Role of CRAB Criteria as Modality for Prediction of State of Multiple Myeloma

Mohamed Gamal Mohamed Yousef*, Esam Nasr Mohamed El-Zorkany, Ayman Fathy Abd El-Halim, and Elsayed Anany Metwally
Internal Medicine Department, Hematology Unit, Faculty of Medicine, Zagazig University, Zagazig, Egypt
Corresponding author: Mohamed Gamal Mohamed Yousef
E-mail: dr.mgmy@gmail.com ,
m.yousef021@medicine.zu.edu.eg
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Abstract
Multiple myeloma is a malignancy of plasma cells originating from the bone marrow; it is a clonal plasma cell disorder that produces excess monoclonal immunoglobulin. The disease most commonly presents with hypercalcemia, renal failure, anemia and bone lesions (CRAB features).
Myeloma is preceded by an indolent phase termed monoclonal gammopathy of undetermined significance (MGUS), which is defined by the presence of a monoclonal protein (<3 g/dL) without any end organ damage or features of myeloma. The cause of MGUS is currently unknown, but this disorder can evolve into symptomatic myeloma. The risk of progression to myeloma is about 1% per year, with risk factors being a high monoclonal protein level, high percentage of plasma cells in the bone marrow, presence of IgA monoclonal protein, and an abnormal free light chain ratio.6 The prevalence of MGUS increases with age, with 3.2% of cases presenting in persons aged over 50 years, and 5.3% of cases in persons aged over 70 years.
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Introduction:

Going back to the 1960s, the clinical paradigm for multiple myeloma used to be watch and wait and to initiate therapy once the patient was clinically ill and suffered from symptoms. Certainly, a key limitation, at the time, was the lack of available therapies (restricted to alkylating chemotherapy and steroids) **(Cherry et al., 2013)**. In that era, once the decision was made to start therapy, the clinician had few other treatment options when therapy stopped working and the

disease became active again. Fortunately, the myeloma field has changed substantially, and today, many new drugs exist that have been approved for the treatment of multiple myeloma. To adapt to this new reality, in 2014, the updated IMWG diagnostic criteria changed the definition of multiple myeloma from being a disease defined by symptoms to a disease defined by biomarkers **(Rajkumar et al., 2014)**.

Specifically, there were three biomarkers added to the former "CRAB" (hypercalcemia, renal failure, anemia, and lytic bone lesions) criteria, so now there are seven variables that can make the diagnosis. Thus, the criteria for the diagnosis of multiple myeloma requiring therapy are 10% or more plasma cells in the bone marrow, abnormal immunoglobulins in the blood and/or urine [monoclonal protein and/or free light chains (FLC)] unless the patient is nonsecretory (which is rare), and one or more of the seven listed criteria are fulfilled (Table 5) **(Landgren & Rajkumar, 2016)**.

Table 1. Definition of multiple myeloma based on 2014 IMWG criteria **(Landgren & Rajkumar, 2016)**.

(i) Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma
(ii) Any one or more of the following myeloma-defining events (which have to be attributed to the underlying plasma cell proliferative disorder):
Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL).
Renal insufficiency: creatinine clearance <40 mL/minute and/or serum creatinine >173 μmol/L (>2 mg/dL).
Anemia: hemoglobin value of >2.0 g/dL below the lower limit of normal, or a hemoglobin value <10.0 g/dL.
Bone lesions: one or more osteolytic lesions on skeletal radiography (i.e., X-ray), low-dose CT, or PET/CT.
Clonal bone marrow plasma cell percentage ≥60%
Involved/uninvolved serum-free light chain ratio ≥100, and the involved serum-free light chain concentration 10 mg/dl or higher.
Two or more focal lesions based on MRI studies of the skeleton.

NOTE: Both (i) and (ii) have to be fulfilled. See details and discussion in the text regarding the above myeloma defining event variables.

The three newly added biomarkers are (i) abnormal serum (s) FLCs defined as an abnormal sFLC ratio (involved/uninvolved sFLC) of 100 or greater and the involved sFLC being 10 mg/dL or greater; (ii) 60% or higher plasma cell infiltration of the bone marrow; and (iii) two or more focal lesions in the bone or bone marrow as defined by whole-body (or at least spine and pelvis) MRI. These arbitrary cutoffs were initially reported in retrospective single-center studies, suggesting these biomarkers to be associated with, on average, around 1 year for the progression

from smoldering myeloma to multiple myeloma. Subsequently, smaller efforts were launched to replicate these observations, and upon review of these reports, the IMWG consensus group felt it was clinically justifiable to integrate these biomarkers into the disease definition of multiple myeloma, to have them written up by a writing committee, and to launch them as the updated IMWG diagnostic criteria for multiple myeloma requiring therapy **(Rajkumar et al., 2014)**.

In addition to the three biomarkers discussed above, the updated IMWG criteria included several adjustments and improvements of the definitions of the CRAB criteria. Although there are no changes to the definitions of hypercalcemia and anemia, the definitions of renal failure and lytic bone disease have been revised. Renal failure was previously defined as an increased serum creatinine >173 μmol/L (>2 mg/dL), which is a nonreliable marker. Therefore, the new definition advises clinicians to use either the Modification of Diet in Renal Disease equation or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations in estimating glomerular filtration rate (eGFR) in patients with myeloma, but a slight preference was given to using the CKD-EPI equation. Unless the renal insufficiency is due to another known cause, patients with an eGFR value below 40 mL/minute and/or a serum creatinine >173 μmol/L (>2 mg/dL) are considered to fulfill the definition of renal insufficiency as part of the diagnostic criteria for multiple myeloma **(Rajkumar, 2016)**.

Although it is well-known that X-ray has major sensitivity limitations when it comes to the detection of bone disease, in the clinical management of multiple myeloma, skeletal surveys have historically been used to identify lytic bone lesions in multiple myeloma. The revised IMWG criteria state that (i) skeletal survey, (ii) PET/CT, or (iii) low-dose CT represent valid methods, which can be used to rule out lytic bone lesions. The definition of a lytic lesion is arbitrarily set to 5 mm or greater diameter bone destruction. As a point of reference, in routine clinical care at Memorial Sloan Kettering Cancer Center (MSKCC, New York, NY), Landgren and colleagues implemented PET/CT as the default method to rule out lytic bone lesions in patients with plasma cell disorders. PET/CT has more than 20- to 30-times higher sensitivity than a skeletal survey **(Cherry et al., 2013)**.

Another clinical way of illustrating the difference in sensitivity between the two methods comes here: among 100 smoldering myeloma patients with a negative skeletal survey, we typically find 20 to 30 to have lytic bone lesions by PET/CT. It should be emphasized that lytic lesions are defined by the CT portion of the PET/CT, independent of whether there is PET uptake or not. In fact, the PET portion has many limitations in the setting of multiple myeloma; it is nonspecific and non-sensitive. For example, patients with multiple myeloma who have known lytic bone lesions may be PET negative due to slow metabolism of the myeloma cells **(Hillengass & Landgren, 2013)**.

Also, positive PET uptake is commonly seen due to inflammation, degenerative joints, or other causes. Importantly, on a practical note, PET/CT is used to monitor other diseases, and increased PET SUV uptake has direct clinical impact (e.g., in the management and treatment of

lymphomas). In contrast, quantification of abnormal SUV uptake is currently not part of the routine clinical management in multiple myeloma. Instead, the clinical focus is dependent on the CT portion's ability to identify or rule out lytic bone lesions. Although this may sound trivial, due to lack of communication between physicians managing patients with plasma cell disorders and physicians reading PET/CT results, in many clinics around the world, the full imaging reports from PET/CT are done by nuclear medicine specialists and not radiologists **(Landgren & Rajkumar, 2016)**.

Consequently, in these instances, the PET/CT report reflects mostly (only) SUV uptake by the PET tracer, and the value of the more sensitive CT portion (compared with skeletal survey) might be missed for the purpose of detecting early bone disease. Therefore, clinicians seeing patients with plasma cell disorders need to be aware of these facts and, if needed, should be encouraged to seek contact with their corresponding imaging colleagues to ensure that the PET/CT assessments and reports are optimized for the detection of lytic bone lesions. For example, in centers where nuclear medicine specialists are leading the work with PET/CT, two parallel reports can be generated for myeloma PET/CT evaluations: one by a radiologist (CT portion) and one by a nuclear medicine specialist (PET portion) **(Rajkumar et al., 2014)**.

On a clinical note, we would like to add further perspectives and discuss more details on the new biomarkers that were added to the IMWG diagnostic criteria. Specifically, we would like to address the issue with 60% or more plasma cell infiltration of the bone marrow. Typically, patients with such high percentage of infiltration of the bone marrow have other abnormalities, such as anemia, pain, and perhaps lytic bone lesions. However, there are cases where the plasma cell infiltration is high in the absence of other criteria. It should be stressed that there are different ways to determine the plasma cell percentage in the bone marrow **(Rajkumar, 2016)**.

In clinical practice, typically, there are three measures of plasma cell percentage of the bone marrow reported to the clinician: (i) plasma cell percentage determined by counting cells on a core biopsy with immunohistochemical staining with CD138 antibody, (ii) plasma cell percentage determined by counting cells on an aspirate smear, and (iii) plasma cell percentage as determined by the flow cytometry machine **(Landgren & Rajkumar, 2016)**.

Finally, we would like to give a few final comments on MRI assessment of the skeleton. The original study by Hillengass and colleagues used whole-body MRI in a series of 149 patients with smoldering myeloma, and they showed that, among those with two or more focal lesions (n = 23/149, 15%) in the bone or bone marrow, 12 of 23 (50%) had progression to multiple myeloma within 13 months and 16 of 23 (70%) had progression to multiple myeloma within 2 years **(Hillengass et al., 2010)**.

To expand on these findings, a Greek study group assessed 67 patients with smoldering myeloma with MRI of the spine and the pelvis; 9 of 67 (14%) patients had two or more focal lesions, and all 9 had progression to multiple myeloma within 4 years **(Kastritis et al., 2014)**. On the basis of these data, the IMWG consensus panel decided to use MRI as a biomarker for the diagnosis of multiple myeloma **(Rajkumar et al., 2014)**.

Although the IMWG criteria allow either of the two approaches (due to differences in availability of MRI around the world), several clinical questions remain. In the study by Hillengass and colleagues, 90% of the focal lesions were observed in the spine and pelvis; thus, 10% may be missed if whole-body MRI is not conducted **(Hillengass et al., 2010)**.

Also, a common clinical question pertains to the use of PET/CT versus MRI: Is there added value in doing both, or can MRI be skipped? The correct answer is: "There are not enough data to give a definitive answer; the IMWG guideline states that both methods shall be done." Imaging wise, MRI is a better method to assess soft tissue (such as bone marrow), and CT is better for hard tissue (such as bone). In clinical practice at MSKCC, Landgren and colleagues order PET/CT first, and if negative for lytic bone lesions, they order whole-body MRI to rule out focal bone marrow areas. If the PET/CT is positive, typically, they do not proceed with MRI as the patient already fulfills the criteria for having multiple myeloma. It should be stressed that there is no universal definition of a "focal bone marrow lesion by MRI" in the literature. Future IMWG guidelines will benefit from involving imaging specialists in addition to myeloma specialists **(Rajkumar et al., 2014)**.

Although the IMWG diagnostic criteria are not perfect, the intent and the implications of the updated version are to facilitate earlier detection and earlier initiation of therapy with the aim of improving overall survival in multiple myeloma. Indeed, population-based data support earlier detection and initiation of therapy in multiple myeloma **(Sigurdardottir et al., 2015)**.

In addition to the previous discussion on incorporation of additional biomarker-defined myeloma-defining events to the standard CRAB features, updates are also needed that take into account the substantial changes to laboratory testing and imaging used in the diagnosis of multiple myeloma that have happened since the initial publication of the IMWG diagnostic criteria. These include better methods of detecting bone and extramedullary disease using CT (including low-dose whole body CT), MRI, 18F-fluorodeoxyglucose (FDG) PET, and FDG-PET with CT (PET-CT). They also include better estimation of renal damage by use of creatinine clearance in addition to serum creatinine measurements, and the criteria for clonal bone marrow plasma cells needed on bone marrow examination have been revised **(Regelink et al., 2013)**.

Bone disease in multiple myeloma, to meet the CRAB criteria, has been defined as the presence of osteolytic bone lesions or the presence of osteoporosis with compression fractures attributable to the underlying clonal plasma cell disorder. Traditionally, bone disease has been identified on the basis of conventional skeletal radiography. The 2003 IMWG criteria for the diagnosis of multiple myeloma concluded that MRI and CT can be used to clarify the presence of bone disease (International Myeloma Working Group, 2003a).

Although the criteria did not explicitly state that these modalities can be used in isolation to fulfil the CRAB criteria in the absence of bone disease on skeletal radiography, it was the intent of the investigators that a definite osteolytic lesion detected on CT should be regarded as fulfilling CRAB criteria even if it was not visible on conventional skeletal radiography (RAK, unpublished

data). In the past 10 years substantial advances have been made in imaging technology, as well as more widespread use of MRI, low-dose whole-body CT, and FDG-PET to assess bone disease and bone marrow infiltration in multiple myeloma **(Kastritis et al., 2014)**.

A 2013 systematic review compared modern imaging methods including MRI, FDG-PET, PET-CT, and whole-body CT with conventional wholebody skeletal radiography. Newer imaging techniques had greater sensitivity than radiographic bone survey for detection of multiple myeloma bone lesions, with as many as 80% or more lesions detected by the newer imaging techniques. CT and MRI were equally sensitive, and thus either test can be used, depending on availability and access. Furthermore, the IMWG recommended the use of these techniques during the diagnostic assessment of patients with smouldering multiple myeloma and solitary plasmacytoma. The IMWG recommends that one of PET-CT, low-dose whole-body CT, or MRI of the whole-body or spine be done in all patients with suspected smouldering multiple myeloma, with the exact imaging modality determined by availability and resources **(Regelink et al., 2013)**.

Renal insufficiency is defined in the 2003 IMWG criteria as a serum creatinine concentration of more than173 µmol/L (roughly >2 mg/dL) that is attributable to multiple myeloma; this value corresponds to an increase of 40% above the normal upper limit of the serum creatinine.10 However, use of a fixed concentration of serum creatinine to defi ne renal insufficiency results in patients needing widely different levels of renal dysfunction, based on age, sex, and race, to fulfil the diagnostic criteria for multiple myeloma. For example, a serum creatinine concentration of 173 µmol/L in an individual weighing 70 kg corresponds to glomerular filtration rates of 38 mL/min in a 40-year-old man, 28 mL/min in a 40-year-old woman, 35 mL/min in a 65-year-old man, and 26 mL/min in a 65-year-old woman **(International Myeloma Working Group, 2003b)**.

This drawback is well-recognized, and has already been addressed in most modern clinical trials, in which creatinine clearance (estimated glomerular filtration rates) is used for eligibility criteria. The IMWG therefore recommends that measured or estimated glomerular filtration rates (according to the modification of diet in renal disease [MDRD] or chronic kidney disease epidemiology collaboration [CKD-EPI] formulae) less than 40 mL/min (which corresponds to about a 40% decrease from the lower limit of the normal glomerular filtration rates) be used instead of a fixed serum creatinine concentration to fulfil the CRAB criteria. This ensures that a similar level of renal dysfunction attributable to the underlying plasma cell disorder is used to define the disease **(Rajkumar, 2016)**.

The criteria have also been updated to clarify that only renal failure caused by light-chain cast nephropathy (based on typical histological changes or presumptive diagnosis based on the presence of high involved FLC levels, typically >1500 mg/L) is regarded as a myeloma-defining events. Although other forms of renal damage (eg, AL amyloidosis, monoclonal immunoglobulin deposition disease, light-chain Fanconi syndrome, monoclonal gammopathy-associated membranoproliferative glomerulonephritis) can occur in multiple myeloma, this association is not

characteristic of multiple myeloma and can be seen with other types of plasma cell dyscrasias (eg, MGUS) or lymphoproliferative disorders **(Rajkumar et al., 2014)**.

Although they can occur in conjunction with multiple myeloma, in most patients they occur independently without evidence of other myeloma defining events. For this reason, these renal disorders are not regarded as myeloma-defining events, and should not lead to multiple myeloma diagnosis, unless they meet criteria for multiple myeloma as listed in the panel. These entities represent unique disease states with clearly defined pathological features, diagnostic criteria, prognosis, and therapy. Some investigators have collectively referred to these disorders under the term monoclonal gammopathy of renal significance **(Leung et al., 2012)**.

Other causes of acute and chronic renal failure (eg, diabetic nephropathy, nephrotoxic drugs, pre-renal failure) should be carefully excluded. We recommend a renal biopsy to clarify the underlying cause of the renal failure in patients with suspected cast nephropathy, especially if the serum involved FLC levels are less than 500 mg/L, which is also consistent with the recommendations of the International Kidney and Monoclonal Gammopathy Research Group **(Rajkumar et al., 2014)**.

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