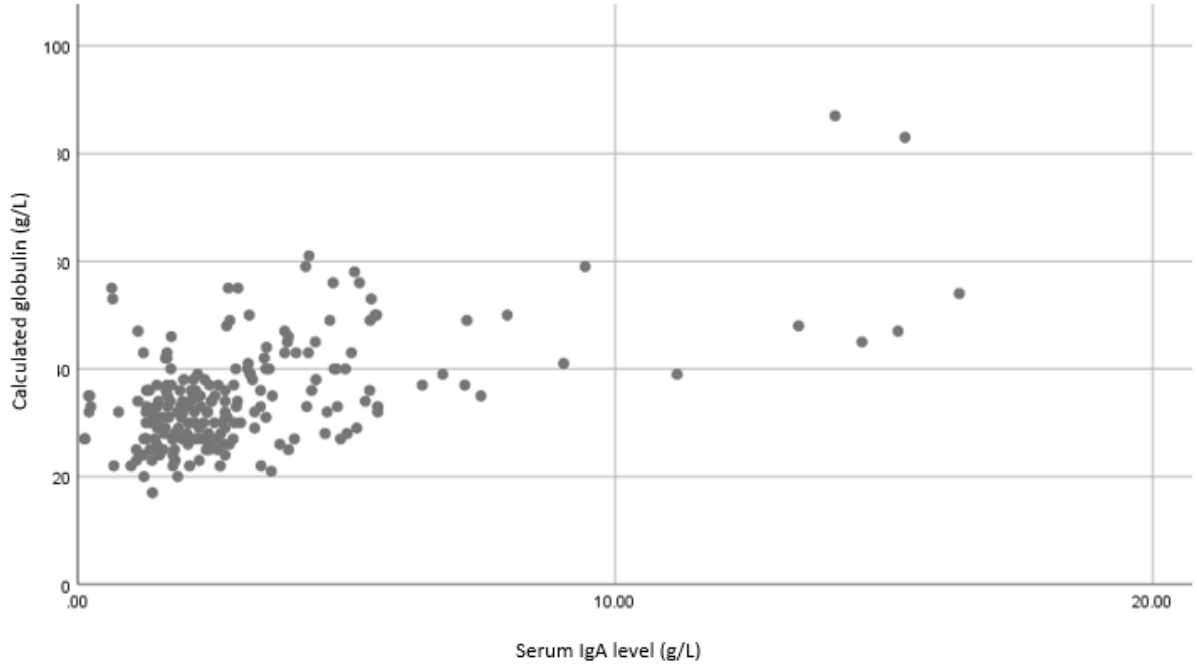


Figure 5.12: Correlation between serum IgA level and calculated globulin.
Serum IgA level and calculated globulin in g/L. 218 results from 56 patients with autoimmune hepatitis at UHB.
Spearman's rank-order correlation: $r_s(216)=0.445$ ($p<0.0005$).

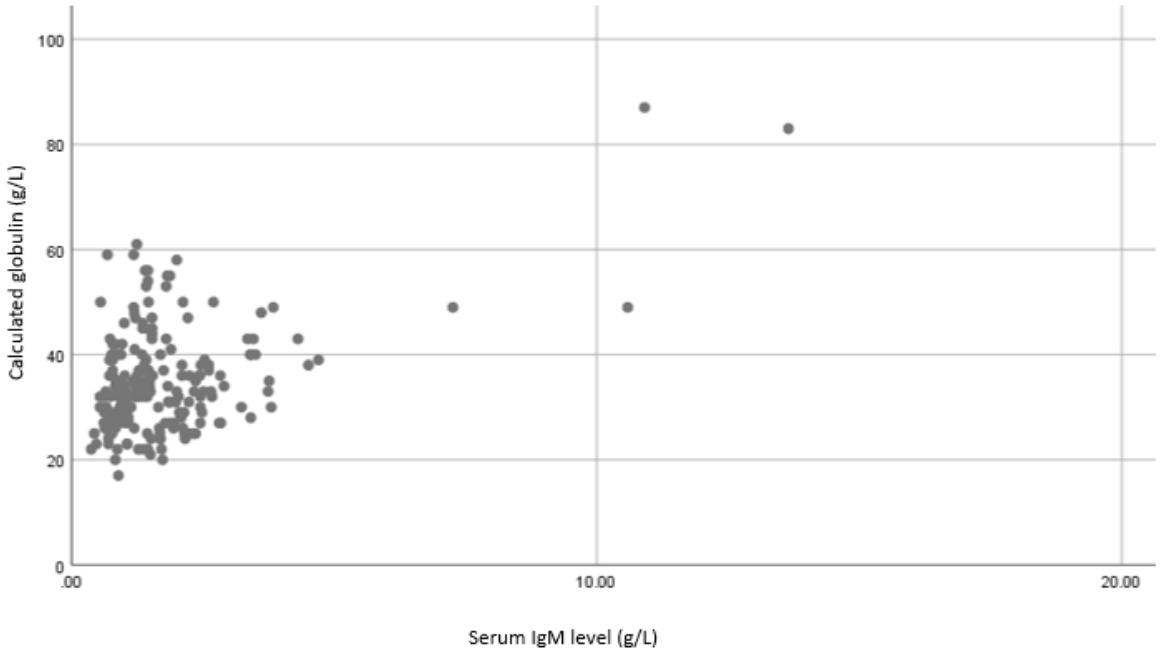


Figure 5.13: Correlation between serum IgM level and calculated globulin.
Serum IgM level and calculated globulin in g/L. 218 results from 56 patients with autoimmune hepatitis at UHB.
Spearman's rank-order correlation: $r_s(216)=0.24$ ($p<0.0005$).

Results comparing only the immunoglobulin results from the CIS showed a strong positive correlation between CG and total measured Ig level (Spearman's Rho, $r_s(207)=0.927$ ($p<0.0005$)), and between CG and IgG level (Spearman's Rho, $r_s(207)=0.877$ ($p<0.0005$)). Only a weak correlation was shown between IgA and CG (Spearman's Rho, $r_s(207)=0.445$ ($p<0.0005$)) and minimal correlation between IgM and CG (Spearman's Rho, $r_s(207)=0.213$ ($p<0.0005$)).

The 9 results available from samples run by Biochemistry at UHB showed a strong positive correlation between total measured Ig level and CG (Spearman's Rho, $r_s(7)= 0.979$, $p<0.0005$). There was also a strong positive correlation between the IgG results and CG (Spearman's Rho, $r_s(7)=0.946$, $p<0.0005$). There was no statistically significant correlation between IgA level and CG (Spearman's Rho, $p=0.412$). There was a significant positive correlation between IgM level and CG (Spearman's Rho, $r_s(7)=0.828$, $p=0.006$).

5.5.4.2 Patients with myeloma

75 patients with myeloma had a result with albumin, total protein, and immunoglobulin levels measured within 24 hours, in the 14 days prior to diagnosis. Calculated globulin results in this group ranged from 15g/L to 133g/L. Comparison between calculated globulin and the total measured immunoglobulin level (combined IgG, IgA and IgM levels) showed a strong positive correlation (Spearman's Rho, $r_S(73)= 0.961$, $p<0.0005$), as shown below in Figure 5.14.

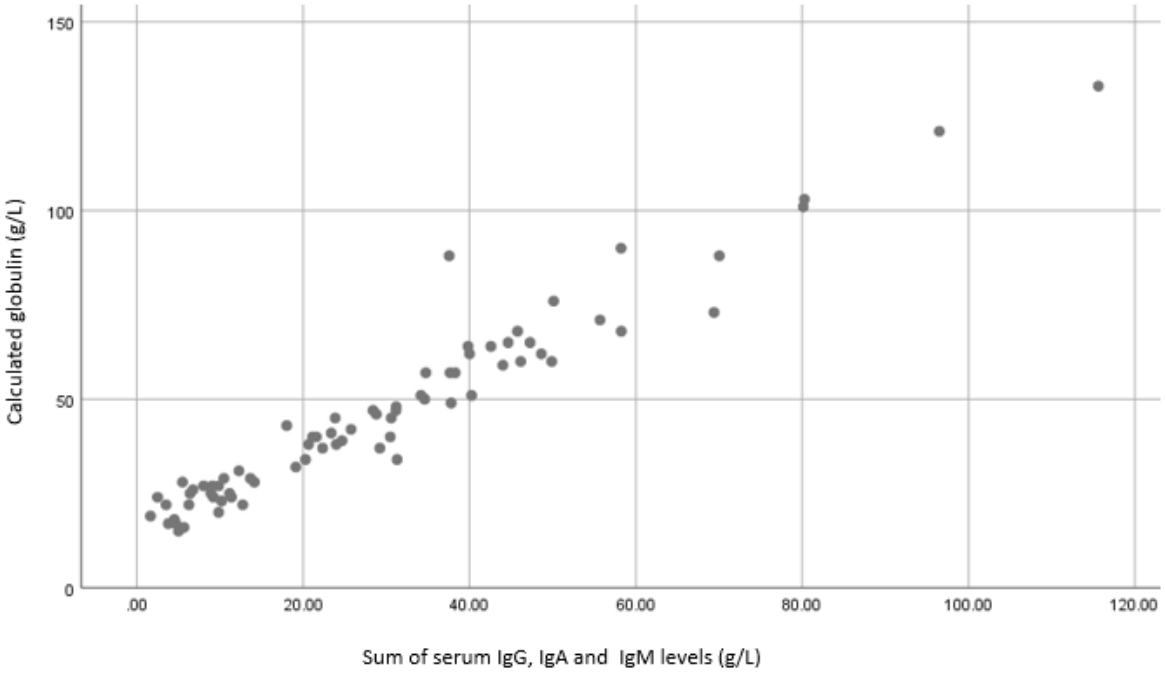


Figure 5.14: Correlation between calculated globulin and the sum of measured immunoglobulin in patients with myeloma. Results for 75 patients diagnosed with multiple myeloma at UHB, within 14 days of diagnosis. Results measured in g/L. Spearman's rank-order correlation (data not normally distributed): $r_s(73)= 0.961$ ($p<0.0005$).

However, when comparing calculated globulin to the levels of each of the measured class of immunoglobulins (IgG, IgA and IgM), scatterplots of the two variables showed that there was not the linear relationship that was noted in the patients with autoimmune hepatitis described in section 5.5.4.1. Figures 5.15, 5.16 and 5.17 show the relationship between calculated globulin and serum levels of IgG, IgA and IgM in these patients.

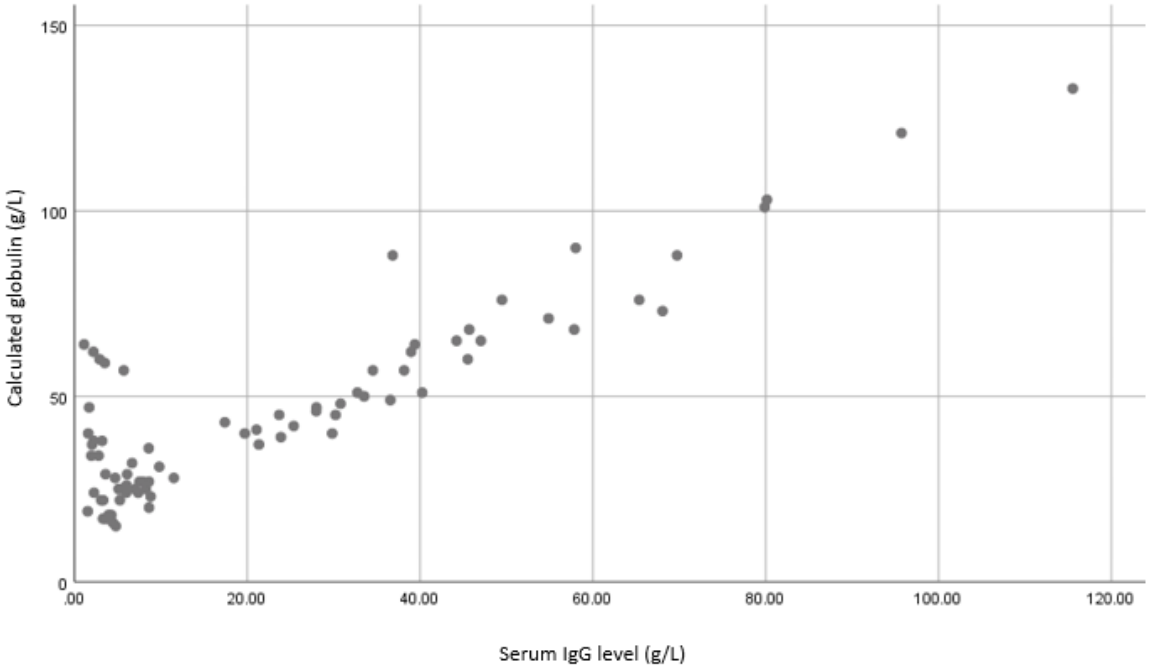


Figure 5.15: Correlation between calculated globulin and serum IgG level in patients with multiple myeloma. Results for 75 patients diagnosed with multiple myeloma at UHB, within 14 days of diagnosis. Results measured in g/L.

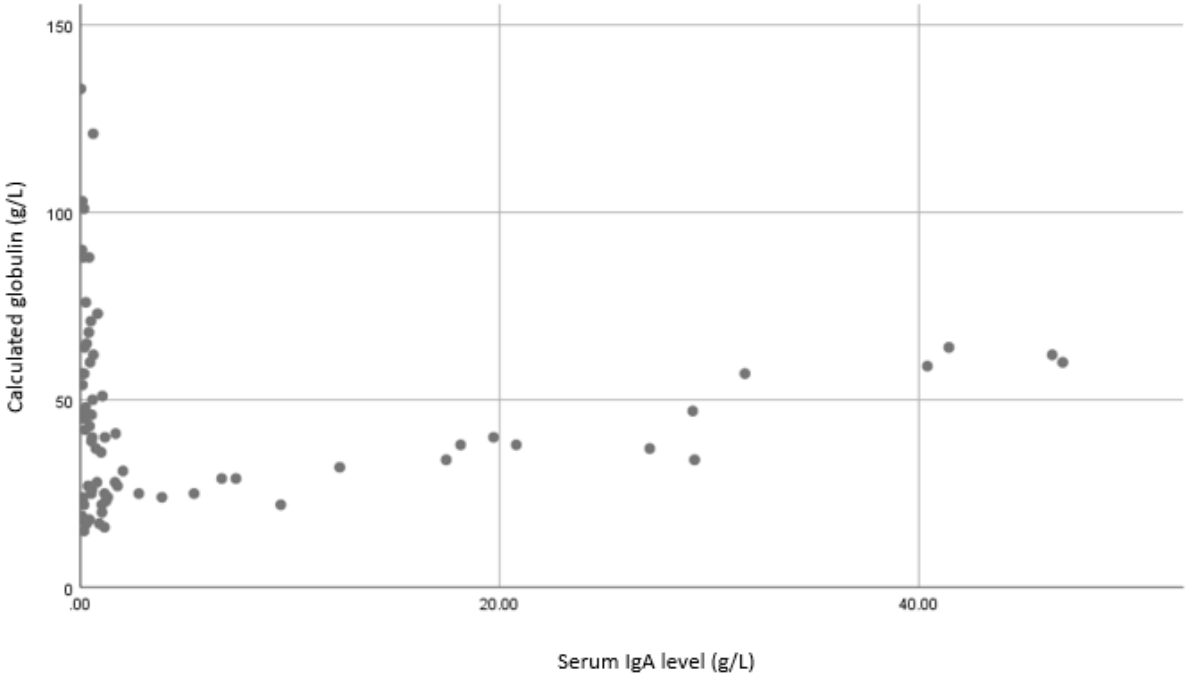


Figure 5.16: Correlation between calculated globulin and serum IgA level in patients with multiple myeloma. Results for 75 patients diagnosed with multiple myeloma at UHB, within 14 days of diagnosis. Results measured in g/L

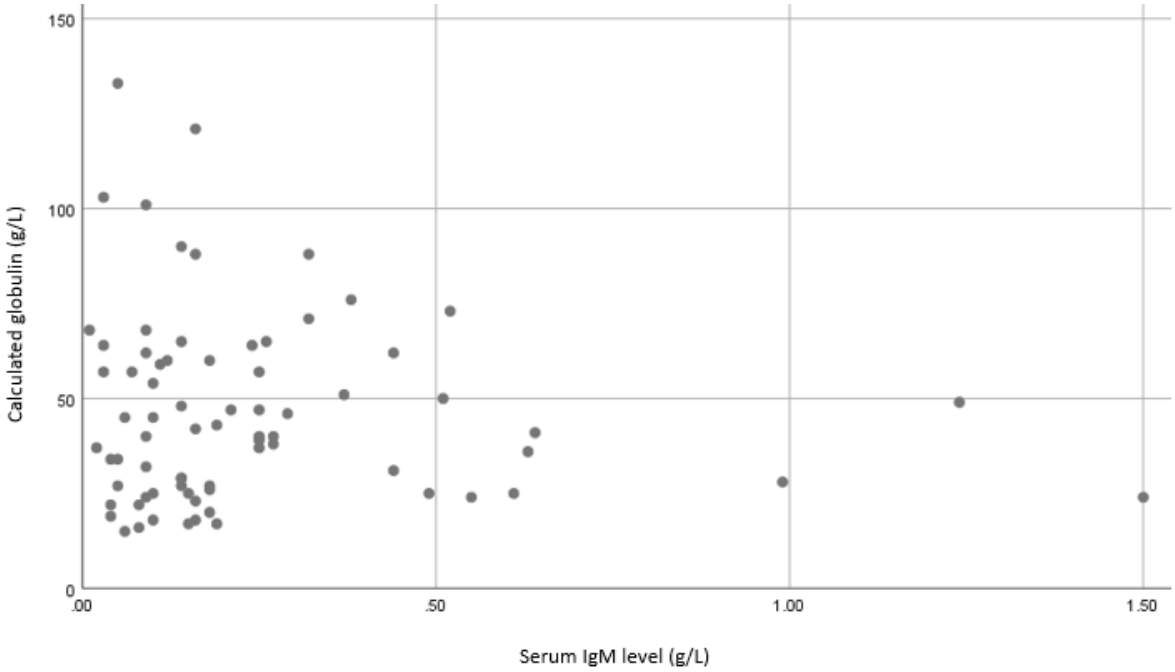


Figure 5.17: Correlation between calculated globulin and serum IgM level in patients with multiple myeloma. Results for 75 patients diagnosed with multiple myeloma at UHB, within 14 days of diagnosis. Results measured in g/L

5.5.4.3 Calculated globulin prior to diagnosis

Table 5.17 shows the mean calculated globulin level in 90-day intervals prior to diagnosis in patients diagnosed with multiple myeloma at UHB. This is also shown in Figure 5.18.

Interval (days before diagnosis)	Number of results	Mean calculated globulin (g/L)	95% Confidence interval
0-89	1021	43.57	42.21-44.93
90-179	101	37.98	35.14-40.82
180-269	80	35.24	32.08-38.4
270-359	91	31.49	29.14-33.84
360-449	65	31.45	29.01-33.89
450-539	55	32.91	30.15-35.67
540-629	41	32.34	29.3-35.38
630-719	39	36.51	34.04-38.98
720-809	45	39.6	36.66-42.54
810-899	44	37.36	34.98-39.74
900-989	18	31.17	27.52-34.82
990-1079	28	36.68	33.74-39.62
1080-1169	14	34.21	30.58-37.84
1170-1259	11	33.82	30.93-36.71
1260-1349	22	34.77	32.02-37.52
1350-1439	16	33.06	30.66-35.46
1440-1529	21	32.1	30.36-33.84
1530-1619	15	32.8	29.91-35.69
1620-1709	15	32.07	29.78-34.36
1710-1799	6	36.17	31.85-40.49
1800-1890	18	29.11	25.73-32.49

Table 5.17: Mean calculated globulin prior to diagnosis
Mean calculated globulin (g/L) in 90-day intervals prior to date of diagnosis, 95% confidence interval for the mean. Results for patients with multiple myeloma diagnosed at UHB. Results are shown to 2 decimal places.

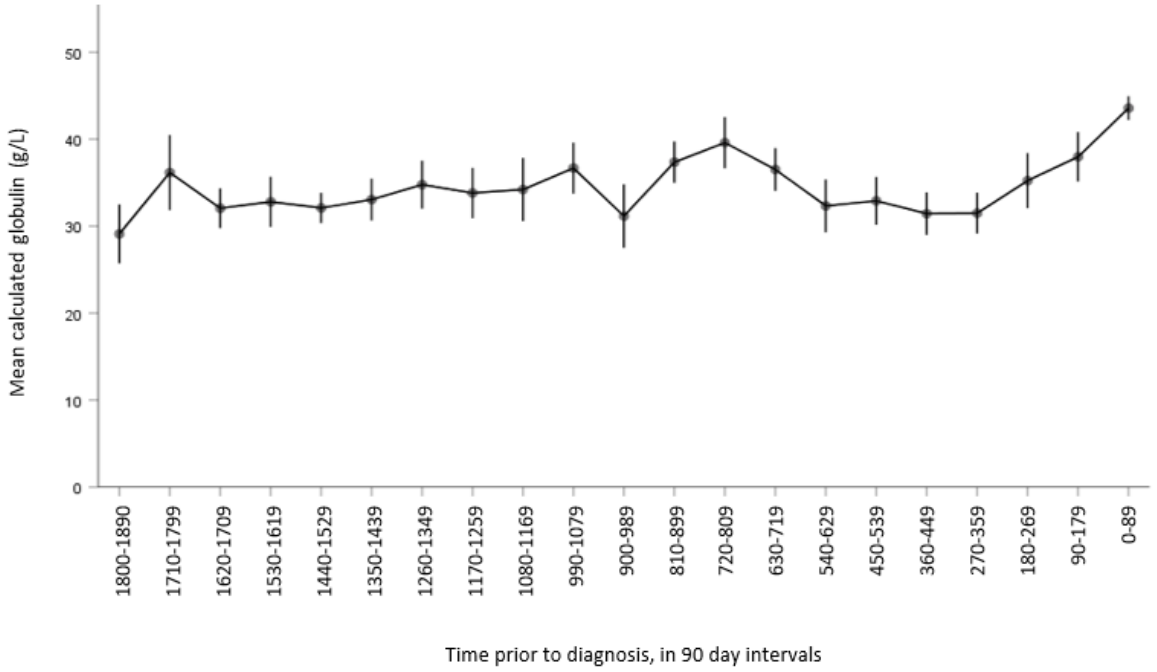


Figure 5.18: Mean calculated globulin prior to diagnosis in patients with multiple myeloma
Mean calculated globulin level (g/L) in 90-day intervals prior to date of diagnosis, from results available for 285 patients diagnosed with multiple myeloma at UHB, shown with 95% confidence intervals.

Calculated globulin could be determined for 242 patients diagnosed with multiple myeloma at UHB in the 14 days preceding the date of diagnosis. The number with an abnormal calculated globulin result is shown in Table 5.18.

	Number with results	**Calculated globulin above 45g/L**		**Calculated globulin below 18g/L**	
Overall	242	43.8%	106/242	2.5%	6/242
By subtype:					
IgG	119	68.9%	82/119	0%	
IgA	46	50%	23/46	0%	
IgD	6	0%		16.7%	1/6
Biclonal	1	0%		0%	
Light chain	66	1.5%	1/66	7.6%	5/66
Unknown/ non-secretory	4	0%		0%	

Table 5.18: Abnormal calculated globulin in patients newly diagnosed with multiple myeloma.
Results in the 14 days prior to diagnosis for patients diagnosed with multiple myeloma at UHB. Data available for 242 patients.

5.6 Discussion

The key findings demonstrated in this chapter are:

- The most common abnormalities found on blood test results in newly diagnosed myeloma were low haematocrit, low haemoglobin, raised total protein and raised creatinine.
- Most patients with a low haemoglobin level had a normal MCV
- There was a statistically significant decline in haemoglobin over the two years prior to diagnosis
- Calculated globulin derived from serum albumin and total protein results correlates well with the combined level of IgG, IgA and IgM in the serum
- In those without myeloma, calculated globulin correlates well with serum IgG levels
- Calculated globulin is abnormal in a proportion of patients with myeloma, but not all patients

Most patients identified as having a new diagnosis of multiple myeloma had preceding blood test results available on the system. The most common abnormalities were low haematocrit, which was seen in 86% of patients, and low haemoglobin, which was seen in 81% of patients. Abnormalities in other components of the full blood count were less common.

When assessing changes in blood test results in the time preceding diagnosis, mean haemoglobin appeared to decline from the period that was 540-629 days prior to diagnosis. There appeared to be a decline in mean haematocrit over the same period. There was a statistically significant decrease in haemoglobin and haematocrit over the two years prior to diagnosis. Analysis of statistical differences before this time period was limited by patient numbers.

This decline in haemoglobin was seen in research by Koshiaris et al.(201) They also demonstrated that changes in creatinine and calcium levels appeared to occur close to diagnosis. This was similar to the findings demonstrated here, where a marked changed in mean corrected calcium and creatinine levels could be seen in the 90 days immediately preceding diagnosis. They demonstrated that CRP did not appear to change prior to diagnosis. The results shown here suggest there was considerable variation in CRP over the time prior to diagnosis, although it did appear to increase in the year prior to diagnosis. These abnormalities in CRP may reflect other concurrent conditions,(203) for instance infection, which is also likely to occur around the time of diagnosis.(200)

When identifying patients diagnosed with multiple myeloma at UHB, there were many patients who had been coded as having multiple myeloma on their electronic records who did not have multiple myeloma, or who had been diagnosed at other hospitals. The large number of patients diagnosed at another centre and then referred to UHB likely reflects patients being referred in to the local tertiary centre for specialist treatment such as stem cell transplantation.(8) The number of patients identified here as having myeloma diagnosed at UHB is appropriate for the incidence rate of myeloma and the size of population served by UHB.(189, 204) Because of the number of patients included, for some time periods prior to diagnosis there were only small numbers of results available within that time period. Comparing across time periods, there were only small numbers of patients with samples available in every time period, which allows statistical comparisons of change in test results over time. These small numbers limit the reliability of the results, and also mean that subtle changes in blood test results may not have been seen. The small number with results in every time period also limits the analysis of changes in multiple test results at the same time. Construction of an algorithm that could automatically detect these differences requires larger

sample sizes as the differences in test results are potentially small. This would require the inclusion of patients with newly diagnosed myeloma from multiple centres, as the incidence rate of myeloma means that relatively few patients will be diagnosed at each centre.

There was a strong correlation demonstrated between calculated globulin and the total measured immunoglobulin levels in those with and without myeloma. Patients with autoimmune hepatitis were chosen as a cohort for assessing this correlation as they are monitored using both liver function tests (including serum albumin and total protein levels) and immunoglobulin levels,(183) and therefore had multiple samples with all these results available for assessment. A 24-hour discrepancy in date of result between the albumin/total protein and immunoglobulin results was permitted as immunoglobulin results from the same sample are reported later due to logistics and local procedures.

There was a strong correlation between the total measured immunoglobulin levels (combined IgG, IgA and IgM). In those with autoimmune hepatitis there was also a strong linear correlation between CG and IgG. This relationship was not seen in those patients with myeloma, where the association between IgG and CG was not linear. Some patients with low levels of IgG had a raised calculated globulin level. This was also seen when comparing IgA levels and CG in those with myeloma. This is likely due to the associated immunoparesis that can be found in patients with myeloma.(205) Those with low IgG or IgA with a high calculated globulin likely have a paraprotein from a different immunoglobulin class, causing a raised calculated globulin overall.

In those with myeloma, there appeared to be an increase in calculated globulin in the year prior to diagnosis, with a similar increase in serum total protein level, although this was not

statistically significant. As discussed, the reliability of these results is affected by the relatively small sample sizes in each time period.

Although many patients diagnosed with myeloma did have an abnormal calculated globulin level, 54.5% of patients had a normal calculated globulin level at diagnosis. Compared to those with IgG or IgA myeloma, fewer of those with light chain myeloma had an abnormal calculated globulin at diagnosis. Light chains are present at a lower concentration than heavy chains (mg/L rather than g/L) (206) and are therefore unlikely to affect the calculated globulin (also measured in g/L). Calculated globulin may therefore be useful as a component in any strategy to prompt reflex testing, but cannot be used as a lone predictor, as there are cases where it will not prompt testing, particularly in light chain myeloma.

In summary, there are features that are detectable on blood test results which could be used in strategies for reflex testing, including calculated globulin. The results discussed in this chapter form preliminary work for feasibility, which will be used to guide future research to create an algorithm for detection of abnormal blood test results suggestive of myeloma.

The blood test result abnormalities discussed here are unlikely to detect all cases of myeloma, and therefore are unlikely to improve diagnosis in all cases. Other strategies should therefore be assessed as well, including strategies involving the identification of people with monoclonal gammopathy of undetermined significance.

6 THE PREVALENCE OF MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE IN ACUTE HOSPITAL ADMISSIONS

6.1 Introduction

As discussed in previous chapters, all patients with myeloma will have a preceding phase of monoclonal gammopathy of undetermined significance (MGUS) prior to the development of active multiple myeloma, although this may not be identified before progression.(88) There is evidence that prior knowledge of MGUS is associated with improved survival in myeloma and decreased complication rates at the point of diagnosis.(116, 117) It is now recognised that MGUS is associated with a range of complications as well as the risk of transformation to myeloma. These complications include renal impairment and increased rates of infection.(152, 207) There is a growing body of evidence describing the complications related to MGUS, however guideline groups do not currently recommend screening for MGUS outside of clinical trials.(182) In fact, a number of organisations state that MGUS is asymptomatic.(208, 209) As complications related to MGUS become more widely recognised, the recommendations regarding screening may change, however there are still many gaps in the evidence that is needed to support a structured screening program aimed at identifying patients with MGUS. Although MGUS is common, occurring in 3.2% of over 50s overall,(100) one area where further information is needed is the identification of a specific population with a high prevalence, where screening could be targeted.

Infection is one of the most common causes of hospital admission, with over 1 million hospital admissions due to infection in the year 2014-2015, accounting for 16% of all emergency admissions.(210) As discussed in Chapter 1, those with MGUS are predisposed to infection(207) and other conditions such as renal impairment,(129) which are common causes

of hospital admission. Therefore, higher rates of MGUS may be expected in those patients admitted to hospital. By comparing rates of MGUS in hospital admissions with known population rates, this study aimed to assess whether this cohort of patients has a higher rate of MGUS. If hospital admissions did have a higher rate of MGUS, then this population may reflect a group where targeted screening could be implemented.

6.2 Hypothesis

Patients being admitted to hospital as an acute admission have a higher prevalence of MGUS than the general population, as MGUS may lead to complications requiring hospital admission, such as infection or renal impairment.

6.3 Aims

- To assess the prevalence of MGUS in patients being admitted to hospital as an acute medical admission
- To compare the rate of MGUS in acute admissions to previously published population rates, to determine if acute admissions are a high-risk group
- To assess whether patients who are admitted due to an infection are more likely to have MGUS than patients admitted with no evidence of infection
- To determine whether there are particular groups within the population of acute admissions where there may be a higher rate of MGUS, for instance those with particular blood test abnormalities, where further research could be targeted

6.4 Methods

6.4.1 Prevalence of MGUS in Acute Hospital Admissions Study

As discussed in Section 2.1.4, this study was conducted on the Clinical Decisions Unit (CDU) at University Hospitals Birmingham (UHB) between November 2016 and August 2018.

Ethical approval was given by the NHS Research Ethics Committee West Midlands - Coventry and Warwickshire (reference 16/WM/0279). Local approval was given by University Hospitals Birmingham (reference RRK5862). Sponsorship was provided by the University of Birmingham.

6.4.2 Recruitment

Patients were included in the study after giving written informed consent. Potential participants were recruited from CDU following identification of potential eligibility by the clinical team. The initial ethics did not include those without capacity to give consent, but this was amended to allow the inclusion of those without capacity as per the Mental Health Act.

Recruitment started in November 2016 and finished in March 2018.

6.4.2.1 Inclusion and exclusion criteria

<u>November 2016 to November 2017:</u>

Inclusion criteria:

- Aged 18 year or over
- Admitted to hospital as an acute medical admission
- Able to provide written informed consent

Exclusion criteria:

- Unable to provide written informed consent

November 2017 onwards:

Inclusion criteria:

- Aged 18 years or over
- Admitted to hospital as an acute medical admission

Exclusion criteria:

- Unable to provide written consent **and** unable to attain assent from a personal consultee

An acute medical admission was defined as someone who had been admitted to hospital as an emergency, and was under the care of the acute or general medical team.

6.4.2.1.1 Change to exclusion criteria

Initial ethical approval was provided to consent only from participants with capacity to provide informed consent. An amendment was made to allow inclusion of those without capacity, if assent was provided by a personal consultee. This change was made due to concern that excluding those without capacity may exclude a group with a higher rate of MGUS, for example those patients with delirium related to infection.

6.4.3 Study procedures

Blood samples were taken on CDU, and then transported directly to the Clinical Immunology Service (CIS) at University of Birmingham for processing. For each participant, one additional 6ml tube of blood was collected, using a BD Vacutainer® Plus Plastic Serum Tube containing

spray-coated silica (Becton, Dickinson and Company, USA). Where possible, these samples were taken at the same time as clinical blood sampling, to reduce the burden placed on participants.

6.4.4 Sample processing

All samples were processed within the CIS, for:

- Serum protein electrophoresis (SPE)
- Immunofixation to identify paraprotein if SPE was abnormal

SPE was performed using LAUNCH Microgel using Interlab G26 and Sebia HYDRASYS.

Immunofixation was performed using Sebia HYDRASYS.

Paraprotein was classified according to the heavy chain and light chain component on immunofixation. Paraproteins <30g/L were classified as suggestive of MGUS.

6.4.5 Clinical data

After recruitment, information was collected from written patient notes and electronic systems for each participant. This included:

- Demographic details:
    - Age
    - Gender
    - Ethnicity
- Reason for admission
- Comorbidities
- Regular medication

- Blood test results on admission:
    - Full blood count (FBC)
    - Urea and electrolytes (U&Es)
    - Liver function tests (LFTs)
    - C reactive protein (CRP)
- Previous testing for serum protein electrophoresis, with date of previous sample

The blood test results collected were the first result available on the electronic records system for the admission during which they were recruited to the study.

6.4.6 Feedback of abnormal results

Results from the tests performed as part of the study were not added to the participant's electronic clinical record. Abnormal results were fed back to the general practitioner (GP) for follow-up in a standard letter that had been approved by the Research Ethics Committee.

6.4.6.1 Suggestive of MGUS

During the consent process, participants were asked if they wished to be informed of any result suggestive of MGUS.

For those who wished to be informed, results suggestive of MGUS were reported to the participant and to the GP. A Bloodwise (Blood cancer research charity) patient information sheet regarding MGUS was provided to the participant, and instructions given to the GP on how to repeat the appropriate blood tests for confirmation. For those who did not wish to be informed, results suggestive of MGUS were not reported to the patient or to their GP.

6.4.6.2 Suggestive of myeloma

No results were found that were suggestive of myeloma. All participants were informed that they would be contacted if a result was suggestive of myeloma, including those participants

who did not wish to be informed of MGUS. If a result suggestive of myeloma had been found, the participant and clinical team would have been contacted urgently by telephone.

6.4.7 Division into subgroups

6.4.7.1 Infection

Participants were divided into those with or without infection based on the clinical coding for the reason for admission, taken from their discharge letter.

6.4.7.2 Acute kidney injury

Participants were divided into those with or without acute kidney injury (AKI). Participants were included in the acute kidney injury group if they had either:

- An electronic alert on the pathology result system indicating AKI based on blood test results on admission
- Acute kidney injury documented as the reason for admission

6.4.8 Statistics

Statistical methods are discussed in Section 2.6, however the following power calculation and statistics are relevant to this chapter only.

A sample size of 670 participants was needed in order to detect a rate of MGUS of 5% (in comparison to an expected rate of 3%) with an 80% power and 5% level of significance.

This pilot study was aimed at assessing the rate of MGUS in the sample as a whole. Rates of MGUS in this study sample were compared to expected rates using the Chi square test. Subgroups within the study were compared where possible, however were limited by the sample size, as the study was not powered to detect differences between subgroups within the sample.

6.5 Results

In total, 674 patients were recruited to take part in the study. Seven were excluded as they had already participated, 1 was excluded as they did not meet the inclusion criteria, and 6 were excluded as a blood sample could not be obtained. 660 samples were therefore available for testing.

Demographic details of patients recruited to the study are shown in Table 6.1. The age of participants is shown in Figure 6.1.

657 participants had capacity to provide informed consent. 3 participants did not have capacity and assent was provided by a personal consultee.

Age (years)		
Median	65	
IQR	*49-77*	
Range	*18-99*	
Gender		
Male, n (%)	321	(48.6%)
Ethnicity		
Black African	5	(0.75%)
Black Caribbean	13	(2%)
Black – other	4	(0.6%)
Asian - Bangladeshi	4	(0.6%)
Asian – Indian	9	(1.4%)
Asian – Other	10	(1.5%)
Asian – Pakistani	22	(3.3%)
Chinese	2	(0.3%)
Other	9	(1.4%)
Mixed – Other	4	(0.6%)
Mixed – White & Black Caribbean	2	(0.3%)
White British	494	(74.8%)
White Irish	20	(3%)
White – Other	15	(2.3%)
Unknown	47	(7.1%)
Residence		
Own home	650	(98.5%)
Residential home	0	
Nursing home	2	(0.3%)
Other	8	(1.2%)

Table 6.1: Demographics of patients recruited to Prevalence of MGUS in Acute Hospital Admissions study.
Of the 660 participants recruited, age shown in years, gender, ethnicity and normal place of residence. Number and percentage of participants for gender, ethnicity & residence.

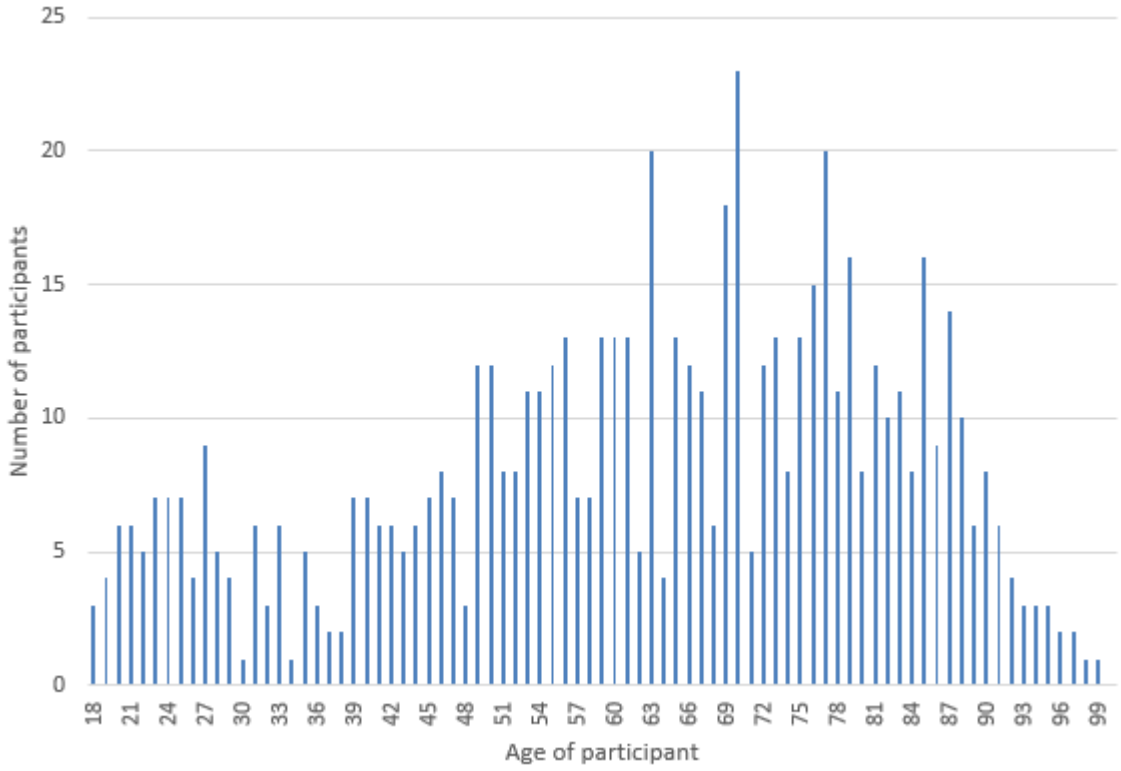


Figure 6.1: Age of participants in the study Prevalence of MGUS in Acute Hospital Admissions
Graph showing the age (in years) of the participants at entry to the study.

Participants were asked whether they wished to be informed if their results were suggestive of MGUS. 96.1% (634 participants) said they would like to be informed. 3.9% (26 participants) said they would not want to be informed.

6.5.1 Results of serum protein electrophoresis & immunofixation

Figure 6.2 shows the type of result returned from initial SPE testing. 573 samples had a normal serum protein electrophoresis, 87 samples had an abnormal SPE result.

Of the abnormal samples, 12 were identified by the automated lab processes as a polyclonal increase in immunoglobulins, the remaining 75 required immunofixation.

Of the 75 that had immunofixation performed, 35 samples showed a detectable paraprotein.

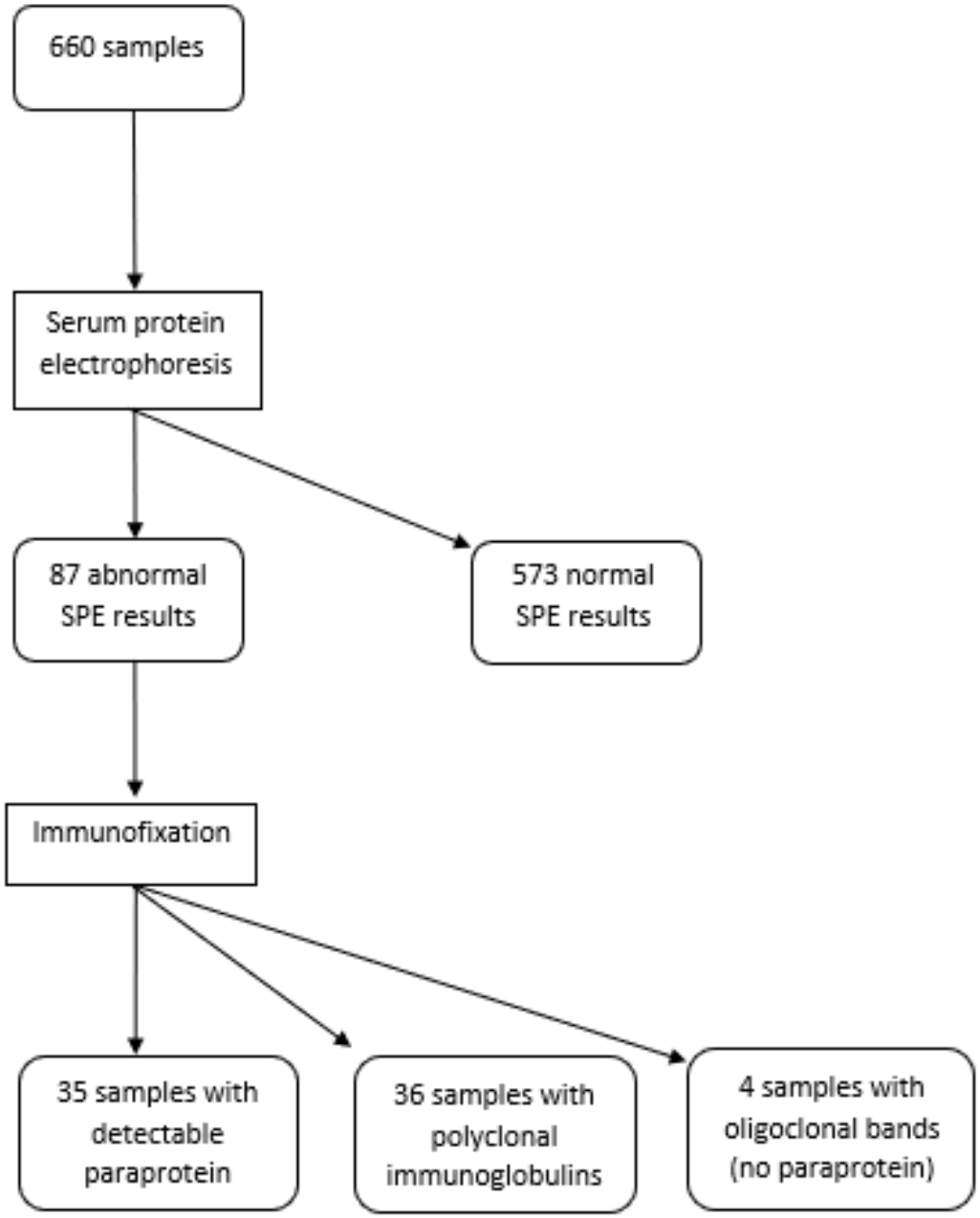


Figure 6.2: Modified consort diagram showing sample testing process.
Process for sample testing, results for the 660 participants included in the study. SPE: serum protein electrophoresis

6.5.2 Prevalence of MGUS in acute hospital admissions

35 participants were identified as having a monoclonal paraprotein suggestive of MGUS.

The demographics of these participants are shown in Table 6.2. The type of paraprotein identified is shown in Table 6.3. One participant identified as having a monoclonal paraprotein did not have capacity to provide consent.

Age (years)	
<50	1
50-59	2
60-69	7
70-79	10
80-89	10
90 or over	5
Gender	
Male	20
Female	15
Ethnicity	
White British	30
Black Caribbean	1
Black – other	1
Chinese	1
Unknown	2

Table 6.2: Demographics of those found to have MGUS.
Age in years, gender and ethnicity of the 35 participants in the study identified as having MGUS.

Type of paraprotein	**Number of participants**	**% of those with a paraprotein**
IgG	18	51.4%
IgG kappa	*14*	*40%*
IgG lambda	*4*	*11.4%*
IgA	5	14.3%
IgA kappa	*5*	*14.3%*
IgA lambda	*0*	*0%*
IgM	8	22.9%
IgM kappa	*5*	*14.3%*
IgM lambda	*3*	*8.6%*
Biclonal	4	11.4%
IgM kappa & IgM kappa	*1*	*2.9%*
IgA kappa & IgA kappa	*1*	*2.9%*
IgM kappa & IgM lambda	*1*	*2.9%*
IgG kappa & IgG lambda	*1*	*2.9%*

Table 6.3: Type of paraprotein detected in participants with MGUS
For the 35 participants identified as having a detectable paraprotein in this study, the type of paraprotein detected following immunofixation

The rate of MGUS in this sample overall was 5.3%. The prevalence of MGUS in those over 50 years old in this sample was 6.94%. Compared to previously published rates of MGUS that suggested MGUS was found in 3.2% of over 50s,(100) the rate of MGUS found in over 50s in our sample was significantly higher (Chi square, $p<0.0005$).

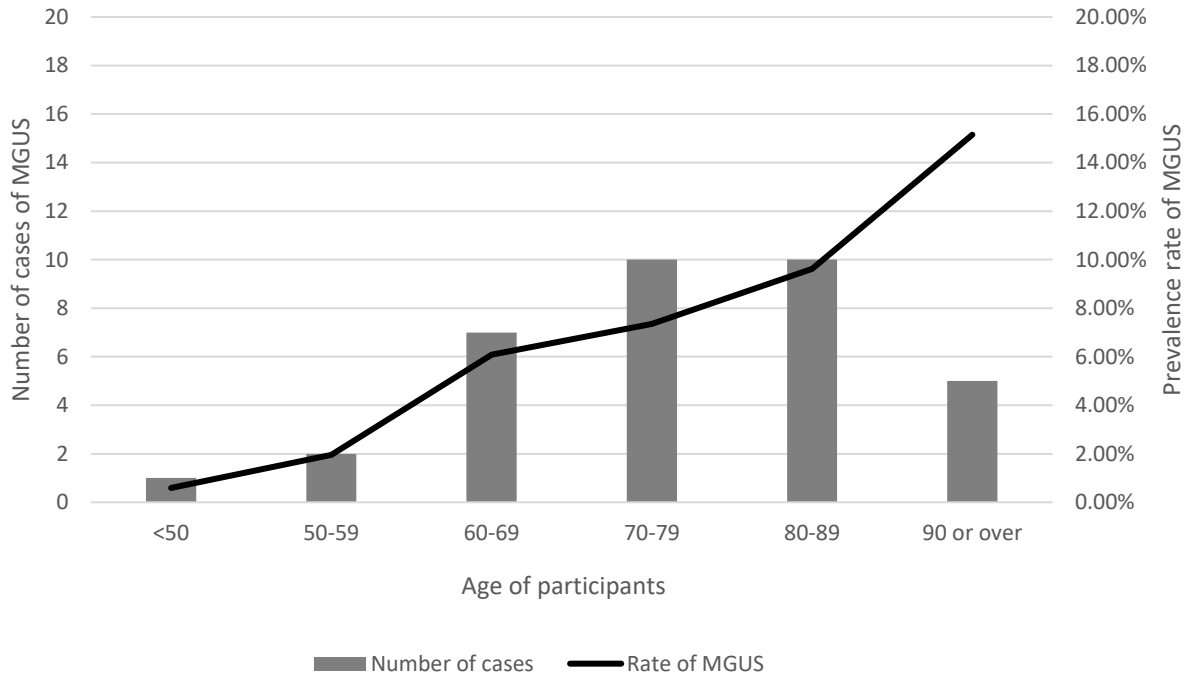
MGUS was found in 6.2% of male participants, and in 4.4% of female participants. There was no statistically significant difference in the proportion of male participants and female participants who were found to have MGUS (Chi square, $p=0.301$).

6.5.3 Prevalence of MGUS by age group

The prevalence of MGUS within each age group is shown in Table 6.4 and Figure 6.3.

	Number of participants in age group	**Number of participants with MGUS in age group**	**Prevalence of MGUS in age group**
Age (years)			
<50	170	1	0.59%
50-59	102	2	1.96%
60-69	115	7	6.09%
70-79	136	10	7.35%
80-89	104	10	9.62%
90 or over	33	5	15.15%

Table 6.4: Prevalence of MGUS by age group
For the 660 participants in the study, how many participants were in each age group, the number of participants with MGUS in each age group, and the prevalence of MGUS in each age group.



<u>Figure 6.3:</u> Rate of MGUS by age group.
Rate of MGUS in the 660 participants, by age group. Line denotes the rate of MGUS in each age group (as percentage, shown on the secondary y axis), bars denote the number of MGUS cases within each age bracket.

There was a statistically significant difference in the prevalence of MGUS between age groups (Chi square, p=0.001). The proportion of participants in the under 50 age group with MGUS was significantly lower than that in the 70-79 year old, 80-89 year old or over 90 year old age groups (Chi square post hoc analysis). The proportion of participants in the 50-59 year old age group with MGUS was significantly lower than the proportion with MGUS in the over 90 year old age group (Chi square post hoc analysis). There was no statistically significant difference in the rate between the 50-59 year old, 60-69 year old, 70-79 year old or 80-89 year old age groups.

The rate of MGUS according to age group and gender is shown in Table 6.5.

Age group	Male		Female	
50-59	2.2%	1/46	1.8%	1/56
60-69	8.1%	5/62	3.8%	2/53
70-79	4.2%	3/72	10.9%	7/64
80+	16.7%	10/60	6.5%	5/77

Table 6.5: Comparison of rates of MGUS by age group and gender
Comparison of the proportion of MGUS in each age group by gender), for the 490 participants who were aged 50 years old or over.

6.5.4 Comorbidities

Haematological malignancy

Of the 35 participants who had a monoclonal paraprotein detected, 3 participants had a haematological malignancy documented in their past medical history (non-Hodgkin's B cell lymphoma, marginal zone lymphoma of the parotid, and chronic lymphocytic leukaemia).

There were 5 participants who did not have a detectable monoclonal paraprotein, who had a documented haematological malignancy in their past medical history (treated B cell lymphoma, anaplastic large cell lymphoma, and 3 participants with non-Hodgkin's lymphoma).

37.5% of those with an active or previous haematological malignancy had a detectable paraprotein.

In addition, one participant had a result on the electronic patient records showing detection of a monoclonal paraprotein in the two months prior to this hospital admission but this was not documented in the clinical records and the patient was not aware of the diagnosis. Another two had a result on the clinical system showing detection of a monoclonal paraprotein (one in June 2009 and one in November 2015), however this was not documented in their records, and the patients were not aware of the result.

Non-haematological malignancy

Nine participants with a detectable paraprotein had a documented non-haematological malignancy in their past medical history. These were: liver, breast, pancreatic, prostate, skin, oesophageal, basal cell carcinoma of the jaw, and two participants with bladder cancer. 71 participants who did not have a paraprotein had a documented non-haematological malignancy in their past medical history.

11.25% of participants with an active or previous non-haematological malignancy had a detectable paraprotein.

Within the sample overall, there was a difference in age between those diagnosed with non-haematological cancer and those without. The average age of participants with a non-haematological cancer was higher than that of those participants who did not have a malignancy (Mann-Whitney U test, mean rank 311.5 for those without cancer, 466.31 for those with cancer, $p<0.0005$).

Chronic kidney disease

There were 80 participants who were known to have chronic kidney disease (CKD). There was no significant difference in the age of participants with and without CKD (Mann-Whitney U test, $p=0.118$). 11 participants with CKD had MGUS (13.8%). This was significantly higher than the rate of MGUS among those that did not have CKD (13.8% vs 4.1%, Chi square $p<0.0005$).

6.5.5 Admission reason in participants with MGUS

The reason for admission in participants who were found to have MGUS is shown in Table 6.6.

<table>
<tr><th>Infection</th><th>Renal</th><th>Cardiac</th><th>Other</th></tr>
<tr><td rowspan="3">Pneumonia
Pneumonia
Pneumonia
Influenza
Diabetic foot infection
Cholangitis
Suspected urinary tract infection
Salmonella gastroenteritis</td><td>Acute kidney injury
Progressive renal failure</td><td rowspan="3">Bradycardia
Exacerbation of heart failure
Congestive cardiac failure
Acute myocardial infarction
Chest pain of unclear cause</td><td rowspan="3">Hyponatraemia
Transient ischaemic attack
Exacerbation of asthma
Musculoskeletal pain/reflux
Accidental digoxin overdose
Haemoptysis
Ulcerative colitis
Drug induced interstitial lung disease</td></tr>
<tr><td>Haematological</td></tr>
<tr><td>Extensive DVT
Suspected DVT
Suspected DVT
Raised INR and bruising
Anaemia</td></tr>
<tr><td colspan="3">Multiple causes</td></tr>
<tr><td colspan="3">Lower respiratory tract infection & dehydration
Lower respiratory tract infection & congestive cardiac failure
Cholecystitis & hyponatraemia
Gastroenteritis & AKI on background chronic kidney disease
Gastroenteritis & AKI
Diarrhoea and vomiting & AKI
COPD and right heart failure</td></tr>
</table>

Table 6.6: Reason for admission in participants found to have MGUS.
As documented in their clinical notes, the reason for admission for the 35 participants found to have MGUS, for the admission during which they were recruited to the study.

Admission due to infection

Overall, 216 participants had infection documented as a reason for admission. The rate of MGUS amongst participants with documented infection was 6.5% (14/216). This was not significantly different to the rate in those who did not have infection documented as a reason for admission (4.7%, 21/444, Chi square, p=0.346).

6.5.6 Comparison of blood test results on admission

Table 6.7 shows the proportion of blood test results that were abnormal in those who were found to have MGUS and those who did not have MGUS. Table 6.8 shows a comparison of results below the normal range in those with MGUS compared to those who did not have MGUS. Table 6.9 shows a comparison of results above the normal range in those with MGUS compared to those who did not have MGUS.

	With MGUS				**Without MGUS**			
Blood test	**Low**		**High**		**Low**		**High**	
Haemoglobin	55.9%	19/34	2.9%	1/34	31.2%	193/618	1%	6/618
MCV	5.9%	2/34	2.9%	1/34	10.4%	64/618	5.8%	36/618
Platelets	20.6%	7/34	0	0	10.5%	65/618	3.4%	21/618
WCC	0	0	61.8%	21/34	1.6%	10/618	33%	204/618
Neutrophils	2.9%	1/34	67.6%	23/34	1%	6/618	38.3%	237/618
Lymphocytes	32.4%	11/34	5.9%	2/34	22.3%	138/618	1.8%	11/618
Monocytes	2.9%	1/34	35.3%	12/34	1.1%	7/618	32.5%	201/618
Eosinophils	n/a	n/a	2.9%	1/34	n/a	n/a	3.7%	23/618
Haematocrit	58.8%	20/34	2.9%	1/34	36.6%	226/618	1.8%	11/618
Sodium	25.7%	9/35	2.9%	1/35	14.2%	88/618	0.5%	3/618
Potassium	5.7%	2/35	8.6%	3/35	3.3%	20/615	3.6%	22/615
Urea	8.6%	3/35	51.4%	18/35	12%	74/618	23.1%	143/618
Creatinine	2.9%	1/35	42.9%	15/35	2.6%	16/618	20.9%	129/618
CRP	n/a	n/a	52.9%	18/34	n/a	n/a	51.3%	271/528
Corrected calcium	3.1%	1/32	0	0	4.2%	22/525	1.7%	9/525
Albumin	5.7%	2/35	0	0	5%	30/604	5%	30/604
Total protein	3%	1/33	12.1%	4/33	7.4%	39/525	6.8%	36/525
Bilirubin	n/a	n/a	8.6%	3/35	n/a	n/a	9.1%	54/593
ALT	0	0	5.7%	2/35	0.2%	1/590	15.6%	92/590
ALP	0	0	31.4%	11/35	0.5%	3/602	29.4%	177/602

Table 6.7: Abnormalities in blood test results in those found to have MGUS vs those without MGUS
Blood test results on admission for the 660 participants in the study. For each test, the percentage of participants with a result below or above the normal range is shown, for those participants found to have MGUS and those who did not have MGUS. The number of participants with an abnormal result, and with data available is also shown. MCV: mean corpuscular volume; WCC: white cell count; CRP: C reactive protein; ALT: alanine aminotransferase; ALP: alkaline phosphatase

Blood test	Percentage with result below the normal range With MGUS		Without MGUS		Chi square p value
Haemoglobin	55.9%	19/34	31.2%	193/618	0.003*
MCV	5.9%	2/34	10.4%	64/618	0.4
Platelets	20.6%	7/34	10.5%	65/618	0.068
WCC	0	0	1.6%	10/618	n/a
Neutrophils	2.9%	1/34	1%	6/618	0.278
Lymphocytes	32.4%	11/34	22.3%	138/618	0.175
Monocytes	2.9%	1/34	1.1%	7/618	0.351
Haematocrit	58.8%	20/34	36.6%	226/618	0.009*
Sodium	25.7%	9/35	14.2%	88/618	0.063
Potassium	5.7%	2/35	3.3%	20/615	0.433
Urea	8.6%	3/35	12%	74/618	0.544
Creatinine	2.9%	1/35	2.6%	16/618	0.923
Corrected calcium	3.1%	1/32	4.2%	22/525	0.769
Albumin	5.7%	2/35	5%	30/604	0.844
Total protein	3%	1/33	7.4%	39/525	0.342
ALT	0	0	0.2%	1/590	n/a
ALP	0	0	0.5%	3/602	n/a

Table 6.8: Blood test results below the normal range.
*The percentage of blood test results on admission below the normal range, for the 660 participants in the study. Percentage with an abnormal result among participants found to have MGUS and who did not have MGUS. The number of participants with an abnormal result, and with data available, is also shown. MCV: mean corpuscular volume; WCC: white cell count; ALT: alanine aminotransferase; ALP: alkaline phosphatase. * signifies a significant difference.*

Blood test	Percentage with result above the normal range With MGUS		Without MGUS		Chi square p value
Haemoglobin	2.9%	1/34	1%	6/618	0.278
MCV	2.9%	1/34	5.8%	36/618	0.479
Platelets	0	0	3.4%	21/618	n/a
WCC	61.8%	21/34	33%	204/618	0.001*
Neutrophils	67.6%	23/34	38.3%	237/618	0.001*
Lymphocytes	5.9%	2/34	1.8%	11/618	0.096
Monocytes	35.3%	12/34	32.5%	201/618	0.737
Eosinophils	2.9%	1/34	3.7%	23/618	0.814
Haematocrit	2.9%	1/34	1.8%	11/618	0.624
Sodium	2.9%	1/35	0.5%	3/618	0.08
Potassium	8.6%	3/35	3.6%	22/615	0.135
Urea	51.4%	18/35	23.1%	143/618	<0.0005*
Creatinine	42.9%	15/35	20.9%	129/618	0.002*
CRP	52.9%	18/34	51.3%	271/528	0.855
Corrected calcium	0	0	1.7%	9/525	n/a
Albumin	0	0	5%	30/604	n/a
Total protein	12.1%	4/33	6.9%	36/525	0.256
Bilirubin	8.6%	3/35	9.1%	54/593	0.915
ALT	5.7%	2/35	15.6%	92/590	0.112
ALP	31.4%	11/35	29.4%	177/602	0.798

Table 6.9: Blood test results above the normal range.
*The percentage of blood test results on admission above the normal range, for the 660 participants in the study. Percentage with an abnormal result among participants found to have MGUS and who did not have MGUS. The number of participants with an abnormal result, and with data available, is also shown. MCV: mean corpuscular volume; WCC: white cell count; CRP: C reactive protein; ALT: alanine aminotransferase; ALP: alkaline phosphatase. * signifies a significant difference*

There were 6 blood tests where there was a significantly higher rate of abnormal results in those with MGUS: low haemoglobin, low haematocrit, raised WCC, raised neutrophil count, raised urea and raised creatinine. The rate of MGUS in participants with these abnormalities was assessed.

Low haemoglobin

There was a significantly higher rate of MGUS in those with a haemoglobin result on admission that was below the normal range (9% vs 3.3%, Chi square p=0.003).

Low haematocrit

There was a significantly higher rate of MGUS in those with a haematocrit result on admission that was below the normal range (8.1% vs 3.4%, Chi square p=0.009).

Raised WCC and neutrophil count

There was a significantly higher rate of MGUS in those with a white cell count on admission that was above the normal range (9.3% vs 3%, Chi square p=0.001).

There was a significantly higher rate of MGUS in those with a neutrophil count on admission that was above the normal range (8.8% vs 2.8%, Chi square p=0.001).

Raised urea and creatinine

There was a significantly higher rate of MGUS in those with a urea result on admission that was above the normal range (11.8% vs 3.3%, Chi square p<0.0005). There was also a significantly higher rate of MGUS in those with a creatine result on admission that was above the normal range (9.7% vs 3.9%, Chi square p=0.002).

6.5.6.1 Acute kidney injury

50 participants had an AKI (documented in reason for admission or calculated from blood test results). In those with AKI, the rate of MGUS was 8% (4 participants out of 50). This was not significantly different from the rate of MGUS in those who did not have an AKI (8% vs 5.1%, Chi square p=0.407).

6.5.7 Clinical requesting of serum protein electrophoresis

Assessing how many participants had had an SPE performed as part of their clinical care, 184 of participants had an SPE result available on the clinical system from any time point (27.9%).

44 participants had a SPE requested during this admission (6.7%). A further 26 participants had an SPE result available that had been performed in the year preceding this admission (3.9%), therefore in total 70 participants (10.6%) had an SPE result available from this admission or in the year before.

Of the 50 participants with AKI, 10 patients had a sample sent for electrophoresis during the admission, or in the month before.

6.6 Discussion

The key findings demonstrated in this chapter are:

- This sample of patients admitted as an acute medical admission had a prevalence of MGUS of 5.3% overall
- The prevalence of MGUS in those over 50 years old was 6.94%
- The prevalence of MGUS in this group was significantly higher than previously reported rates
- The prevalence of MGUS was higher in older patients
- Those with chronic kidney disease were more likely to have MGUS
- Those with MGUS were more likely to have a low haemoglobin, low haematocrit, raised WCC and neutrophil count, and raised urea and creatinine

The main aim of this study was to identify whether acute hospital admissions were a group with a higher prevalence of MGUS. The rate of MGUS in this study was significantly higher than that expected based on previous research. When limited to those over 50 years old, which is the population for which rates are often quoted, the prevalence was 6.94%.

The prevalence rates determined by Kyle et al were used as our expected rate for comparison,(100) as these are the rates that are commonly quoted in patient information and clinical literature. Although their study was conducted in the USA, there are no published studies regarding the prevalence of MGUS in the UK. To allow comparison to these previously published rates, a similar method was used for detection of paraproteins, with initial testing of the sample by serum protein electrophoresis, and then immunofixation if there was an abnormal result detected by serum protein electrophoresis (SPE).

The immunoglobulin class of paraprotein detected in this study was most commonly IgG, followed by IgM and IgA. Biclonal paraproteins were the least common. This distribution was also demonstrated by Kyle et al.(100) Although all paraproteins have a risk of progression to multiple myeloma, the risk of progression in those with IgM paraproteins is largely related to progression to Waldenstrom's macroglobulinemia.(89) Three patients identified as having a detectable monoclonal paraprotein in this study had a known previous haematological malignancy. For these patients the paraprotein may be related to another lymphoproliferative disorder, rather than to MGUS alone.(8)

The method used in this study (SPE followed by immunofixation for abnormal results) will not detect all patients with MGUS or myeloma, as it will not detect those with disease that produces a light chain only or a non-secretory myeloma.(8) The prevalence of MGUS reported here is therefore an underestimate as light chain only disease accounts for 15-20% of myeloma(10) and 3% of myeloma is non-secretory.(211)

Our study found an increased prevalence of MGUS in a cohort of patients who are acutely admitted to hospital compared with previously reported rates. The reasons for this increased rate cannot be fully explained within this study as it was designed as a pilot study and is therefore inadequately powered to detect differences between all subgroups and the numbers of those with MGUS precludes further analysis of potentially confounding features. However, we have made some observations that can be further explored in a larger population-based study.

The results suggest that rates of MGUS increase with age, which has been demonstrated in previous research.(100) The increased rate of MGUS within medical admissions seen here may be at least in part relate to the difference in age distribution in the population who are

admitted to hospital as an acute admission when compared to the general population.(212) The prevalence of MGUS has been reported in previous studies by gender and age group, giving rates in the general population adjusted for these factors, which is the prevalence rate that is widely quoted.(100) This analysis has not been repeated in this pilot study due to the small numbers included in each subcategory of age and gender. When analysing the rates within each subgroup, there appeared to be a higher rate in women aged 70-79 years old than in women over 80 years old, and a marked increase in rate if MGUS in men over 80 years old compared with men aged 70-79 years old. These discrepancies are likely due to the small numbers in these subgroups, however this should be further assessed in research with a larger sample size.

Analysis of the prevalence of MGUS in those who were admitted with infection did not show any increased rate in patients who had infection documented and coded as a reason for admission. There was however an increased rate of MGUS in those participants with a raised white cell count and a raised neutrophil count, both of which are markers of infection. There was no difference in the rate of MGUS in those with an elevated CRP compared to those with a normal CRP, which is another marker of infection. The discrepancy between the findings in those with documented diagnosis of infection and those with blood test markers of infection may be related to limitations of clinical coding, if not all patients with an active infection had this documented.

Although patients with MGUS are at a higher risk of renal impairment, there was no higher rate demonstrated in those admitted with acute kidney injury. There was a higher rate of MGUS found in those with known chronic kidney disease and those whose admission blood test results showed raised urea or raised creatinine.

There was also a higher prevalence of MGUS in those with a low haemoglobin on admission, and those with a low haematocrit. Anaemia is not commonly recognised as a complication of MGUS, and this finding requires further research to explore the relationship between MGUS and anaemia.

This pilot study has therefore suggested that these factors (age, renal impairment, infection, and anaemia) require further research to fully explore their relationship with MGUS.

As discussed, the small numbers included in subgroups of this study limit the analysis that can be performed. Future research should use a larger sample to further investigate the findings suggested here, with adequate numbers included within all subgroups of the study. To include larger numbers of participants, alterations to study processes may be beneficial. For this study, participants needed to provide an extra sample of blood, which increased the burden on participants. Another strategy would be to use surplus sample from that already taken during routine clinical care. This was the initial strategy that was planned for this study, however it was not feasible due to logistical issues within laboratory services. Future research using this method may allow recruitment of larger numbers of patients.

In this cohort, 3 of the 35 participants who were found to have a detectable paraprotein had a result available on the clinical system showing a paraprotein detected previously, however it was not clear how this result had been acted on and the patients were not aware that they had previously been found to have MGUS. This highlights a need to address local processes to ensure that patients are receiving adequate and appropriate follow-up of abnormal paraprotein results.

As part of the consent process for the study, participants were asked whether they would wish to be informed of a result suggestive of MGUS. This option was included as current

guidance does not recommend screening for MGUS as part of clinical care.(7) This is in part due to concerns that knowledge of MGUS may cause unnecessary stress and anxiety for patients, although the evidence base for this is limited. Participants were therefore given the choice of whether they would wish to know, after receiving the participant information sheet with details about the risk of progression, potential complications of MGUS, and need for long term monitoring. 96% of participants said that they would want to be informed if they were found to have MGUS. This may have over-estimated the percentage of admitted patients that would wish to know, as those who did not want to know the diagnosis may have chosen not to participate in the study at all. Unfortunately this could not be fully assessed during this study, however should be explored in future qualitative research, as the acceptability of screening is an important factor in the implementation of any screening program.(176)

Due to the methods used in this study, there are differences in the range of patients that were recruited compared to the population of acute medical admissions as a whole. In part, this is due to the inclusion criteria of the study, which initially required potential participants to have capacity to provide written informed consent. Within acute medical admissions there is a substantial proportion of patients that have conditions that can impair capacity. Delirium is found in 30% of hospital admissions,(213) and dementia in 40% of those over 70 years old who are admitted to hospital.(214) Patients who are severely unwell, for instance those with sepsis, may not have capacity to consent.(215) The inclusion criteria initially specified the need for patients to have capacity at the request of the NHS Research Ethics Committee (REC), as they felt that the decision regarding whether the participant wished to be informed if they were found to have MGUS was a substantial burden to place on a personal consultee who was providing assent. Following a period of initial recruitment, this was reviewed and re-discussed, and the inclusion criteria amended to include those without capacity, if a personal

consultee provided assent. Due to the initial inclusion criteria which were used for the first 12 months of the study, very few participants were included who did not have capacity to provide consent. This may therefore have led to lower rates of inclusion of those with certain conditions, such as dementia or delirium. This is also reflected in the low number of participants who were nursing home residents, which normally make up 6.2% of acute admissions,(195) and reflect a group with multiple comorbidities and complex care needs.(216) Future research to confirm the results of this study should include those without capacity to consent, with assent from a consultee, to ensure these groups of patients are not under-represented, and to assess whether this group of patients have a higher prevalence of MGUS, as this could not be assessed here.

In summary, this pilot study identified those being admitted to hospital as an acute medical admission as a group that have a higher prevalence of MGUS. Acute medical admissions may therefore offer a population where a future screening strategy for MGUS could be targeted.

7 DISCUSSION

The results discussed in this thesis have provided further information regarding pathways to diagnosis in multiple myeloma, and the symptoms that patients experience before diagnosis. This work has also highlighted two areas where strategies aiming to improve diagnosis could be developed further, based on the identification of abnormal blood test results prior to diagnosis, and the identification of MGUS in a high-risk population.

7.1 Findings discussed in this thesis

The majority of patients with myeloma are diagnosed from direct referral to haematology from primary care. Patients diagnosed after referral to a non-haematology secondary care service have a significantly longer pathway to diagnosis. Patients diagnosed through acute services do not have a longer pathway to diagnosis, but have more severe disease at diagnosis, as evidenced by performance status, disease staging, and end organ damage. The symptoms reported by patients are varied and wide ranging, and patients may develop multiple symptoms while waiting for their diagnosis.

Previous research had described routes to diagnosis in myeloma (27) – the work discussed here has provided new knowledge regarding pathways to diagnosis in patients diagnosed via non-haematology secondary care specialties, and how the acute and non-haematology secondary care pathways related to length of pathway. Comparison of pathway length to markers of severity has been performed previously,(34) but has not been used to compare between pathways to diagnosis, as has been demonstrated here. The results discussed confirm the findings of previous research regarding the presenting symptoms of myeloma,(38) as well as contributing new knowledge regarding symptoms that develop after initial consultation.

Analysis involving patients who had knowledge of a monoclonal gammopathy of undetermined significance (MGUS) diagnosis before the development of multiple myeloma suggested that these patients have less symptoms, better performance status and stage of disease, and less features of end organ damage at diagnosis, than those who were not known to have MGUS. This provides further evidence to support previous research by Go et al (117) that suggested MGUS follow-up leads to lower complication rates at diagnosis of myeloma.

Blood test results prior to diagnosis were analysed for a local cohort of patients. This demonstrated that there was a significant decline in haemoglobin over the two years prior to diagnosis. This supports recent research published by Koshiaris et al,(201) which demonstrated a decline in haemoglobin, as well as changes in other markers such as erythrocyte sedimentation rate (ESR). Calculated globulin provides a simple method to estimate immunoglobulin levels, however the results discussed here demonstrate that this is not a marker that is abnormal in all patients with myeloma.

Patients admitted to hospital as an acute medical admission have a higher rate of MGUS than has been previously reported in the general population.(100) In this research, a detectable paraprotein was found in 5.3% of acute medical admissions, and 6.94% of patients over 50 years old who were admitted as an acute medical admission. The prevalence of MGUS has not been assessed in a UK population previously.

7.2 Implications of these findings

Those who are diagnosed through acute services have more aggressive disease, as evidenced by more severe disease developing within the same length of time as those who are diagnosed via more direct pathways to diagnosis. This may contribute to the increased mortality seen in these patients. These results suggest that strategies to reduce diagnostic delay that are aimed purely at earlier recognition

by GPs may not improve outcomes for all patients at the current time, as the increased mortality for some is a reflection of the nature of their disease, rather than missed opportunities for earlier intervention after the development of initial symptoms. However, advances in the treatment of myeloma may include better treatments for more aggressive disease, and therefore early identification may improve outcomes in the future. The complex and varied burden of presenting symptoms in myeloma may not facilitate early diagnosis and if earlier recognition of symptoms by clinicians is not possible, then there are at least two feasible strategies.

There are detectable abnormalities on blood test results prior to diagnosis, for example the decline in haemoglobin demonstrated here. The results from this study are an element of initial assessment of feasibility for future work that will be performed aiming to use these abnormalities to prompt automated testing.

The complications of MGUS as a disease are increasingly recognised, however, the main concern remains the risk of progression to myeloma. The results discussed here support previous research suggesting that a prior diagnosis of MGUS is associated with reduced complications at diagnosis of myeloma. Screening for MGUS is not currently recommended, however if knowledge of MGUS does impact the rate of complications in myeloma, then increased identification of MGUS may improve outcomes for patients with myeloma. Further evidence is needed to confirm this association, as well as to provide evidence regarding how patients with MGUS should be identified and monitored. The identification of acute medical admissions as a group with a higher prevalence of MGUS provides a potential population that could be assessed during the development of a screening strategy.

7.3 Limitations

The data gathered from the TEAMM trial discussed in Chapter 3 and 4 provided detailed information regarding patient symptoms, and data regarding healthcare consultation, however all data was self-reported. This introduces the potential for recall bias. The data collected regarding pathways to diagnosis assumed a relatively straightforward pathway, and

only captured one consultation date for primary care and for non-haematology services, potentially missing complicated pathways involving multiple steps and repeated consultations that could lead to prolonged pathways. Although the results discussed here suggest that those patients diagnosed through acute services may have more aggressive disease, as evidenced by more severe disease developing in the same length of time, data was not collected on genetic abnormalities that are used to assess aggressiveness in myeloma.(217)

The comparison between patients with and without MGUS from the TEAMM cohort was a post hoc analysis of the data. As participants were not asked to specify whether they had been diagnosed with MGUS or smouldering multiple myeloma, patients may have been misclassified by the methods used to identify these subgroups.

The findings regarding blood test results prior to diagnosis were limited by the number of patients included. As the work discussed here was assessing feasibility of this approach, only a single centre was included. Due to the incidence of myeloma in the general population, only small numbers of patients are diagnosed at a single centre. As the results discussed here used retrospective results from previous clinical requests, only small numbers of patients had results available in every time period for comparison. Although a change in haemoglobin over time was demonstrated, this requires comparison to a matched control group to confirm that this change is related to myeloma rather than to other factors – no control group was used in the analysis discussed here.

The cohort of patients recruited to the study 'Prevalence of MGUS in Acute Admissions' discussed in Chapter 6 differs from the population of patients seen in acute medical admissions as a whole, due to the inclusion criteria used in the study. Nursing home residents

are under-represented, and few patients with dementia were included. Although the study demonstrated a higher rate of paraprotein detected in the sample overall, the sample size limited the comparisons that could be reliably assessed between subgroups of the cohort.

Overall, the findings discussed in this thesis provide evidence that can used in the development of future strategies aimed at improving earlier recognition of myeloma, but there remain many other areas where further knowledge is needed to fully develop these strategies, for instance how MGUS should be monitored and risk stratified after identification.

7.4 Future research

7.4.1 Do those presenting through acute services have more aggressive disease?

The results discussed in this thesis suggest that those diagnosed through acute services may have more aggressive disease. This should be confirmed through investigation of whether patients admitted through acute services have a higher rate of genetic features of aggressiveness, compared to those diagnosed through other routes. Data could be collected in a similar manner to TEAMM, however using dates of consultation taken from healthcare records could provide data that is not affected by recall bias. As discussed, the method used in TEAMM may have missed more complicated pathways to diagnosis. In order to capture these pathways fully, more data on individual steps and number of steps within the pathway would be needed. In order to fully understand these pathways, qualitative research involving a more detailed discussion with a small cohort of patients would likely be beneficial.

7.4.2 Do those with previously diagnosed MGUS have improved outcomes from myeloma?

The findings discussed here suggesting reduced rates of complications and better stage disease at diagnosis of myeloma in those with known MGUS need further confirmation. This could be through a retrospective or prospective method. Data could be collected from

patients newly diagnosed with myeloma regarding the features assessed in TEAMM (complications, performance status, stage of disease) as well as whether they had previously been diagnosed with MGUS or smouldering multiple myeloma, and the follow-up that they were receiving. Alternatively, patients with MGUS could be recruited and followed prospectively, until the development of active multiple myeloma. Although this would require a larger cohort, as not all patients with MGUS progress to myeloma, and a long period of follow-up, as patients may not progress for many years, it may also provide valuable information regarding which patients progress to myeloma and how this progression is identified.

The subgroup analysis within TEAMM looked at factors present at diagnosis, however data regarding survival in these patients will be available after a suitable period of follow-up.

7.4.3 Development of an algorithm to prompt reflex testing for myeloma

The results discussed here in Chapter 5 provide preliminary evidence that will be used to support the development of a larger research study. This study will use similar methods to identify patients newly diagnosed with multiple myeloma at several centres, and the blood tests results available for several years prior to diagnosis. This will be compared to a control population without myeloma, to identify features that are specific to myeloma. These features will then be combined into a model that could be used to prompt reflex testing, so that when this combination of abnormalities is detected then blood testing for myeloma is automatically performed. This model will require testing in a large validation cohort, to assess how well the model performs in identifying those with myeloma.

7.4.4 Are acute medical admissions a high-risk group where screening for MGUS could be targeted?

The results of the study 'Prevalence of MGUS in acute admissions' require confirmation in a larger cohort. As discussed in Chapter 6, comparison of subgroups within the cohort were limited by sample size. This study should be repeated with a larger cohort of patients, to explore whether particular subgroups within medical admissions have a higher rate of paraproteinaemia. Specific groups where this needs to be assessed include those with anaemia, infection and renal impairment. This study should be designed to allow the inclusion of patients without capacity, to ensure a representative sample is obtained.

Further evidence is still needed to support other aspects of any screening program for MGUS, particularly around the acceptability of a screening program. Guidance has suggested that patients would not wish to know about a diagnosis of MGUS due to the anxiety that this may cause. There is little evidence available regarding this, and further research is needed regarding public perception of MGUS, particularly whether patients would wish to know about a diagnosis of MGUS if they were given appropriate information regarding risk of progression, complications and monitoring. Qualitative research is needed in this area, regarding both public & patient views, and clinician opinions and perceptions.

7.5 Summary

In conclusion, diagnostic delay in multiple myeloma remains a problem for patients with this disease. Multiple factors affect the pathway that patients take to reach their diagnosis, including aggressiveness of disease. There are feasible strategies that could be developed to improve diagnosis, including the development of automated processes based on routine blood test results to prompt testing for myeloma, and identification of those with MGUS, for

instance in acute medical admissions, as those with previous MGUS have less complications of end organ damage at diagnosis of myeloma.

APPENDIX 1: NORMAL RANGES FOR BLOOD TEST RESULTS AT UNIVERSITY HOSPITALS BIRMINGHAM

Test	Normal range	Units
Alanine aminotransferase (ALT)	5-43	U/L
Albumin	34-51	g/L
Alkaline phosphatase (prior to January 2012)	70-330	IU/L
Alkaline phosphatase (January 2012 onwards)	35-105	IU/L
Aspartate aminotransferase (AST)	5-43	U/L
Bilirubin	1-22	µmol/L
C reactive protein (CRP)	<10	mg/L
Corrected calcium	2.10-2.60	mmol/L
Creatinine	50-111	µmol/L
Haematocrit Male Female	 0.4-0.54 0.37-0.47	L/L
Haemoglobin Male Female	 135-180 115-165	g/L
Immunoglobulins IgG IgA IgM	 6.00-16.00 0.8-4.00 0.5-2.00	g/L
Mean corpuscular volume (MCV)	80-99	fL
Platelets	150-450	10^9/L
Potassium	3.4-5.2	mmol/L
Reticulocytes	20-80	10^9/L
Serum free light chains Kappa (κ) Lambda (λ) Ratio (κ/λ)	 3.3-19.4 5.71-26.3 0.26-1.65	mg/L
Sodium	134-146	mEq/L
Total protein	60-80	g/L
Urea	3.4-8.0	mmol/L
White cell count (WCC) *(total)* *Basophils* *Eosinophils* *Lymphocytes* *Monocytes* *Neutrophils*	4.0-11.0 *0.0-0.2* *0.0-0.4* *1.0-4.0* *0.2-0.8* *2.0-7.5*	10^9/L

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