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Clinical features and diagnosis of multiple myeloma: a population-based cohort study in primary care

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ABSTRACT

Objectives Patients with multiple myeloma (MM) experience significant delays in diagnosis due to non-specific symptomatology. The aim of this study was to characterise the frequency and timing of clinical features in the primary care setting prior to MM diagnosis.

Design Population-based cohort study.

Setting Electronic health records data of approximately 17 million patients (2006–2016) within the UK Clinical Practice Research Datalink.

Participants Patients aged ≥18 years with newly diagnosed MM (NDMM), no history of solid tumours and ≥2 years registration in a primary care practice prior to MM diagnosis.

Main outcome measures Clinical features and symptoms including bone pain, skeletal-related events (SREs), investigation and confirmation of MM diagnostic CRAB criteria (hyperCalcaemia, Renal impairment, Anaemia, Bone lesions) during the 2 years prior to MM diagnosis; time between symptom manifestation and/or relevant investigation and diagnosis of MM.

Results Among 2646 patients with NDMM, 47.5% had a bone pain record during the 2-year period prior to MM diagnosis, mainly affecting the back. Regardless of baseline bone pain, investigations for serum calcium level were used in 36.4% of patients prior to MM diagnosis, followed by haemoglobin (65.6%) or renal function (74.1%). Median (Q1, Q3) time from first-recorded bone pain to MM diagnosis was 220 (80, 476) days. Median (Q1, Q3) time from first-recorded hypercalcaemia, renal impairment or anaemia to MM diagnosis was 23 (12, 46), 58 (17, 254) and 73 days (28, 232), respectively. An imaging investigation or referral for imaging was recorded for 60.0% of patients with bone pain/SRE and 32% without.

Conclusions Nearly half of patients diagnosed with NDMM presented with bone pain approximately 7 months prior to MM diagnosis. Investigations to evaluate all CRAB criteria, including targeted imaging, were underused. Early recognition of myeloma clinical features and optimised use of investigations in primary care may potentially expedite MM diagnosis.

Strengths and limitations of this study

- ► Our study provides more clarity to the occurrence and timing of key myeloma clinical features and use of diagnostic investigations prior to the diagnosis of multiple myeloma (MM).
- ► Our study is the first attempt to provide key diagnostic information such as patient symptoms and laboratory testing on a large representative sample of patients who are newly diagnosed with MM in primary care over a 10-year period.
- ► Demographic characteristics, comorbidities, symptoms, clinical events, drug exposures and laboratory investigation definitions have been validated during a reproducibility study and published separately.
- ► This study relies on the quality and completeness of data collected in the Clinical Practice Research Datalink database.
- ► In this study, medications, investigations or events occurring typically within the hospital settings may be under-reported.

INTRODUCTION

Multiple myeloma (MM) is the second most common haematological malignancy in Europe, with an estimated age-standardised incidence of 9.6 per 100 000 people in the UK for the year 2017, projected to increase to 12 per 100 000 people by 2035.[1 2] The UK-based Haematological Malignancy Research Network (HMRN) raised awareness on potential diagnostic delays in primary care, recognising non-specific symptomatology as a main barrier to MM diagnosis.[3 4] Patients with myeloma have one of the longest time-to-diagnosis intervals among cancers, with an average time between symptom onset and MM diagnosis of 99 days.[5 6] Compared with patients with other cancers, they also have the most repeated consultations occurring in primary care before referral to a specialist, with 50% experiencing three or more repeat consultations.[7] While 57% of patients are ultimately diagnosed through general practitioner (GP) referral, timely recognition and diagnosis of MM are challenging;[8] patients typically present to their GPs or family physicians with a myriad of non-specific symptoms such as bone pain or aches occurring at multiple sites, and fatigue.[9] Because the average age of MM presentation is 70 years,[10]

these clinical signs may be overlooked as gradual ageing. Furthermore, the average primary care physician in an individual clinical practice may see fewer than ten patients with MM throughout their career given the rare cancer status of MM.

Despite the presentation of non-specific symptoms, MM causes disabling complications including skeletal-related conditions (destructive lytic lesions, osteoporosis and hypercalcaemia, skeletal-related events (SREs)), renal impairment, infection, neurological complications and anaemia.[9 11 12] The 1-year survival of patients diagnosed through GP referral or emergency presentation after MM diagnosis was 70% and 42%, respectively.[13] Early detection is a high priority for patients and improves survival; 84% of patients with myeloma survive for >5 years if diagnosed at the earliest stage, compared with only 26% if diagnosed at advanced stage.[14] Early diagnosis and subsequent management of myeloma improve patients' quality of life and reduce symptom burden and serious complications of the disease.[15] The International Myeloma Working Group (IMWG) recommends a series of laboratory and imaging investigations to evaluate patients with a suspected diagnosis of MM, namely diagnostic imaging and blood tests to assess the CRAB (hyperCalcaemia, Renal impairment, Anaemia, Bone lesions) diagnostic criteria for MM.[8] In the primary care setting, access to laboratory testing (eg, haemoglobin, calcium levels, kidney function, paraprotein and light chains) is readily available and diagnostic testing can identify underlying cause of clinical features following evidence gained through the physical examination (signs and symptoms). The presence of bone pain in combination with laboratory abnormalities, such as anaemia, hypercalcaemia or unexplained renal impairment, have a high diagnostic certainty for MM.[16]

The extent to which these common clinical features have been used to diagnose MM in the primary care setting has not been widely investigated. Most existing studies on MM have represented a population with more advanced disease in clinical secondary care settings.[9] As the first point of contact for patients, primary care practices provide an opportunity to investigate patients presenting with clinical features underlying MM and direct the diagnostic pathway for patients with suspected MM. In our study, we used primary care electronic medical records (EMRs) to characterise early clinical features of patients newly diagnosed with MM in the UK and describe investigations for the diagnostic CRAB criteria undergone by patients prior to MM diagnosis.

METHODS

Study design and data source

This study was a population-based cohort study of newly diagnosed MM (NDMM) patients using the UK Clinical Practice Research Datalink (CPRD) GOLD database. The CPRD is based on standardised EMR systems in UK primary care.[17] The database contains routinely collected GP data from patients registered in over 600 primary care practices. The geographical distribution of GP practices has been shown to be representative of the UK and the patients are broadly representative of the UK general population in terms of age and sex distributions as reported by the national population census.[18]

Study population

The study population included NDMM patients over the age of 18 at diagnosis who were registered with GP practices across the UK and contributed to the CPRD database. Patients who were continuously registered with GP practices during a minimum 2-year baseline period prior to (and not including) the MM diagnosis date (index date) were included in the cohort on their first record of MM diagnosis between 1 January 2006 and 31 December 2016. Patients were eligible for inclusion if their record was labelled as acceptable by CPRD quality control. Patients were excluded if they had one or more record of a solid tumour (including skin cancer) diagnosis during any time prior to (and including) the index date to avoid the inclusion of patients experiencing bone pain due to metastases of their tumour to the bone. Figure 1 presents the study design diagram.[19]

Defining MM and clinical features

Primary care Read codes were used to identify MM diagnosis, comorbidities, bone pain and SREs from clinical and referral records.[20] Product codes were used to identify prescribed medications. Laboratory investigations and confirmation of the CRAB criteria, including serum calcium, haemoglobin and creatine level, were identified using Read codes from clinical and referral records and Entity type from Test records. Investigation and confirmation of bone lesions was identified through Read codes from clinical and referral records, Entity type and Medcodes from Test records (figure 2). Testing of interest included haemoglobin level, blood calcium level, serum creatinine level and diagnostic imaging (bone scan, CT scan, MRI scan, positron emission tomography scan and any X-ray). Reasons for imaging procedures were not available and patients may have received those for reasons not related to the CRAB criteria work-up. Details and lists of Read code have been previously described.[21]

Symptoms of MM, including bone pain and SREs prior to diagnosis, and clinical features of the CRAB criteria during the baseline period were retrieved.

Statistical analysis

Patients were described in terms of demographic characteristics at baseline, prevalent comorbidities, clinical features and symptoms. Prescribed medications related to bone health and pain management including bisphosphonates, considered standard of care for bone disease, were also described.[22] Summary statistics included frequencies (%) for categorical variables and mean (SD) and median (Q1, Q3) for continuous variables such as time of the diagnostic interval from first recorded bone pain, SRE and CRAB investigations. Time of symptom presentation or relevant diagnostic CRAB criteria to the

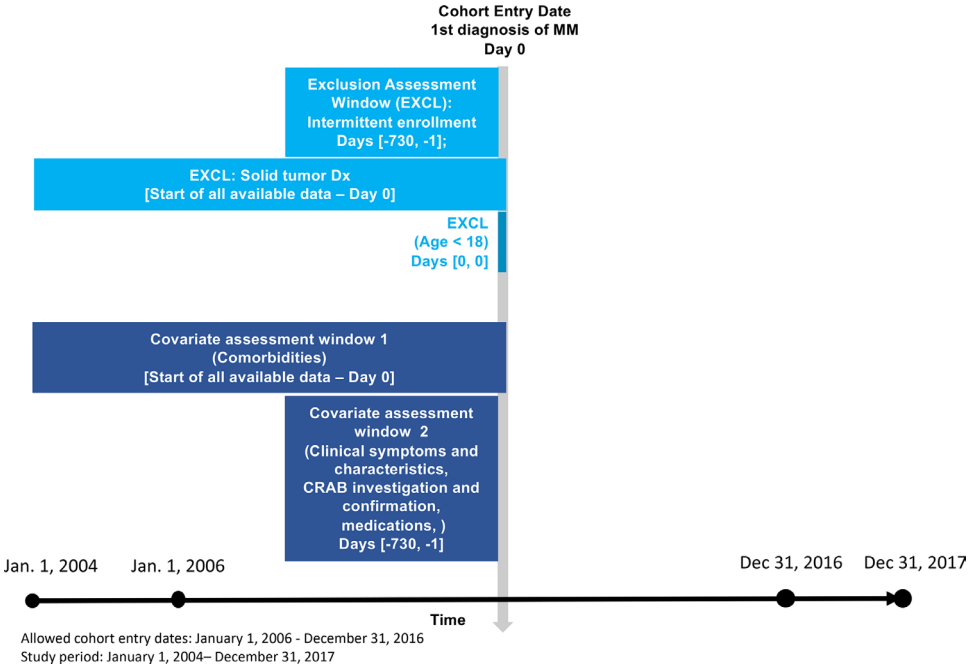

Figure 1 Study design. The study design diagram visually displays study design implementation. The vertical line represents the cohort entry date (index date), which is the first-order temporal anchor. The boxes represent second-order temporal anchors (time windows). The brackets in the boxes show time intervals anchored on day 0. Dx, diagnosis; EXCL, exclusion; MM, multiple myeloma.

diagnosis of MM were also evaluated. Results were stratified by the presence of a record for bone pain and/or SRE at baseline (symptomatic) or absence of bone pain and/or SRE at baseline (asymptomatic).

All analyses were conducted using the Aetion Evidence Platform (V.3.12), a rapid-cycle analytic tool which has been validated in a range of studies and therapeutic areas including oncology.[23]

Patient and public involvement

Although, there has been no specific patient or public involvement (contact) in this retrospective database study,

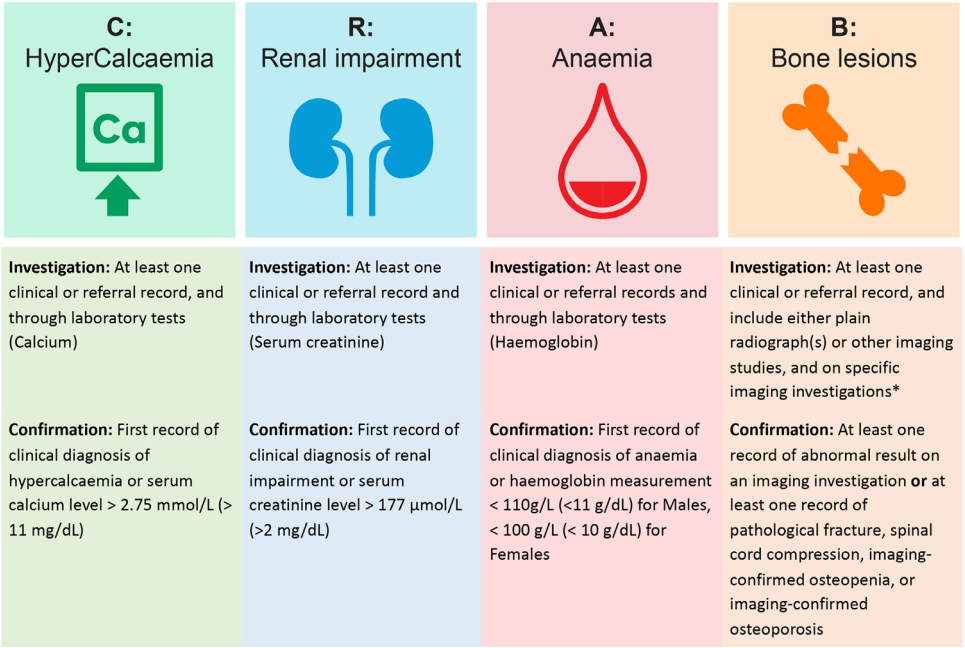

Figure 2 CRAB criteria for multiple myeloma investigation and confirmation. *Plain radiographs coded as a record of X-ray; other imaging studies coded as a record of bone scan or CT scan or MRI or positron emission tomography scan; diagnostic imaging investigations.

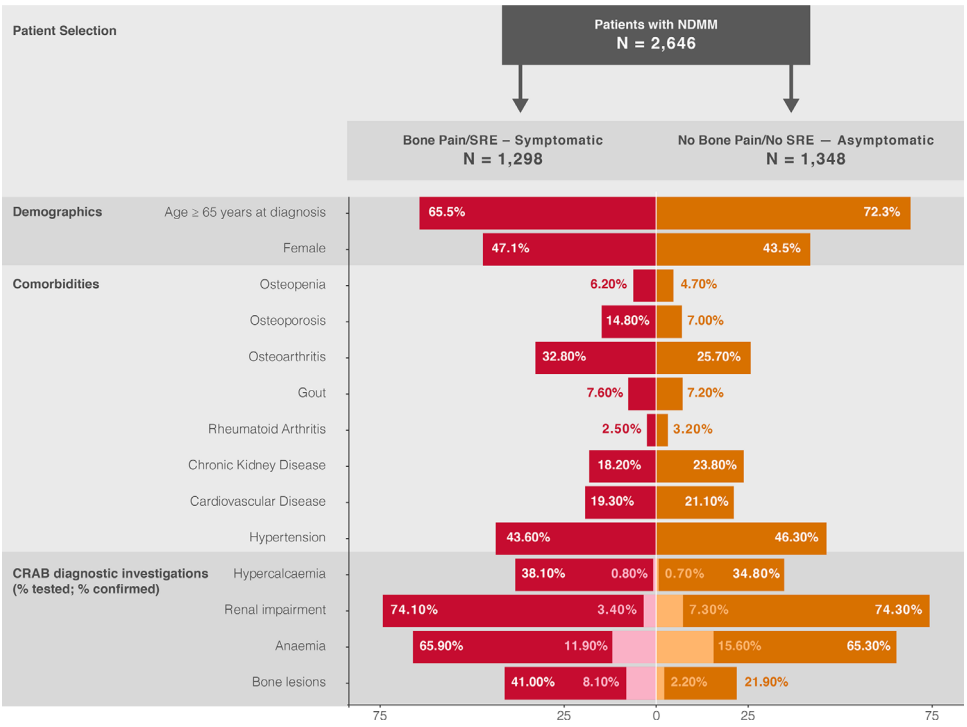

Figure 3 Baseline clinical characteristics and CRAB-related presentation prior to multiple myeloma (MM) diagnosis among patients with symptomatic and asymptomatic MM. Percentage of patients for each characteristic is shown among symptomatic patients with bone pain and/or SRE (red bars) and asymptomatic patients without bone pain and/or SRE (orange bars). For CRAB diagnostic investigations, the percentages of patients tested for hypercalcaemia, renal impairment, anaemia and bone lesions are shown for symptomatic patients (red bars) and asymptomatic patients (orange bars). Percentages of patients with confirmation are shown for symptomatic (pink bars) and asymptomatic patients (light orange bars). CRAB criteria investigations and confirmations prior to MM diagnosis between 2006 and 2016. A maximum of 2 years minus 90 days before (and not including) the MM index date was used. Patients were required to be continuously enrolled throughout each time window to be included into these subgroups. CRAB, hyperCalcaemia, Renal impairment, Anaemia, Bone lesions; NDMM, newly diagnosed MM; SRE, skeletal-related event.

CPRD works diligently and independently with contributing practices to ensure patients are aware of how their anonymised data are used and of their right to opt out of their data being shared for research (https://www.cprd.com/public).

RESULTS

Study population

At the time of analysis, the CPRD database contained 17 756 119 patients. Among 4823 patients with NDMM, 2177 patients were excluded for not meeting the eligibility criteria, leading to a total of 2646 NDMM patients between 2006 and 2016 included in our analysis (online supplemental figure S1). Among all patients with NDMM, the median (Q1, Q3) age was 71 (63, 79) years and 54.7% were men. On average, patients were observable in the CPRD database for 11.5 years prior to their initial MM diagnosis and for 2.7 years post MM diagnosis. Overall, 43.8% of patients with NDMM had at least one musculoskeletal comorbid condition (29.2% with osteoarthritis and 10.8% with osteoporosis); 45.0% of all patients had hypertension, 21.2% chronic kidney disease, 20.2% cardiovascular disease.

Figure 3 shows the baseline demographic and clinical characteristics of the NDMM patients by the presence (symptomatic) or absence (asymptomatic) of bone pain/SREs at baseline. Musculoskeletal comorbidities were observed among symptomatic patients and asymptomatic patients, including osteopenia (6.2% and 4.7%), osteoporosis (14.8% and 7.0%) and osteoarthritis (32.8% and 25.7%), respectively. Both symptomatic and asymptomatic patients frequently received analgesics during baseline, including non-opioid analgesics (88.1% and 62.4%, respectively), weak opioid (73.4% and 40.9%) and strong opioid use (41.8% and 14.6%). A prescription for bisphosphonates was observed for 17.3% of symptomatic patients during baseline (online supplemental table S1). Among a subgroup of 361 patients with NDMM and a prescription of oral bisphosphonates in the 2 years prior to MM diagnosis, 62.3% (n=225) had a record of bone pain or SRE and 37.7% (n=136) did not.

Clinical features and CRAB investigation

Overall, 49.1% of the patients with NDMM were symptomatic with either bone pain and/or SRE during baseline. Among patients with NDMM, 47.5% of patients had a baseline bone pain record, mainly affecting the back

(33.7%) or other joints (17.3%). Only 4.8% of patients with NDMM had a record of an SRE, mostly captured as pathological fracture (3.7%). Records of spinal cord compression and surgery to bone were rare (<1%) (online supplemental table S2). An imaging investigation or referral for an imaging investigation was recorded for 60.0% of symptomatic bone pain/SRE and 31.7% of asymptomatic patients. Among NDMM patients who had an imaging investigation, 19.0% had an MRI and 22.1% had a CT scan (online supplemental table S3). Confirmed bone lesions were recorded in 8.1% of symptomatic patients and 2.2% of asymptomatic patients (online supplemental table S4).

During the baseline period, most patients with NDMM received a laboratory investigation for renal impairment (approximately 74%) or anaemia (approximately 65%), regardless of being symptomatic or asymptomatic (figure 3, online supplemental table S4). Confirmation of hypercalcaemia was infrequently observed prior to MM diagnosis regardless of the presence or absence of bone pain/SRE (figure 3, online supplemental table S4). The proportion of patients who met any one of the CRAB criteria was 0.8% and 0.7% for hypercalcaemia, 3.4% and 7.3% for renal impairment, 11.9% and 15.6% for anaemia among symptomatic and asymptomatic patients, respectively (online supplemental table S4).

During the 12 months prior to MM diagnosis, the proportion of CRAB-related diagnostic test combinations received by patients were 75.7% for renal impairment and anaemia, 50.4% for hypercalcaemia and renal impairment, 50.2% for hypercalcaemia and anaemia, and 48.9% for hypercalcaemia, renal impairment and anaemia. Only 18.9% of all patients with NDMM underwent investigations for all four CRAB criteria (figure 4, online supplemental table S5). We observed complete CRAB criteria testing with all four components in 26.7% of symptomatic patients and 11.5% of asymptomatic patients (online supplemental table S5).

Timing of clinical features and CRAB investigation

Among all patients with NDMM, the median time (Q1, Q3) between MM diagnosis and the initial laboratory diagnostic workup to ascertain renal impairment or anaemia were 488 (203, 626) and 380 (95, 594) days, respectively. We observed a 6-month interval between MM diagnosis and the initial investigation for hypercalcaemia (median (Q1, Q3) of 176 (44, 507) days) (online supplemental table S6). The median time (Q1, Q3) between date of ascertainment of renal impairment or anaemia (via the first record of a confirmed abnormal test result) and date of MM diagnosis were 58 (17, 254) and 73 (28, 232) days, respectively. The median (Q1, Q3) diagnostic interval between a confirmed hypercalcaemia and the MM diagnosis was only 23 (12, 46) days (figure 5, online supplemental table S7).

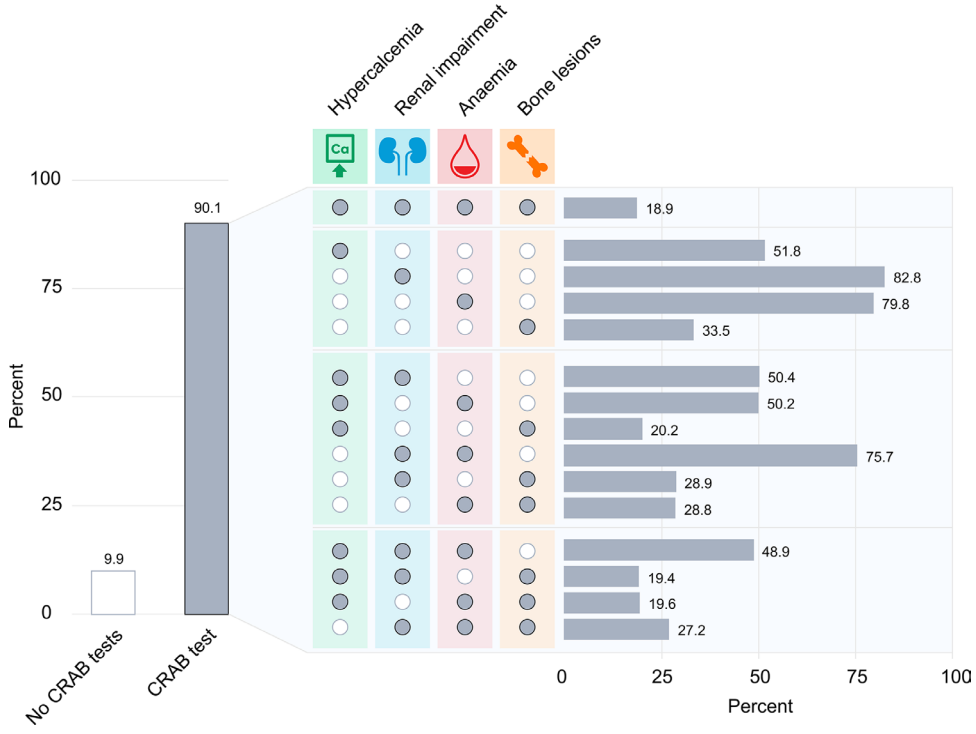

Figure 4 Combination of CRAB investigations for hypercalcaemia, renal impairment, anaemia and diagnostic imaging for bone lesion. The frequency of CRAB criteria testing was assessed in the 12 months prior to and not including the cohort entry date. The testing includes laboratory tests only; total tests measure the number of patients who had the specific test or combination of tests, alone or with additional tests. CRAB investigation categories are not mutually exclusive. Patients included in each category were required to have, at minimum, the tests indicated by the black circles; they may or may not have had the tests indicated by the white circles. CRAB, hyperCalcaemia, Renal impairment, Anaemia, Bone lesions.

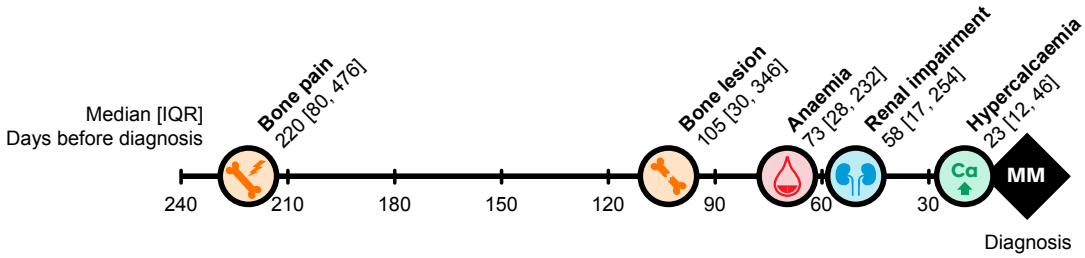

Figure 5 Timing of clinical CRAB (hyperCalcaemia, Renal impairment, Anaemia, Bone lesions) criteria between confirmation to diagnosis of MM. The timing and event occurrence were measured during baseline period, 730 days to 1 day prior to the MM diagnosis date; the time periods were counted starting from the first ever laboratory investigation or diagnosis during the 730 days prior to and including the cohort entry date. MM, multiple myeloma.

Overall, we observed a 6-month interval between the initial investigation for bone lesion (median (Q1, Q3) of 195 (59, 452) days) and MM diagnosis (online supplemental table S6), and a median (Q1, Q3) diagnostic interval of 105 (30, 346) days between confirmed imaging results for bone lesions and the MM diagnosis. Among symptomatic patients, the median (Q1, Q3) time from the initial bone pain record to MM diagnosis was 220 (80, 476) days. The median (Q1, Q3) time from bone pain to investigations with bone X-ray, MRI scan, bone scans or CT scan was 34 (8, 175) days, 93 (38, 256) days, 112 (44, 259) and 181 (58, 406) days, respectively (online supplemental table S8).

DISCUSSION

This population-based cohort study using real-world data revealed that nearly half of 2646 patients with NDMM had a record of symptomatic bone pain, approximately 7 months prior to MM diagnosis in primary care. Approximately 71% of symptomatic patients presented with back pain. Diagnostic intervals (ie, the time from investigation to MM diagnosis) ranged from 6 months to over 12 months among both symptomatic and asymptomatic patients. Abnormal laboratory results for the CRAB criteria were observed closer to MM diagnosis time, with a median time of 1–2 months. Investigations for hypercalcaemia were uncommon in patients presenting with bone pain, and diagnostic tests to identify CRAB criteria were underused. Among symptomatic patients (with bone pain/SRE), advanced bone imaging investigation recommended by IMWG and National Institute for Health and Care Excellence (NICE)[24] with MRI or CT scan was limited; 20% of symptomatic patients had a record of MRI or CT imaging.

Strengths and limitations

The main strength of our study is that it fills the knowledge gap about key clinical features and diagnostic timing leading up to the diagnosis of myeloma in a primary care setting by providing a comprehensive picture for both symptomatic and asymptomatic patients. Our study is based on electronic health records data from a large representative sample of the UK population registered with GPs in the primary care setting with a wide geographic coverage.[16] Over a 10-year study period, our study captured a large number of newly diagnosed patients with MM. Additionally, to minimise misclassification, a group of clinical experts and epidemiologists developed algorithms to identify conditions of interest. We also investigated the frequency of bone pain recording on an annual basis over the study period and found consistency in recording of the symptom across the different years.

The study also has some limitations. First, since our study relies on recorded diagnoses in electronic health records, conditions or comorbidities not reported to the GPs might not be captured. Similarly, CPRD data are collected at the time of GP clinical care and not for research purposes; therefore, the completeness of medical information from specialists and inpatient care, is not known. Our study only focused on the CRAB diagnostic criteria and did not investigate other relevant tests such as protein electrophoresis, Bence-Jones protein urine test, serum free light chain test or erythrocyte sedimentation rate, which may also be conducted to assess myeloma. In addition, plain radiographs and other imaging studies were part of the CRAB criteria for bone lesions; however, patients may have received a chest X-ray for other reasons not related to the CRAB criteria work-up. Reasons for imaging procedures were not available and patients may have received those for reasons not related to the CRAB criteria work-up. Finally, the study only looked at bone pain in the 2 years prior to diagnosis and patients may have had bone pain prior to the start of the baseline assessment period.

Comparison with existing literature

Previous studies have reported that most patients with MM complained about their bone pain at presentation. In a comprehensive review of the literature, Nador *et al* showed that 59% of patients with MM presented with bone pain.[11] Goldschmidt *et al* conducted an analysis using EMRs and Israeli Health Maintenance Organization data and reported that back pain was the most common complaint during the 2 years before MM diagnosis.[25] In our study, the frequency of bone pain recorded in primary care was consistent with these studies despite differences in geographic region and data source. As previous studies highlighted, findings about diagnostic delays in MM can vary from one study to another due to differences in data

sources, data collection methods, study design and study periods. For example, Howell *et al*, used data from the UK-based HMRN, and estimated that the total interval between time to help-seeking (self-reported symptoms) was 163 days.[4] In a systematic review and meta-analysis of seven studies, Koshiaris *et al* reported that the median diagnostic interval between first presentation to primary care and MM diagnosis was approximately 109 days.[26] Our observational findings support substantial delays between recorded symptoms and MM diagnosis in a primary care setting. However, there is considerable heterogeneity in symptoms (patient-reported vs predefined symptoms) and time periods reported in previous studies,[26] which makes comparing findings across studies difficult.[4]

Clinical and policy implications

The current pathway to diagnosing myeloma is recognised as being complex, with multiple GP appointments and significant delay before diagnosis. There is limited evidence regarding the clinical scenarios in which MM should be suspected.[13 16] Our study provides more clarity on the occurrence and timing of key clinical features and diagnostic investigations leading to the diagnosis of MM.

Our findings suggest that GPs could have significant input in improving the time to diagnosis of MM. The first National Audit of Cancer Diagnosis in Primary Care collected data on primary care referrals submitted voluntarily by GPs on their patients diagnosed with cancer in England. This audit showed avoidable delays in 27% of patients with MM receiving their diagnosis in primary care in England.[5] During the COVID-19 pandemic, there have been additional delays in myeloma diagnosis due to markedly reduced CT and MRI imaging, longer waiting times for investigations, and a fall in urgent cancer referrals.[27 28] At the end of September 2020, there were a total of 215 463 patients waiting for a diagnostic MRI, and the number of patients waiting 6 weeks or more for an MRI increased by 20% compared with September 2019.[29 30] Further research is warranted to quantify the impact of delays in MM diagnosis and treatment on patient quality of life and outcomes.

To reduce delays in diagnosing of MM in the primary care, there is a need for improved diagnostic safety netting, that is, the process of managing diagnostic uncertainty during the GP consultation and communicating to patients when and how to follow-up on potential symptoms.[31] Various stages of the pathway to MM diagnosis would benefit from tailored safety nets to manage diagnosis uncertainty and timely evaluation. Reflecting on insights from our study and other published studies, we propose a plethora of actions in different settings to be undertaken by both the patient and the GPs, using the action, actor, context, target, time framework (figure 6).[32]

One aspect of safety netting is to provide advice on potential red-flag symptoms and on accessing further medical care. Targeted awareness campaigns co-produced with patients and the public on the clinical

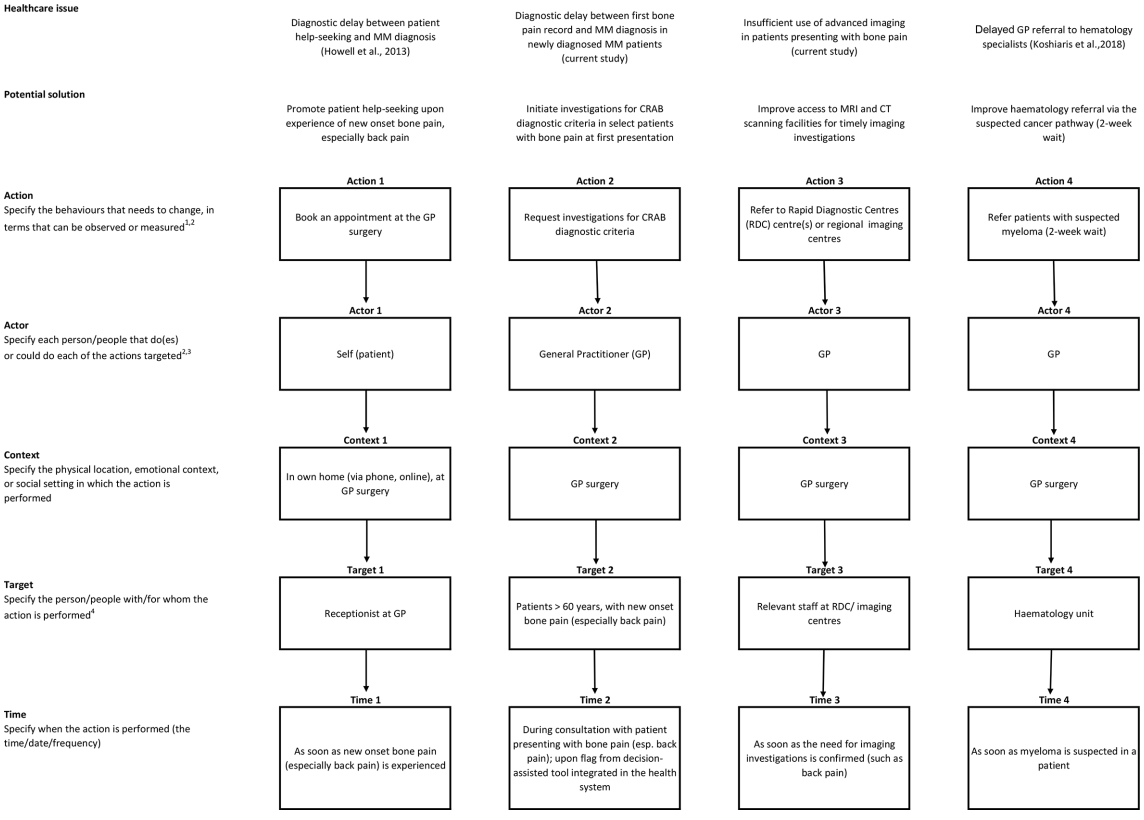

Figure 6 Proposed action, actor, context, target, time specification to improve diagnosis of multiple myeloma (MM) (adapted from Presseau *et al*).[32] CRAB, hyperCalcaemia, Renal impairment, Anaemia, Bone lesions; GP, general practitioner.

features and symptom profiles of MM may help reduce delays in MM diagnosis in primary care. Tailored GP education programmes on MM diagnosis through their regular channels would be an enabler for early diagnosis. Back pain combined with other symptoms such as fatigue and weight loss, or back pain combined with abnormal blood tests warrant definitive investigation for MM.[33 34] Such focused approach may be more impactful to address the delays in seeking help, representation and diagnosis. Such delays, with myeloma patients taking half a month to 7 months from initial symptom/health change to first seeking help, were recently reported.[35]

In the case of patients without bone pain and/or SRE (asymptomatic), further research is required (figure 6)[36] to identify biomarkers/precursors of MM, and to help identify those who may benefit from early screening haematological investigations. For example, Koshiaris *et al* used CPRD data to develop a prediction tool based on patient characteristics, symptoms and blood tests to identify patients at risk of MM in primary care.[37] Patients with monoclonal gammopathy of unknown significance (MGUS), however, were excluded from the analysis. Since premalignant plasma cell disorders such as MGUS often precedes MM, research is currently underway to monitor MGUS in community or secondary care, identify biomarkers and better predict patients who progress from MGUS to myeloma.

Another aspect of safety netting includes the follow-up and management of investigations. Improved access to diagnostic facilities may enable GPs to request timely laboratory and advanced imaging investigations, thereby accelerating the time to MM diagnosis. There is already a call for one stop shop diagnostic services directly within the community, closer to patients' homes.[38 39] This cross-collaboration aligns with efforts across the UK, as outlined in the National Health Service Long Term Plan, to focus on a radical overhaul of services for the diagnosis of suspected cancer, including the introduction of Rapid Diagnostic Centres, and the organisation of imaging networks with better access to MRI and CT scanners.[40 41]

Early recognition of red-flag symptoms and self or GP referral to these diagnostic services with rapid turnaround time for results will result in early diagnosis and prompt treatment. Further research, in close partnership with the patient, their support networks and the public, is required on the development, implementation and effectiveness of these potential safety netting.[42]

CONCLUSION

Nearly half of patients with NDMM presented with a bone pain symptom in primary care, approximately 7 months prior to MM diagnosis. Diagnostic tests to explore evidence of the CRAB criteria were underused. Investigations for hypercalcaemia and advanced imaging were not frequent in patients presenting with bone pain. Increased awareness of clinical features of MM, including its early presentation as bone pain, may lead to early recognition and testing of MM in primary care, thereby potentially accelerating disease diagnosis and timely medical care.

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Contributors AS, NP-I, VLB, DN made substantial contributions to the design of the work. NP-I, VLB and JRW contributed to the analysis of the data. AS, NP-I, JRW, AA and KR contributed to the interpretation of data. AS, NP-I, AA drafted the work; AS, NP-I, VLB, JRW, AA, DN and KR made substantial contributions to substantively revise the manuscript. All authors provided final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. AS is the guarantor and accepts full responsibility for the work and/or the conduct of the study, had access to the data and controlled the decision to publish.

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Competing interests AS and DN are employees of and hold stock options in Amgen. AA is a contract worker at Amgen. During the study conduct and reporting, VLB was a contract worker for Amgen. NP-I and JRW were employees of Aetion at the time the study was conduct and reporting and hold equity in Aetion. KR reports honoraria, research grant and advisory board from Janssen, Celgene, Takeda and Amgen.

Patient consent for publication Not applicable.

Ethics approval The research protocol was reviewed and approved by the Independent Scientific Advisory Committee (reference ISAC, protocol No 18_292). In this study, all data were completely anonymised and no participant's consent was required.

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