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## Barriers to the Early Diagnosis of Multiple Myeloma in General Practice: A Narrative Review

**Aleksandra Adamczyk**, ORCID <https://orcid.org/0009-0007-8002-385X>

Email: [oolaadamczyk@gmail.com](mailto:oolaadamczyk@gmail.com)

*Wojewódzkie Wielospecjalistyczne Centrum Onkologii i Traumatologii im. M. Kopernika w Łodzi, Łódź, Poland*

**Karolina Żeżawska**, ORCID <https://orcid.org/0009-0007-9563-5576>

Email: [karolina250700@gmail.com](mailto:karolina250700@gmail.com)

*Central Clinical Hospital of the Medical University of Łódź, ul. Pomorska 251, 92-213 Łódź, Poland*

**Adrian Pal**, ORCID <https://orcid.org/0009-0004-0518-3923>

Email: [adrian.b.pal@gmail.com](mailto:adrian.b.pal@gmail.com)

*Central Clinical Hospital of the Medical University of Łódź, ul. Pomorska 251, 92-213 Łódź, Poland*

**Patryk Cegielka**, ORCID <https://orcid.org/0009-0007-8311-3279>

Email: [patryk.cegielka@onet.pl](mailto:patryk.cegielka@onet.pl)

*Central Clinical Hospital of the Medical University of Łódź, ul. Pomorska 251, 92-213 Łódź, Poland*

**Maria Sicińska**, ORCID <https://orcid.org/0009-0005-3768-8405>

Email: [maria.sicinska@stud.umed.lodz.pl](mailto:maria.sicinska@stud.umed.lodz.pl)

*Uniwersytecki Szpital Kliniczny nr 1 im. N. Barlickiego w Łodzi, Łódź, Poland*

**Alicja Cienkowska**, ORCID <https://orcid.org/0000-0001-7163-5351>

Email: [a.cienkowska@rfrwl.pl](mailto:a.cienkowska@rfrwl.pl)

*Regional Development Fund of the Łódź Voivodeship, Traugutta 25, 90-113 Łódź, Poland*

**Marcin Ślot**, ORCID <https://orcid.org/0009-0002-9947-9957>

Email: [marcin.slot.poczta@gmail.com](mailto:marcin.slot.poczta@gmail.com)

*Maria Skłodowska-Curie Voivodeship Specialist Hospital in Zgierz, Parzęczewska 35, 95-100 Zgierz, Poland*

**Izabella Głowacka**, ORCID <https://orcid.org/0009-0006-3645-2684>

Email: [iza.glowacka@icloud.com](mailto:iza.glowacka@icloud.com)

*Faculty of Medicine, Medical University of Lodz, Lodz, Poland*

**Mikołaj Szczesny**, ORCID <https://orcid.org/0009-0003-1010-9712>

Email: [mikolaj.szczesny@poczta.fm](mailto:mikolaj.szczesny@poczta.fm)

*Independent Public Health Care Institution of the Ministry of Interior Affairs and Administration in Kraków, ul. Anonima Galla 25, 30-053 Kraków, Poland*

**Małgorzata Katra**, ORCID <https://orcid.org/0009-0007-3772-3455>

Email: [katramalgorzata@gmail.com](mailto:katramalgorzata@gmail.com)

*Independent Public Health Care Institution of the Ministry of Interior Affairs and Administration in Kraków, ul. Anonima Galla 25, 30-053 Kraków, Poland*

**Corresponding Author:** Aleksandra Adamczyk — [oolaadamczyk@gmail.com](mailto:oolaadamczyk@gmail.com)

## **Abstract**

### **Background**

Multiple myeloma is a malignant hematological neoplasm characterized by the uncontrolled proliferation of monoclonal plasma cells in the bone marrow and monoclonal protein synthesis, resulting in numerous organ complications. Despite significant therapeutic advances early diagnosis still remains a critical factor in treatment efficacy. Diagnostic delays in multiple myeloma are among the longest of all hematological malignancies, often leading to irreversible organ damage. This issue is most prevalent in primary care, where low oncological vigilance and difficulties in interpreting early non-specific clinical manifestations often result in multiple consultations before a specialist referral.

### **Aim**

The aim of this study is to analyze the factors contributing to diagnostic delays of multiple myeloma in general practice, evaluate the most common non-specific symptoms, and emphasize the importance of timely diagnosis.

### **Material and Methods**

A narrative review was conducted using databases such as PubMed and Polish medical journals. The study analyzed publications concerning multiple myeloma patients, with a

particular focus on the frequency of specific symptoms and the underlying causes of delayed diagnosis.

## **Conclusions**

The average time to diagnose multiple myeloma is one of the longest in oncology. A key barrier is the non-specific clinical presentation, which leads to symptoms being attributed to more common chronic conditions. Consequently, nearly half of all patients require at least three primary care visits before receiving a preliminary diagnosis. Because diagnosis within three months correlates directly with longer remission, rapid intervention is vital. Improving the diagnostic process by routinely incorporating CRAB criteria and increasing oncological vigilance among primary care physicians are priority challenges to improve patient prognosis.

## **Keywords**

Multiple myeloma, primary care, diagnostic delay, CRAB criteria, oncological vigilance.

## **1. Introduction**

Multiple myeloma is a hematologic malignancy originating from mature immune cells known as plasma cells. It is characterized by the uncontrolled proliferation of monoclonal plasma cells within the bone marrow and the production of monoclonal protein, which subsequently leads to extensive organ dysfunction. [1] Although the disease remains incurable, the past few years have witnessed spectacular progress in its treatment. Patient prognosis has significantly improved, and the median survival time has doubled. Nevertheless, a critical challenge remains in shortening the time to diagnosis to ensure timely treatment and minimize irreversible organ injury.

The diagnosis of multiple myeloma is based on specific clinical and laboratory criteria. The foundation of the diagnostic process is a bone marrow examination demonstrating a clonal plasma cell infiltration of 10% or greater. Preliminary suspicion of the disease is most frequently based on the identification of typical organ manifestations - defined by the acronym CRAB: hypercalcemia (calcium elevation), renal insufficiency, anemia, and bone lesions - followed by the detection of monoclonal protein in the serum or urine. [1]

Due to its indolent onset, the non-specific nature of its symptoms, and the absence of clear "red flags," multiple myeloma is classified as one of the most challenging cancers to diagnose. It has been demonstrated that a prolonged diagnostic process is a huge contributing factor in half of all premature deaths in hematologic oncology [2]. Furthermore, the diagnostics of myeloma are characterized by the highest frequency of repeat visits compared to other

oncological diseases; in 50% of patients, the diagnosis is preceded by at least three consultations with a primary care physician before a referral to specialist care is issued. [3]

The objective of this study is to analyze the factors determining diagnostic delays in multiple myeloma within primary care practice, highlighting the importance of early detection of non-specific symptoms and a comprehensive approach to the patient.

## **2. Review Methodology**

This study constitutes a narrative literature review, conducted through a non-systematic search of the PubMed database and Polish medical journals. The keywords employed included: multiple myeloma, primary health care, diagnostic delay, CRAB criteria, and oncological vigilance.

The analysis incorporated original research, review articles, case reports, and clinical guidelines retrieved from Polish scientific platforms. The research process focused on publications concerning patients with multiple myeloma, with particular emphasis on clinical manifestations and the frequency of specific symptoms. Additionally, the study analyzed the complex diagnostic challenges of multiple myeloma in primary care settings.

## **3. Epidemiology and Risk Factors**

Multiple myeloma is a hematologic malignancy accounting for approximately 1% of all cancers and roughly 10% of hematologic neoplasms. [4] The epidemiological profile of multiple myeloma is significantly associated with demographic and metabolic factors. An analysis of residence showed a predominance of urban patients, who constituted 60% of the study group, compared to 40% from rural areas [2]. Research indicates that the disease is 1.5 times more common in men, and obesity has been identified as a significant factor increasing the risk of development. Incidence rates show a clear upward trend, particularly in highly developed countries [1]. Nevertheless, the prognosis for multiple myeloma patients has improved significantly in recent decades resulting from the rapid expansion of available treatment options [5].

The etiopathogenesis of multiple myeloma is associated with DNA damage during plasma cell development in the bone marrow; however, in most cases, the direct causative factor remains unidentified. From a primary care perspective, identifying high-risk groups is essential for maintaining diagnostic vigilance. Potential contributing factors include exposure to ionizing radiation (including occupational exposure in radiologists and historical data from atomic blast survivors), various immune system stimulants such as chronic bacterial infections, diabetes

mellitus, the presence of medical implants, allergies, and related disorders, as well as medication use and family history [6]. Furthermore, exposure to toxins and viral infections are also suspected to play a potential role [7].

#### **4. Diagnosis of Multiple Myeloma**

Diagnosis of multiple myeloma relies on meeting specific diagnostic criteria:

##### **TWO CRITERIA MUST BE MET:**

1. Clonal bone marrow plasma cells more than 10% or biopsy-proven bony or extramedullary plasmacytoma

##### **PLUS, ONE OR MORE OF THE FOLLOWING MYELOMA-DEFINING EVENTS:**

1. Presence of CRAB criteria which can be attributed to the underlying plasma cell proliferative disorder, specifically:
  - a) Hypercalcemia: serum calcium > 11mg/dL
  - b) Renal insufficiency: creatinine clearance <40 mL/min or serum creatinine > 2mg/dL.
  - c) Anemia: hemoglobin <10 g/dL or 2g/dL below the lower limit or normal
  - d) Bone lesions: one or more osteolytic lesions on skeletal radiography, CT or PET-CT
2. Clonal bone marrow plasma cell percentage 60% or more
3. Involved/uninvolved serum FLC ratio of 100 or more (involved FLC level must be 100 mg/L or more)
4. More than one focal lesion on MRI studies (at least 5 mm in size)

Tab. 1. Diagnostic Criteria of Multiple Myeloma [1]

The definitive diagnosis is established by a hematologist, who conducts a highly specialized diagnostic process within a hospital or outpatient setting. Patients are most frequently referred to a specialist after a primary care physician suspects the disease. By evaluating basic blood tests and identifying characteristic symptoms, the GP initiates the diagnostic pathway.

## 5. Clinical manifestations

Multiple myeloma is characterized by a heterogeneous clinical picture, and the early stages of the disease are often oligosymptomatic. The manifesting symptoms are highly non-specific, and no single symptom allows for a diagnosis. [8]

Key to the presentation of multiple myeloma are disorders resulting from the direct proliferation of neoplastic plasma cells and the toxic effect of the monoclonal protein, which they produce, on target organs. These complications are traditionally defined by the CRAB acronym, which covers four clinical manifestations [1]

- **C (calcium elevation)** - hypercalcemia,
- **R (renal insufficiency)** - renal failure,
- **A (anemia)**
- **B (bone lesions)** - destructive bone changes.

### 5.1. "C" symptoms -- Hypercalcemia

Hypercalcemia, defined as a serum calcium level exceeding 2.75 mmol/L (11 mg/dL), represents a significant clinical challenge in oncological diagnostics. This disorder is estimated to affect approximately 13% of patients with this diagnosis, being one of the most frequent causes of malignancy-associated hypercalcemia [5, 1]. While hypercalcemia as an isolated parameter is associated with a low risk of multiple myeloma (0.7%), its diagnostic significance increases sharply when other symptoms are present. The highest risk, estimated at approximately 10%, is attributed to hypercalcemia accompanied by skeletal symptoms, such as bone pain or pathological fractures. [8]

The clinical presentation of hypercalcemia is complex and multisystemic, resulting from increased osteolysis and the systemic impact of excess calcium ions. Common, but non-specific symptoms, include: excessive thirst, polyuria, altered mental status, abdominal pain, pancreatitis, and cardiac arrhythmias [1, 9]. A significant elevation in serum calcium levels can lead to severe complications, including acute kidney injury, nephrolithiasis, metastatic calcification, and multi-organ failure. [9] The non-specific nature of these symptoms (e.g., fatigue or nausea) often leads to their misattribution to other internal medical conditions, which significantly delays an accurate diagnosis.

Diagnostic challenges are compounded by the fact that calcium levels often increase markedly only in the final months preceding diagnosis [10]. This suggests that hypercalcemia

may fully manifest only in the advanced stages of the neoplastic process. Consequently, the occurrence of hypercalcemia in combination with any accompanying symptom constitutes an absolute indication for comprehensive diagnostic testing for multiple myeloma.

### **5.2. "R" symptoms - renal insufficiency**

Renal insufficiency, defined as an impairment of excretory function that can no longer be offset by the body's compensatory mechanisms, represents one of the most severe organ complications in the course of multiple myeloma. The development of kidney damage is multifactorial, resulting from monoclonal light chain nephrotoxicity and hypercalcemia, often worsened by dehydration and recurrent infections [11].

Statistics indicate that approximately 50% of patients exhibit features of renal insufficiency at the time of diagnosis [12], with 48% demonstrating significantly elevated creatinine levels [5]. In another 25% of patients, this dysfunction will develop during later stages of the neoplastic process, making it not only a common symptom but also a key factor that negatively affects the prognosis [11]. Retrospective analysis of laboratory dynamics proves that the increase in serum creatinine and calcium levels typically occurs rapidly 3 to 6 months before the final diagnosis [10]. Such a short time interval confirms that both hypercalcemia and advanced reduction in renal function are late clinical manifestations of the disease, requiring immediate medical intervention to prevent further progression of organ damage.

### **5.3. "A" symptoms - anemia**

Anemia, defined as a hemoglobin concentration below 13 g/dL in men and 12 g/dL in women, is one of the most common clinical conditions encountered in primary care. Due to its non-specific nature, symptoms such as chronic fatigue, reduced exercise tolerance, or recurrent infections are often overlooked or misattributed to aging and comorbidities, including diabetes or depression [4].

Although anemia is present in approximately 73% of patients at the time of cancer diagnosis and is the primary cause of reported weakness [5, 12, 13], its first symptoms can precede the diagnosis by many months. Literature data indicate that a decline in hemoglobin levels in multiple myeloma patients is observable up to 3 years before the final diagnosis; on average, the criteria for anemia are met 2 years before diagnosis in men and 15 months in women [10]. These statistics highlight the necessity of regular monitoring of blood count abnormalities. The key to early detection of the disease depends not on relying on a single result, but in the comprehensive analysis and correlation of multiple laboratory parameters.

#### **5.4. "B" symptoms - bone lesions**

Bone lesions are among the most frequent causes of pain reported by patients, and in the case of multiple myeloma, bone pain, particularly back pain, is the most common initial symptom [14]. Statistics indicate that approximately 67% of patients report bone pain at the time of their first medical consultation, with nearly 71% of symptomatic cases involving the spine [3, 14]. These symptoms are often mistaken for common musculoskeletal conditions, which significantly delays diagnosis. More than 40% of patients notice symptoms six months before diagnosis, and over half of this group first consults with a primary care physician [14].

Although back pain affects up to 70% of the adult population, less than 1% of cases have a neoplastic etiology. Nevertheless, the scale of the problem in myeloma is substantial, with bone lesions present in up to 80% of patients at the time of diagnosis [1, 15, 16].

In primary care practice, maintaining oncological vigilance and identifying "red flags" is crucial to prompt further diagnostic investigation. Warning signs associated with bone pain include patient age (<20 or >55 years), pain unrelated to physical activity or localized in the thoracic spine, and pain unresponsive to analgesic treatment. Other concerning features include generalized weakness, unexplained weight loss, bone deformities, and a significant medical history (previous malignancy, steroid use, or HIV infection). [4, 14, 17] It is worth noting that while classic bone pain in myeloma is associated with osteolytic foci, in a significant group of patients (>30%), the disease is diagnosed only at the stage of pathological fractures or incidentally during examinations performed for other reasons [18].

#### **6. Frequency of Clinical Manifestations**

A patient suffering from multiple myeloma presents with a range of non-specific symptoms, including those defined by the CRAB acronym, as well as symptoms resulting from progressive organ damage. Research statistics indicate that at the time of diagnosis, 79% of patients present with bone abnormalities (primarily lytic lesions, followed by fractures and osteoporosis), making this the most frequent clinical manifestation of the disease.

Additionally, anemia was found in 73% of patients, elevated creatinine levels - indicating renal dysfunction - in 48%, and hypercalcemia in 13%. General weakness was reported by 57% of subjects, while 58% complained of bone pain. Other commonly occurring symptoms included neuropathy, paresthesia, repeated infections, unintentional weight loss, and bruising or bleeding [2, 4, 5].

## **Patient characteristic - total CRAB manifestation**

Bone abnormalities	79%
Anemia	73%
Renal insufficiency	48%
Hypercalcemia	13%
Other: bone pain, fatigue, neuropathy, repeated infections, bruising/bleeding	

Tab. 2. Patient characteristic. Main complains at the time of diagnosis. [5]

## **7. Barriers to Early Diagnosis -- A Challenge for Primary Care**

Multiple myeloma is classified as one of the most difficult malignancies to diagnose. This difficulty arises from a combination of several coexisting factors which, together with the non-specific clinical presentation, lead to significant diagnostic delays [19]. Statistical studies show that 48% of men and 44% of women are diagnosed as late as six months or more after the onset of their first symptom [14].

### **7.1. Symptom Overlap with Common Chronic Diseases**

The symptoms of multiple myeloma overlap with those of more common chronic conditions, such as lower back pain, diabetes, chronic kidney disease, or arthritis. Shared symptoms, including polydipsia, polyuria, recurrent infections, or neuropathy, may initially suggest a diagnosis of diabetes. [5] Furthermore, due to the advanced age of most patients, bone pain is often downplayed and attributed to physiological aging or the progression of osteoporosis. Weakness reported by the patient, although correlated with anemia, may be linked to developing depression or the natural aging process [4]. Progressive renal failure may be misinterpreted as more typical causes, such as diabetic nephropathy, hypertensive nephropathy, or drug-induced renal injury, which are significantly more common in the elderly [4, 5]. Similarly, hypercalcemia can be caused by medications (such as thiazide diuretics or lithium), hyperparathyroidism, or PTH-secreting tumors; since these are far more frequent etiologies, they are typically considered first [9]. Following statistical probability and clinical experience, GPs first investigate more common etiologies during the differential diagnosis process.

### **7.2 Age**

Multiple myeloma is a malignancy that primarily affects the geriatric population; over 60% of diagnoses occur in patients over 65 years of age. [1, 20] Median age at diagnosis ranges from 65 to 69 years, depending on the literature. Less than 15% of patients are under the age of 55,

and less than 3% under 40. The incidence of the disease shows a clear correlation with the aging process, and the median age at death oscillates around 75 years (with 80% of MM-related deaths occurring in individuals over 65) [1, 7].

### **7.3. Symptom Normalization by the Patient**

The non-specific nature of early multiple myeloma symptoms, such as anemia, fatigue, or weight loss, leads many patients, especially the elderly, to normalize them. By ignoring these signs, they significantly delay the start of the diagnostic process. Research has shown that patients wait on average 162 days from the onset of the first symptom until their first visit to a primary care physician, and 172 days (range: 5--339 days) before undergoing routine laboratory tests. Subsequently, it takes about 70 days to form an accurate clinical suspicion by a general practitioner, often involving three or more visits before the patient is referred to a hematologist [2, 5].

Unfortunately, fewer than 45% of patients present their concerns to a primary care physician. About one-third of patients are diagnosed in the Emergency Department at an advanced stage of the disease, often presenting with acute conditions [2, 19]. Other specialists also play a significant role in the multiple myeloma diagnostic process, as patients often seek help because of organ complications. 28.17% of subjects were first seen by a nephrologist due to renal failure, while 10.67% went to a rheumatologist, neurologist, or internist. Notably, 11.65% consult a neurosurgeon due to severe back pain or neurological deficits [2]. The overall ambiguity of the clinical presentation makes identifying the disease a challenge for the patient as well, who is often unaware of the severity of the developing symptoms.

### **7.4. Requirement for Specialized Diagnostic Procedures**

Diagnostic procedures for multiple myeloma in primary care settings are significantly restricted by systemic barriers. It should be noted that a definitive diagnosis requires an invasive bone marrow biopsy (demonstrating >10% clonal plasma cells) or confirmation of a plasmacytoma [1]. These procedures are unavailable at the primary care level. Radiological imaging also plays a crucial role in the diagnostic process. Techniques such as whole-body low-dose computed tomography, and most of all whole-body magnetic resonance imaging and PET-CT, allow for the precise assessment of early bone lesions and disease stage [21, 22]. In contrast, standard radiography, the basic imaging tool ordered by general practitioner, often fails in the early stages of the disease, masking osteolytic foci and leading to the misinterpretation of changes as age-related processes [22]. The lack of access to advanced diagnostic tools, combined with the ambiguous clinical presentation, limits the role of the GP to an initial

suspicion of multiple myeloma. Consequently, the necessity of referring the patient for further highly specialized investigations extends the time between the first consultation and the final diagnosis [4].

### **7.5. Multi-Specialist Consultations and Delays**

A key factor affecting the time to a multiple myeloma diagnosis is the interval between the onset of the first symptoms and obtaining a referral to a hematology clinic [14]. Statistics show that patients with multiple myeloma require the highest number of medical consultations before a diagnosis compared to all other oncology patient groups [2, 3]. It has been shown that patients are seen by an average of three different specialists before reaching a hematologist, which generates a delay of 3 to 6 months [4, 23]. Most frequently, patients are first referred to nephrologists, rheumatologists, or orthopedists [14]. Due to these numerous medical visits, the associated waiting times, and initial misdiagnoses, the diagnostic process is significantly prolonged, postponing the initiation of appropriate treatment.

### **7.6. Rarity of Multiple Myeloma in Primary Care**

Multiple myeloma accounts for approximately 1% of all malignancies and about 10% of hematological cancers, making it the second most common hematologic neoplasm (after lymphomas) [4]. In daily clinical practice, this means that the average primary care physician encounters a patient with this disease extremely rarely. According to literature data, a family physician in the UK establishes such a diagnosis on average once every 5 years [19], while other sources indicate that contact with a new case of myeloma may occur only once every 8-10 years [4]. Throughout their career, a family doctor typically encounters no more than 10 patients with multiple myeloma [3]. Such a low frequency over years of practice may lead a physician to overlook the disease in differential diagnosis during the early stages of the non-specific symptoms reported by the patient.

## **8. Benefits of Early Diagnosis**

Early diagnosis is essential for the successful management of any condition, but it is especially important in oncological diseases. The time between the onset of clinical symptoms and the initiation of therapy is a vital prognostic factor, showing a direct correlation with the duration of remission. As shown by data, 78% of patients diagnosed within three months of presenting their first symptoms were in the first phase of remission induction or in a stable phase. In contrast, among patients whose diagnostic process exceeded six months, this figure dropped to just 51%, [14]. Furthermore, bloodwise research indicates that up to 80% of patients

diagnosed at an early stage will survive for more than five years, whereas this survival rate falls to only 26% for those diagnosed with advanced-stage disease [23].

A prolonged diagnostic interval also results in an increased frequency of long-term complications. Patients with a long symptomatic period before diagnosis (>6 months) were more likely to develop multiple organ complications. In comparison, approximately 40% of patients diagnosed in less than three months presented with no complications at the time of diagnosis [14].

Earlier diagnosis also increases the chances of avoiding several other adverse effects, such as limited therapeutic options, the need for aggressive treatment, a significant decline in quality of life, or increased hospitalization rates. It is also worth highlighting the negative impact of diagnostic delays on the patient's psychophysical condition, which can reduce treatment efficacy and lead to lower treatment compliance [4]. Patients with a delayed diagnosis are also prone to a poorer clinical response to therapy, resulting in more aggressive interventions, which take a greater toll on both the healthcare budget and the patient's overall well-being.

## **9. Discussion**

Diagnosing multiple myeloma poses a significant challenge for a doctor, particularly in its early stages. The fact that the diagnostic process for multiple myeloma is among the longest of all neoplastic diseases, adversely affects not only the treatment process and patient prognosis, but also the entire healthcare system [4]. The non-specific nature of symptoms and the limited sensitivity of standard diagnostic tests at the primary care level lead to substantial diagnostic delays. Additionally, multiple myeloma is not characterized by a single, dominant symptom [8]. This requires a comprehensive approach to the patient, incorporating laboratory tests as well as imaging. The inconsistency of the clinical presentation explains why early manifestations of the disease are often overlooked, not only by primary care physicians but also by the many specialists seen during the diagnostic process [6].

Research shows a significant diagnostic gap in primary care, as patients with multiple myeloma rarely receive a full assessment based on the CRAB criteria [5]. However, it should be noted that these symptoms occur much more frequently in the general population due to other conditions than as a result of myeloma itself. Consequently, highly specialized screening tests are not recommended for the general population. They could lead to overtesting and overdiagnosis, which generates unjustified costs and negatively impacts patients by causing stress and reducing their quality of life. [5, 19] The key is to interpret the patient's clinical

presentation holistically, enabling the connection of non-specific warning signs with a rarer neoplastic etiology.

However, there remains significant potential for improvement in this area. Crucially, a high level of awareness, regarding myeloma among physicians, must be combined with the rational use of widely available laboratory tests, to which doctors should have easy access [19]. This will help avoid delays, underestimation of symptoms, or misdiagnoses - all of which the WHO considers as a priority public health challenge [2]. Equally important is patient health education, raising awareness and encouraging individuals not to ignore concerning symptoms and to consult a physician promptly. Nonetheless, the physician's role remains decisive. Any deviation from the norm should result in an in-depth clinical interview and the maintenance of oncological vigilance as part of a comprehensive approach to patient care.

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**Author's contribution:**

**Conceptualization:** AA, MS, AP;

**Methodology:** AA, AC, PC;

**Formal analysis:** AA, MS, MSi;

**Investigation:** MSi, KZ, IG;

**Resources:** MK, MSi, IG;

**Data curation:** MK, AC;

**Writing -- original draft:** PC, AA;

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