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LETTER

A critical analysis of the IMWG multiple myeloma complete response criterion in the era of mass spectrometry

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In the context of multiple myeloma (MM), achieving a "Complete Response" (CR) is a clinically significant milestone, indicating a considerable reduction in disease burden. According to the International Myeloma Working Group (IMWG) criteria, CR is defined by four parameters: "negative immunofixation (IFE) on the serum and urine, disappearance of any soft tissue plasmacytomas, and the presence of less than 5% plasma cells (PC) in bone marrow (BM) aspirates."[1]

The Spanish Myeloma Group and others have previously highlighted the limited clinical value of urine IF in defining CR, raising questions about this requisite in the definition of CR.[2,3] In this context, we aim to assess the value of the morphological PC count in BM examinations in patients in unconfirmed CR based on negative sIFE results. We will also explore the clinical value of mass spectrometry (MS) as a highly sensitive, non-invasive, single serological marker in this population, potentially allowing for a more accurate and less invasive assessment of disease status.

We analyzed a total of 716 paired serum and BM samples obtained from 290 newly diagnosed transplant-eligible (NDTE) MM patients included in the GEM12MENOS65 (NCT01916252), and GEM14MAIN (NCT02406144) (Supporting Information S1: Table S1) clinical trials. Enrollment details and treatment schemas have been previously described.[4–6] Samples were obtained at four predefined time points: post-induction, after autologous stem cell transplant (ASCT), post-consolidation, and after 2 years of maintenance. Serum samples were analyzed using Quantitative Immunoprecipitation Mass Spectrometry (MS) with anti-IgG/A/M, total κ, and total λ beads in the EXENT Analyzer (The Binding Site, part of Thermo Fisher Scientific), and serum protein electrophoresis (SPEP) and immunofixation (IFE) were carried out as per each center's protocol.[7–9] First-pull BM aspirations were used for morphological assessment with May–Grümwald–Giemsa staining. Plasma cell (PC) counts were obtained from a 200-cell differential count, using conventional

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bright-field microscopy. Each study site's independent ethics committee reviewed and approved the protocols, amendments, and informed consent forms. If required, these data can be obtained via the corresponding author.

First, we analyzed the individual clinical value of the two main factors defining CR (i.e., PC counting [<5% vs. ≥5%] and sIFE [positive vs. negative]) in all samples, including all time points, and independently of the conventional response achieved by the patients at each of those moments.[1] As shown in Figure 1A,B, neither PC nor sIFE distinguished patient groups with different median progression-free survival (mPFS); in contrast, MS status clearly separated two cohorts with distinct mPFS (Figure 1C).

Focusing on the 476 samples with unconfirmed CR based on negative sIFE results, we observed that PC counting did not differentiate two groups of patients with different mPFS (Figure 2A). However, a significant reduction in mPFS was noted among the 117 samples that were MS-positive (Figure 2B).

We then combined the results of PC counting and sIFE, therefore dividing the global cohort into samples in CR (<5% PC and sIFE-negative) versus less than CR (≥5% PC and/or sIFE-positive). We have previously shown that, in this group of patients, the CR category only distinguished two groups with different PFS after induction and after ASCT, but no significant differences were observed after consolidation.[10] In this study with longer follow-up, we confirmed the previous findings and additionally showed that the CR category did not discriminate two groups of patients with different PFS after two years of maintenance (Supporting Information S1: Figure 1). Accordingly, no significant differences in PFS between the ≥CR and <CR groups defined as above were found when analyzing all samples globally (Supporting Information S1: Figure 2). In contrast, as shown in Supporting Information S1: Figure 3, among cases in ≥CR, those found to be MS-positive ($n = 91$) displayed a significantly inferior PFS.

Further, analysis of the combined results of PC counting and MS (among sIFE-negative cases) showed that only 36 out of the 476 cases were MS-negative and had ≥5% PC, the majority of them (31/36) with undetectable residual disease in the BM analyzed by flow cytometry and therefore corresponding to polyclonal PC. Therefore, among sIFE-negative cases, the NPV of MS using the results of PC counting as a reference was 90% (86%–93%; $P = 0.0005$). We have previously shown that, in this group of patients, MS identified two cohorts with significantly different mPFS at the four time points analyzed.[11] Among sIFE-positive cases, MS showed a tendency to discriminate between two subgroups of patients with different mPFS, although statistical significance was not reached ($P = 0.058$; Supporting Information S1: Figure 4). These findings confirm the subjectivity of IFE interpretation and are likely explained by results falsely interpreted as positive.

As shown in Supporting Information S1: Figure 5, all BM PC counts and sIFE results available were grouped into conventional CR versus non-CR and then combined with MS findings, resulting in four defined subgroups: (1) ≥CR and MS-negative, (2) ≥CR and MS-positive, (3) <CR and MS-negative, and (4) <CR and MS-positive. PFS analysis across these four cohorts confirmed the independent and added clinical value of MS, which discriminated two prognostic groups regardless of conventional CR status. Furthermore, conventional CR showed no prognostic relevance within either the MS-positive or the MS-negative cohorts.

Our analysis of 716 paired serum and BM samples from 290 NDTE MM cases treated with an intensive schema reveals that on reaching sIFE-negative status, PC counting (with a cut-off of 5%)

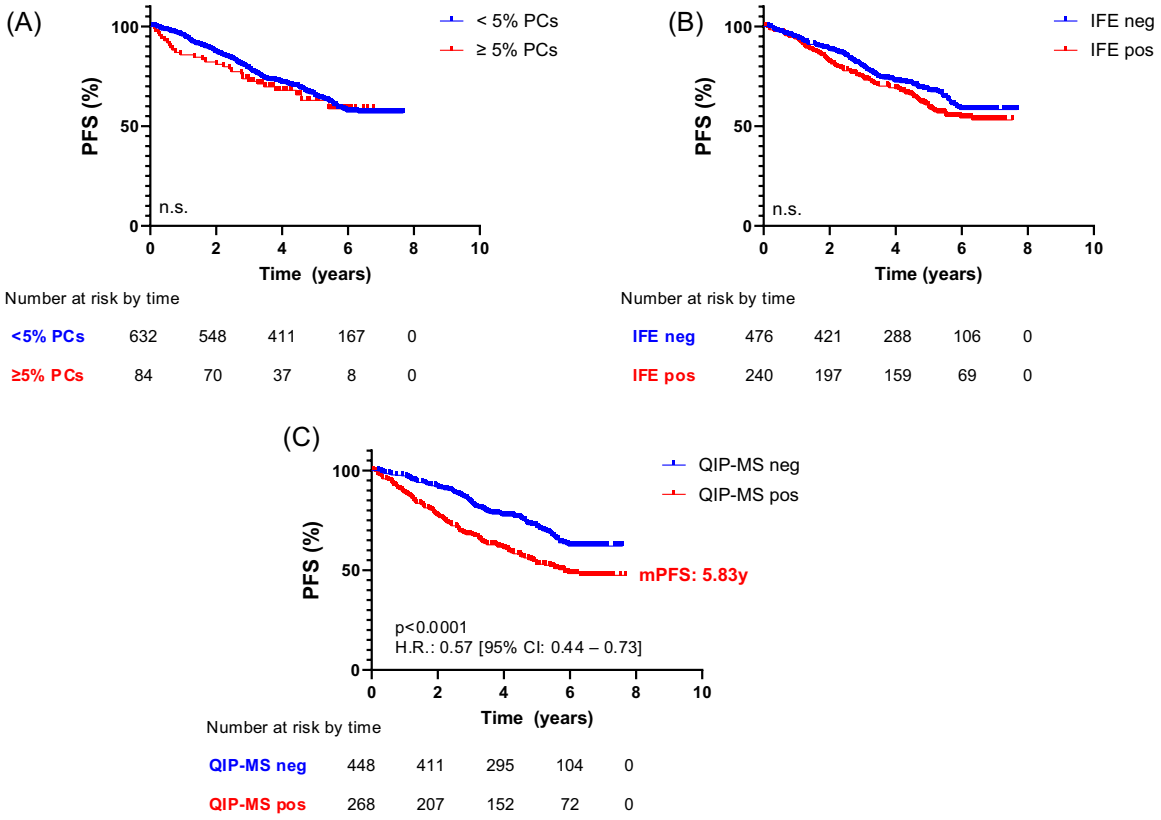


FIGURE 1 Progression-free survival of samples from all patients, calculated from the time the corresponding sample was obtained and based on the results of (A) plasma cell count (<5% vs. ≥5%), (B) serum immunofixation (positive vs. negative), and (C) MS (positive vs. negative).

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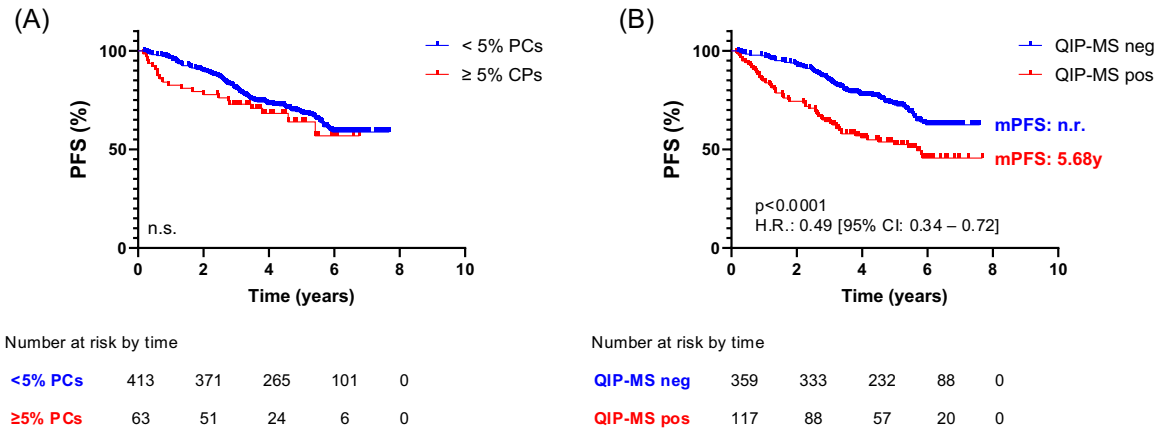


FIGURE 2 **Progression-free survival of IFE-negative patients, calculated from the time the corresponding sample was obtained and based on the results of (A) plasma cell count (<5% vs. ≥5%) and (B) MS (positive vs. negative).**

fails to effectively differentiate groups of patients with different mPFS (Figure 2A). This finding questions the need for a BM aspiration to merely determine the percentage of PC, an invasive examination that causes significant discomfort and anxiety, and carries the risk of complications, while BM remains mandatory for MRD assessment by NGS/NGF.[12] Our study also demonstrates that MS status effectively identifies two groups of patients with different mPFS, both among patients who are sIFE-negative and in those in CR, thus outperforming traditional methods and highlighting its potential as a more accurate and noninvasive tool for assessing disease evolution. Importantly, out of the 414 CR samples analyzed, disease would still be identifiable in 91 (22%) using MS, while in 323 (78%), it would not be detected and thus could be considered as in "MS-CR."

To the best of our knowledge, the criterion of CR regarding the disappearance of plasmacytomas does not specify the imaging modality to be used for that purpose.[1] Current IMWG guidelines recommend low-dose CT or PET-CT at diagnosis and for response assessment (in patients with positive baseline imaging), but mostly when CR and BM-based MRD negativity are achieved, which also suggests the need to revise this requirement for the definition of CR.[13]

In summary, our study highlights the limitations of traditional CR criteria, shows that BM aspiration in patients with MM should primarily serve to assess MRD using IMWG-endorsed methodologies, and discusses the potential use of MS as a noninvasive, accurate alternative for disease assessment. MS negativity could define a more stringent complete response category, with bone marrow evaluation reserved for confirming MRD negativity; however, MS negativity may occur later than MRD clearance because MS reflects systemic tumor burden and is also influenced by M-protein clearance kinetics. Our study has been conducted in a specific subgroup of patients treated with effective strategies, but that did not include anti-CD38 monoclonal antibodies or novel immunotherapies such as CAR-T or bispecific antibodies; further research is warranted to validate these findings across larger and more diverse cohorts, including transplant-ineligible MM patients and those with relapsed and refractory disease. Additionally, exploration of the integration of MS with other non-invasive diagnostic tools could further refine CR criteria. As we move toward more personalized medicine, the adoption of patient-friendly, accurate diagnostic methods like MS will be crucial in optimizing treatment strategies and improving patient outcomes in multiple myeloma.

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AUTHOR CONTRIBUTIONS

Noemí Puig: Conceptualization; investigation; funding acquisition; writing—original draft; methodology; validation; writing—review and editing; software; formal analysis; project administration; supervision; resources; data curation. **Cristina Agulló**: Conceptualization; investigation; writing—review and editing. **Bruno Paiva**: Conceptualization; investigation; writing—review and editing; writing—original draft. **María-Teresa Cedena**: Investigation; writing—review and editing. **Laura Rosiñol**: Investigation; writing—review and editing. **Teresa Contreras**: Investigation; writing—review and editing. **Joaquín Martínez-López**: Investigation; writing—review and editing. **Albert Oriol**: Investigation; writing—review and editing. **María-Jesús Blanchard**: Investigation; writing—review and editing. **Rafael Ríos-Tamayo**: Investigation; writing—review and editing. **Anna Sureda**: Investigation; writing—review and editing. **Sunil Lakhwani**: Investigation; writing—review and editing. **Javier de la Rubia**: Investigation; writing—review and editing. **Valentín Cabañas**: Investigation; writing—review and editing. **Felipe de Arriba**: Investigation; writing—review and editing. **Miguel Paricio**: Investigation; writing—review and editing. **María-Belén Iñigo**: Investigation; writing—review and editing. **Verónica González-Calle**: Investigation; writing—review and editing. **Enrique M. Ocio**: Investigation; writing—review and editing. **Sergio Castro**: Investigation; writing—review and editing; methodology. **Joan Bargay**: Investigation; writing—review and editing. **Joan Bladé**: Investigation; writing—review and editing. **Jesús F. San Miguel**: Conceptualization; investigation; writing—review and editing; writing—original draft. **Juan-José Lahuerta**: Investigation; writing—review and editing. **María V. Mateos**: Conceptualization; investigation; writing—review and editing; writing—original draft.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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