

Review

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Review

Challenges, Difficulties, and Delayed Diagnosis of Multiple Myeloma

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Abstract: **Background:** Multiple myeloma (MM) is a heterogenous plasma cell malignancy with non-specific symptoms and disease heterogeneity at clinical and biological levels. This non-specific set of symptoms, including bone pain, anemia, renal failure, hypercalcemia, and neuropathy can mislead diagnosis as chronic or benign conditions, resulting in a delay in diagnosis. Timely identification is paramount to prevent organ damage and reduce morbidity. **Methods:** In this review, we present an overview of recent literature concerning the factors leading to delayed diagnosis of MM and the impact of delayed diagnosis. This includes factors relevant to physicians and systems, diagnostic processes, primary healthcare services, and laboratory and imaging data access and interpretation. Other emerging technologies to diagnose MM include artificial intelligence-based decision support systems and biomarker-focused strategies. **Findings:** Delayed diagnosis can lead to presentation at advanced disease stages associated with life-threatening complications and shorter progression-free survival. Patients are often seen by many physicians before they are referred to hematology. Understanding of clinical red flags for MM in primary care is inadequate. Our findings indicate that limited access to diagnostic tests and inconsistent follow-up of MGUS/SMM patients, as well as lack of interdepartmental coordination, delay the diagnostic process. **Conclusion:** Multimodal tools are available for early diagnosis of MM. Educational campaigns to raise awareness of the disease, algorithms dedicated to routine care, and novel technologies including artificial intelligence and big data analytics, and new biomarkers may serve this purpose, as well as genomic approaches to the premalignant MGUS stage.

Keywords: Artificial Intelligence; Diagnostic Delay; Multiple Myeloma; Monoclonal Gammopathy of Undetermined Significance; Misdiagnosis

Introduction

Multiple myeloma (MM) is a hematological cancer derived from plasma cells, often defined by the presence of a monoclonal immunoglobulin. It accounts for 1% of cancers and about 10% of hematological malignancies. And findings during the course of the disease may include anemia, leukopenia, thrombocytopenia, renal failure, severe pain, bone fractures and hypercalcemia [1–4]. However, almost all multiple myelomas arise from asymptomatic premalignant condition called monoclonal gammopathy of undetermined significance (MGUS). This is diagnosed after more than 10 years of the disorder in 50% [5–7]. Effective multi-drug regimens are available for most forms of MM, resulting in long-term remission. However, because of the disease's biology, relapse remains frequent, and MM remains incurable due to the emergence of treatment resistance [8–10]. MM has variable clinical findings, nonspecific symptoms as seen in diabetes, arthritis, or chronic renal failure all can lead to diagnosis late [11], especially in elderly patients there are many differential diagnoses

mimicking MM. Patients often develop these symptoms and present to primary healthcare providers or other specialties giving rise to delays in referrals to hematologists. Delayed diagnosis of the disease can negatively impact on patients' quality of life and prognosis [12]. The routine path to diagnosis of multiple myeloma and possible delays is presented in Figure 1. Existing reviews and articles on this topic are sparse. The objective of this review is to present and evaluate the multifactorial factors which create and perpetuate delays in the diagnoses of multiple myeloma, highlight barriers that exist at the patient, physician, and system perspective level, present potential strategies which may facilitate earlier diagnoses and earlier interventions, and provide supplemental data to fill gaps in the existing literature to foster academic progress in this area.

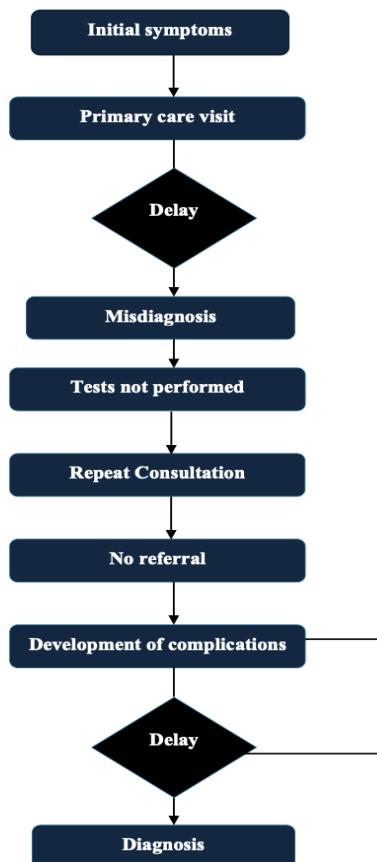


Figure 1. Typical Diagnostic Journey in MM and Delay Points.

Clinical Spectrum of Multiple Myeloma

The symptoms in multiple myeloma is usually nonspecific. Its defining symptoms are the CRAB symptoms (hypercalcemia, renal insufficiency, anemia, bone findings) [1-4]. Among 1027 multiple myeloma patients included in the Czech post marketing observational study, bone pain was reported at diagnosis by 58% of the patients and fatigue by 32% of the patients. Seventy-three percent of the patients had anemia, 48% had elevated creatinine levels, 13% had hypercalcemia and 79% had bone abnormalities (primarily but not limited to lytic lesions, fractures and osteoporosis). Other features typically noted are neuropathy, developing infections (recurrent), loss of weight (involuntary), easy bruising/bleeding [13].

Because most symptoms are nonspecific, they can resemble many other conditions. Diabetes shares some symptoms with multiple myeloma, including excessive thirst and urination, fatigue, frequent infections, and neuropathy [14]. Likewise, renal sufficiency due to multiple myeloma is difficult to separate from renal insufficiency from diabetes or chronic kidney disease in the absence of directed testing [15]. Bone pain or low back pain is frequently shrugged off as arthritis or

osteoporosis and not taken seriously. This results in delayed diagnosis, which consequently leads to increased morbidity and mortality [16]. Presenting symptoms for multiple myeloma Although the most frequent presenting clinical symptoms for multiple myeloma, along with potential misunderstandings and diagnostic delays are outlined in Table 1.

It has been shown that patients consult at least three specialists before arriving at a hematologist, which can cause a lapse of 3 to 6 months in the diagnostic workup [17]. Delayed diagnosis is linked with a higher rate of myeloma-related complications and a significant decrease in disease-free survival, but does not affect the overall survival rate [18]. Worse outcomes have been associated also with presenting with advanced complications (eg, severe infections, spinal cord compression, fractures, renal failure) [19].

Table 1. Common Symptoms of MM and Diagnostic Pitfalls.

Symptom	MM Association	Misdiagnosis Risk	Delay Potential
Back pain	High	Osteoporosis, arthritis	High
Fatigue/anemia	High	Aging, depression	High
Polyuria/polydipsia	Moderate	Diabetes mellitus	Moderate
Renal insufficiency	High	Hypertensive nephropathy	High

Reasons for Delays in Diagnosis

Patient-Related Delay

The median age of presentation for MM is 70 years [20], and most patients are elderly. Symptoms like chronic pain and fatigue are often misattributed to natural ageing or ignored completely by patients, resulting in a delay in diagnosis [21]. Symptoms such as anemia, bone pain, and fatigue are often thought of as a normal part of daily life, leading to delayed consultation with a physician [22]. This delays the process of diagnosis and adds to the probability of the disease being detected at an advanced stage with the associated complications. Diagnostic challenges such as consideration of atypical presentations including extramedullary disease in MM also result in delays in the diagnosis [23].

Physician-Related Delays

The non-specific nature of multiple myeloma symptoms, together with the long asymptomatic phase that can precede the disease's onset, leads to diagnostic delay, both due to patient factors and also because physicians frequently will not suspect the condition [24]. Commonest symptoms such as fatigue, back pain, anemia and recurrent infections are often ascribed to age or to non-malignant conditions [25]. In particular, in primary care settings, general practitioners are often more likely to exclude multiple myeloma and pursue the most commonly encountered diagnoses such as depression, osteoarthritis or viral illness, resulting in delays in making the correct diagnosis that can be many months duration [26].

Above mentioned determinants reinforcing such delay as revealed by a United Kingdom study addressing the pre-diagnostic phase also included physicians attributing symptoms to either "muscle pain" or "age-related issues", neglecting lab abnormalities, restricting physical examination or negligence of series of preclinical steps (the process before a diagnosis) [27]. Moreover, the limited knowledge base of many physicians leads to other myeloma-specific findings (such as elevated Erythrocyte Sedimentation Rate (ESR), normochromic normocytic anemia, hypercalcemia) being attributed to benign conditions [28].

Extramedullary pariskeletal involvement is noted in about 13% of patients: during diagnosis in 7% and additional 6% during treatment. This is because these involvements typically manifest as localized complaints, leading to the consideration of hematological malignancy being missed [31].

System-Related Delays

In the laboratory, tests necessary for the diagnosis of multiple myeloma include a complete blood count (CBC), a erythrocyte sedimentation rate (ESR), biochemistry, serum protein electrophoresis and free light chain levels [1-4]. Although bone marrow biopsy is the key to a diagnosis, sophisticated imaging techniques, such as whole-body low-dose computed tomography (CT), Positron Emission Tomography- Computed Tomography (PET-CT), and whole-body Magnetic Resonance Imaging (MRI), are commonly needed to confirm a diagnosis. But the accessibility, interpretability, and coordination of these tests often cause delays [32].

Additionally, multiple myeloma is a genetically and biologically heterogeneous disease [10]. Aggressive molecular methods (Fluorescence In Situ Hybridization analysis, for instance) are paramount in properly identifying patients with high-risk subtypes but do not capture the whole palette of the disease at a molecular level [33]. Recently, new sequencing technologies (whole-genome sequencing, whole-exome sequencing, and panels) have been established for more accurate risk stratification to elucidate mutations behind drug resistance. The clinical integration of such novel analyses is still limited, and delays in diagnosis persist as an important clinical failure [34].

The disease's clinical features and the potential treatment complications need multidisciplinary assessment between hematologist, laboratory assistant, genetic specialists, nephrologist, radiologist, neurologist, and sometimes neurosurgeon [35]. Nevertheless, a substantial amount of time can be lost during the diagnostic process if the communication and coordination between several specialties are not well established [36]. Table 2 lists some of the patient, physician, and system factors that are relevant to the diagnosis and treatment of multiple myeloma that may lead to delay. Table 3 shows the analysis of factors leading to diagnostic delay, considering physician-related and system-related factors.

Table 2. Factors Contributing to Diagnostic Delays in MM.

Level	Examples	References
Patient-level	Attributing symptoms to aging, neglecting chronic pain	20-23
Physician-level	Misdiagnosing non-CRAB symptoms, labeling as depression	24-31
System-level	Delayed imaging, late referral to hematology	32-36

Table 3. Physician vs System-related Delay Factors.

Delay Factor	Physician-related	System-related
Symptom interpretation	Mislabeling as benign/age-related	Lack of diagnostic pathway algorithms
Test ordering	Not requesting SPEP, sFLC early	Delay in test availability (MRI, PET-CT)
Follow-up	Inadequate follow-up on anemia/ESR	Poor interdepartmental communication
Referral	Delayed referral to hematology	Lack of fast-track hematology referral

Tests and Limitations in the Diagnostic Process

Given that the diagnosis of MM is often made late in the course of the disease process, it is imperative that primary care physicians begin the diagnostic algorithm when they observe any of the aforementioned symptoms (eg, fatigue, weight loss) or abnormalities on routine laboratory testing (eg, anemia, elevated creatinine, hypercalcemia, elevated ESR, or elevated total protein levels [37]). In this setting, relatively simple and directed tests like serum protein electrophoresis (SPEP), serum free light chain (sFLC) testing, and serum immunofixation electrophoresis (IFE) should be the first tests requested [38,39]. At this stage of imaging, a low-dose CT whole-body scan, if available, is to be preferred due to its sensibility in the detection of osteolytic lesions. What alternative methods can be used not covered by CT are advanced ones like PET-CT or MRI and the request for these tests is usually made by a hematologist or an oncologist [40]. Hence, early referral of suspected cases with necessary lab tests from primary care to hematology aids in quicker diagnosis and avoids complications [40]. Widespread implementation of diagnostic algorithms in primary care, better awareness among general practitioners and establishing rapid referral chains are required to prevent delays. The diagnosis is then made according to the International Myeloma Working Group Diagnostic Criteria for Multiple Myeloma and Certain Related Plasma Cell Disorders [41], once a hematologist has completed the workup.

Table 4. International Myeloma Working Group Diagnostic Criteria for Multiple Myeloma and Certain Related Plasma Cell Disorders.

MGUS (non- IgM^a)
All 3 criteria must be met: <ul style="list-style-type: none"> Serum monoclonal protein (non-IgM type) <3 g/dL Clonal bone marrow plasma cells <10% Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) or amyloidosis that can be attributed to the plasma cell proliferative disorder
SMM
Both criteria must be met: <ul style="list-style-type: none"> Serum monoclonal protein (IgG or IgA) of ≥3 g/dL, or urinary monoclonal protein ≥500 mg/24 h, or clonal bone marrow plasma cells 10%-60% Absence of MDEs or amyloidosis
MM
Both criteria must be met: <ul style="list-style-type: none"> Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma ≥1 of the following MDEs: Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically <ul style="list-style-type: none"> Hypercalcemia: serum calcium >1 mg/dL higher than the ULN or >11 mg/dL Renal insufficiency: CrCl <40 mL/min or serum creatinine >2 mg/dL Anemia: Hgb of >2 g/dL below the LLN or <10 g/dL Bone lesions: ≥1 osteolytic lesion(s) on skeletal radiography, CT, or PET-CT Clonal bone marrow plasma cell percentage ≥60% Involved/uninvolved sFLC ratio ≥100 (involved FLC level must be ≥100 mg/L) >1 focal lesions on MRI (at least 5 mm in size)
Solitary plasmacytoma
All 4 criteria must be met: <ul style="list-style-type: none"> Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells Normal bone marrow with no evidence of clonal plasma cells Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion) Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, or bone lesions (CRAB) that can be attributed to a lympho-plasma cell proliferative disorder

CrCl = creatinine clearance; CT = computed tomography; FLC = free light chain; Hgb = hemoglobin; Ig = immunoglobulin; LLN = lower limit of normal; MDE = myeloma-defining events; MGUS = monoclonal gammopathy of undetermined significance; MM = multiple myeloma; MRI = magnetic resonance imaging; PET-CT = positron emission tomography-computed tomography; sFLC = serum free light chain; SMM = smoldering multiple myeloma; ULN = upper limit of normal. SI conversion factors: To convert serum calcium to mmol/L, multiply values by 0.25; to convert serum creatinine to μ mol/L, multiply values by 88.4; to convert Hgb to g/L, multiply values by 10. ^aFor diagnostic criteria associated with other types of MGUS (ie, IgM MGUS and light-chain MGUS), see Rajkumar et al., 2014. ^bBone marrow biopsy can be deferred in patients with low-risk MGUS (IgG-type, M protein <15 g/L, normal FLC ratio) who lack clinical features concerning for MM.

Laboratory and Imaging Methods Used in the Diagnosis of Multiple Myeloma

Laboratory and imaging diagnostic techniques for multiple myeloma report varying sensitivity and specificity for the identification of unique subtypes because of the biological heterogeneity of the disease [42]. Although serum protein electrophoresis and immunofixation tests are the most common techniques to identify monoclonal immunoglobulins, they are known to have low sensitivity, especially in light chain-only (LCO) or non-secretory myeloma [38,43]. In these subgroups, the serum free light chain (sFLC) test is of clear diagnostic utility, indirectly providing evidence of monoclonality due to alterations in the kappa and lambda ratio [44]. However approximately 20% of LCO patients have non-elevated FLC that cannot be reliably identified in urine thus limiting utility both in diagnosis and treatment response assessment while above 100 mg/L offers a significant gain in reliability [45].

However, many advanced diagnostic methods are unavailable in all healthcare facilities. Technologies such as mass spectrometry and isoelectric focusing that are more sensitive, are still not routinely used, and are only available to a handful of centers due to the expense and infrastructure and personnel required. For imaging, techniques such as low-dose whole-body CT, PET-CT, and whole-body MRI are essential for the early detection of osteolytic lesions but often rely on hematologist/oncologist referrals [46]. Moreover, advanced radiological experience is needed for the interpretation of these tests and risks, like interpretational variability, or false negatives can add to the challenge in diagnosis [47]. Table 5 Summary of the main diagnostic techniques for MM and of their sensitivity and specificity and limitations.

Table 5. Diagnostic Tools and Their Characteristics.

Method	Sensitivity	Specificity	Use Case	Limitation
SPEP	Medium	High	Detects M protein	Ineffective in non-secretory MM
Sflc	High	Medium	Light chain disease	Complex interpretation
Bone Marrow Biopsy	High	High	Gold standard	Invasive
Whole-body MRI	High	High	Detects marrow lesions early	Limited access
PET-CT	High	High	Extramedullary/osseous involvement	Cost and availability
Mass Spectrometry	Very High	Very High	Low-level M-protein detection	Limited to specialized centers

In addition, traditional methodologies like Fluorescence In Situ Hybridization analysis can detect high-risk cytogenetic abnormalities but cannot provide a complete picture of molecular heterogeneity in multiple myeloma at the molecular level [48]. Next-generation sequencing technologies (whole-genome or whole-exome sequencing) overlap the ability to probe more deeply into the genetic infrastructure of the disease, but these techniques have not yet gained broad translation into clinical practice due to barriers of cost, interpretation of data, and a lack of infrastructure; thus, are limited in the application to the vast majority of MM patients. Collectively, these factors represent major technical and systematic obstacles towards accurate, rapid, and subtype specific diagnosis of multiple myeloma [49]. New diagnostics in MM The last years have also seen the emergence of new biomarkers and technology for improvement in earlier and more accurate diagnosis of MM as shown in Table 6. Although widely used, many of these diagnostic tests have deficiencies with regard to sensitivity, specificity, or application, as listed in Table 7.

Table 6. Emerging Biomarkers and Technologies.

Marker/Technology	Diagnostic Value	Current Limitation
miRNA	Early marker of transformation	Not yet routine
circulating DNA	Minimally invasive detection	Expensive, technical complexity
circulating tumor cells	Monitoring progression	Low abundance, technical challenges
AI-based algorithms	Risk stratification & early alerting	Not yet fully integrated into systems
Mass Spectrometry	Ultra-sensitive M-protein detection	Requires expertise & infrastructure

Table 7. Diagnostic Tests and Limitations in MM.

Method	Advantages	Limitations
Serum protein electrophoresis	Inexpensive, widely available	Insufficient in non-secretory MM
sFLC assay	Valuable in light-chain only MM	Interpretation complexity
Bone marrow biopsy	Gold standard	Invasive, difficult to repeat
Whole-body MRI	Effective for lytic lesions	Limited accessibility

Consequences of Delayed Diagnosis

These challenges result in patients being diagnosed later, receiving treatment more slowly and experiencing worse clinical outcomes [50]. Late identification raises the risk of potentially fatal issues in patients [50]. This results in increased morbidity and early mortality, leading to more aggressive initial treatments, which drives up costs [51]. Those who present with renal failure at diagnosis have limited therapeutic options and those who present with vertebrae fractures have limited mobility, chronic pain, and reduced quality of life [52]. Moreover, the higher demand for treatment associated with late-stage disease manifests as an increased number of patients requiring hospitalization, intensive care and impact on the healthcare system, which, in turn, has economic implications [53]. Delay in diagnosis also leads to more long-term problems including lower treatment compliance, lower quality of life, loss in workforce productivity and psychosocial effects [54]. Hence, early diagnosis of the disease not only has clinical but also economic and social significance in multiple myeloma [55]. Table 8 Clinical and prognostic implications of delayed diagnosis in multiple myeloma

Table 8. Consequences of Delayed Diagnosis.

Consequence	Description
Late-stage diagnosis	Diagnosis occurs after irreversible organ damage
Increased complications	Renal failure, fractures, spinal cord compression
Need for aggressive treatment	More toxic regimens required at initiation
Reduced treatment options	Limited options in renal failure or frailty
Decreased quality of life	Chronic pain, mobility issues, fatigue
Higher healthcare costs	Greater burden on healthcare system
Increased hospitalizations	Frequent ICU admissions and procedures
Psychosocial impact	Anxiety, depression, loss of productivity

Strategies to Prevent Diagnostic Delays

Diagnostic interval in multiple myeloma is one of the longest in all types of cancer that adversely affect both patient outcomes and a burden on the healthcare system [56]. Such delays often occur in primary care, since general practitioners (GPs) are rarely seeing this rare disease clinically [57]. Moreover, an average GP will see multiple myeloma only once every 8–10 years, making it very unlikely to be suspected early on [58]. Hence, the enhancement of GPs familiarity with myeloma symptomatology and diagnostic pathways as well as the implementation of diagnostic safety nets for persistent and unexplained symptoms remains a key strategic priority [59].

Early diagnosis may easily be established through the recognition of minor abnormalities in routine blood tests, along with the implementation of reflex myeloma screening [60]. Clinical risk algorithms created for this approach seek to identify high-risk patients based on their electronic health records, utilizing parameters including symptoms, hemoglobin, creatinine, and inflammatory markers [61]. There are technical challenges that still exist with it being integrated into decision support systems, including, alignment with clinical workflows, and figuring out triggering thresholds. Active surveillance of precursor conditions such as MGUS and smoldering multiple myeloma (SMM) is also critically important [62]. A population-based screening study conducted in Iceland provides one valuable model, during which all MGUS patients were studied, applying different follow-up strategies [63].

In addition, work with laboratories on early warning systems and proactive collaboration with hematologists can help facilitate diagnoses, particularly in less obvious cases. To facilitate timely referral decisions, critical test results must be interpreted according to pre-defined algorithms and communicated to the clinician with the correct reflex tests [64]. In addition to their reliance on technological integration, cost-effectiveness, sustainability of their impact on the healthcare system, and diagnostic accuracy must be used to assess early diagnostic strategies. This approach can enhance the early detection of myeloma at a much earlier stage with minimal complications and improve basic clinical end-points, such as survival [65]. A graphic comparison of two chosen diagnostic tools according to their speed and sensitivity is presented in Figure 2.

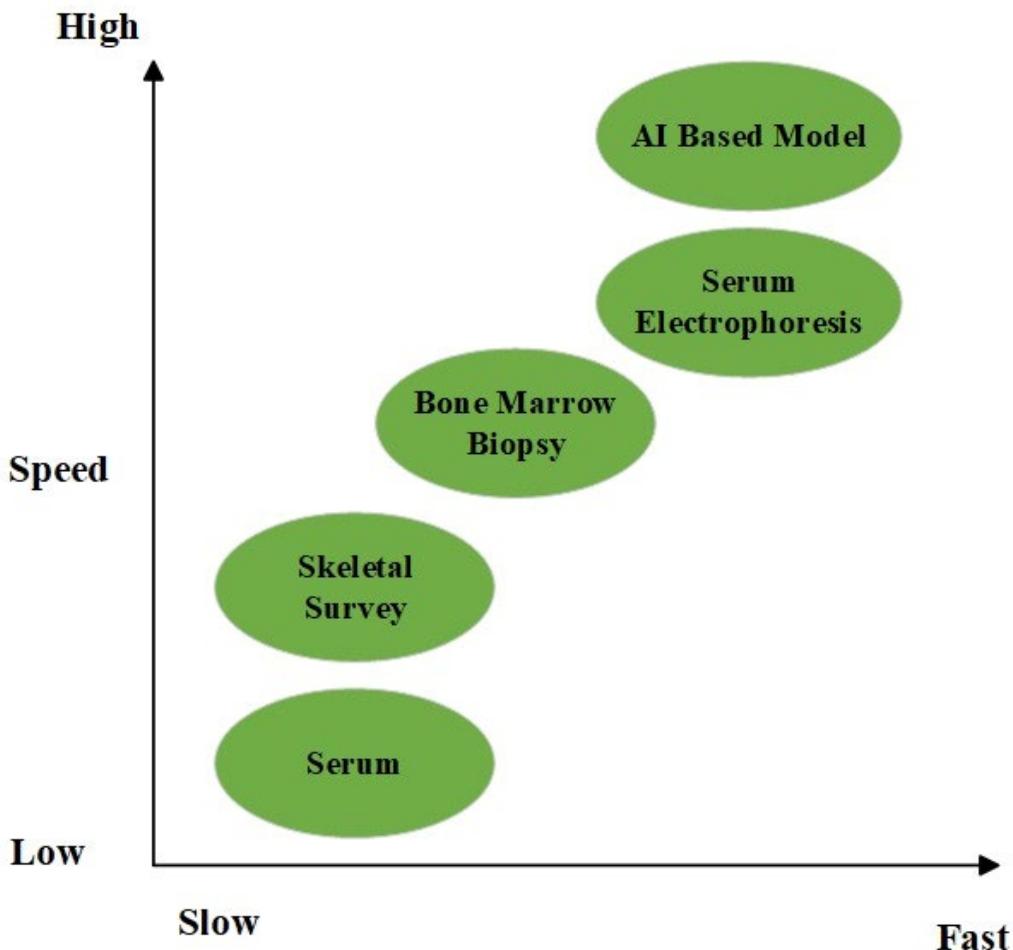


Figure 2. Comparison of Diagnostic Tools in Terms of Speed and Sensitivity.

Future Perspectives and Research Areas

Sufficient studies on enhanced diagnostic and prognostic markers are ongoing due to the rising incidence of multiple myeloma (MM) cases and the burdens and delay in diagnosis [66]. MiRNAs, angiogenic factors, Extracellular Matrix proteins, telomeres and telomerase activities are newer biomarkers with promising capabilities in the diagnostics and prognostics of MM [67]. Ongoing studies on methodologies such as blood/liquid biopsy, which could permit earlier disease detection than the still gold-standard invasive bone marrow biopsy but still allow more frequent and less painful measurements through the variants in circulating tumor cells (CTCs), miRNAs and cell freely circulating DNA (cfDNA) in peripheral circulation [68].

As with other sectors, there is growing use of artificial intelligence in medicine. As the number of cases of multiple myeloma increases so does the volume of data that has been gathered [69]. Such data can be processing using machine learning and deep learning models to expand the knowledge and better understand myeloma mechanisms to better manage MM patients [70,71].

MGUS (monoclonal gammopathy of undetermined significance) is prolonged premalignant phase prior to the development of multiple myeloma [72]. This phase allows to study cancer evolution and to understand plasma cell neoplasm malignant evolution mechanisms, identify MGUS patients with high-risk of progression early and eventually design new therapeutic targets considering previous achievements. This may also delay or extend the process of malignant transformation [73,75].

The application of rapid advances in genomic techniques to study how premalignant cells evolve should also allow for the identification and subsequent targeting of driver events during clonal evolution in MM and in cancer more broadly [74,75].

Conclusion

Multiple myeloma is the second most common hematological malignancy, but late diagnosis of the disease is commonly reported due to non-specific symptoms, lack of awareness, and patient-, physician-, and system-related factors. We would like to remind that the majority of cases are diagnosed at an advanced stage of the disease, which, in turn, increases morbidity and reduces the quality of life. The microbiological, serological, and imaging techniques related to the diagnostic process have made significant progress but face challenges for widespread adoption and standardized implementation.

This opens up several avenues for early diagnosis including raising awareness through educational programs, algorithm development for primary healthcare centers, adoption of state-of-the-art technologies like AI and big data analytics, and genomic research specifically on the MGUS premalignant phase. Therefore, removing obstacles to early diagnosis and treatment initiation at an earlier stage can effectively reduce the morbidity and early mortality and has been associated with statistically significant improvements in patient survival and quality of life.

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