# Clinical and Sociodemographic Characteristics of Patients With Relapsed and/or Refractory Multiple Myeloma and Their influence on Treatment in the Real-World Setting in Spain: The CharisMMa Study

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## Abstract

**The characteristics of patients with RRMM in the real-world setting often differ from those enrolled in clinical trials, challenging therapeutic decisions in day-to-day practice. We retrospectively analyzed the sociodemographic and clinical characteristics of RRMM patients treated in routine clinical practice and their influence on the prescribing patterns in this setting. Treatment patterns among 276 RRMM patients from multiple hospitals were highly heterogeneous. The prescribed regimen was primarily influenced by the number of previous lines and the presence of osteopenia and extramedullary plasmacytomas. Our results rise awareness on the heterogeneity of the therapeutic landscape of RRMM in the real-world and highlight the complexity of therapeutic decision making in this population.**

**Introduction:** Treatment of relapsed and/or refractory multiple myeloma (RRMM) should be established based on multiple factors, including previous treatment and the sociodemographic/clinical characteristics of the patients. However, patients enrolled in randomized-controlled trials often do not mirror the scenario encountered in real-world practice, thus challenging therapeutic decisions in day-to-day practice. **Patients and methods:** This observational, cross-sectional, multicenter study aimed to investigate the sociodemographic and clinical characteristics of patients with RRMM treated in routine practice in Spain and their influence on treatment regimens. **Results:** The study included 276 RRMM patients (median age 69 years; no gender predominance). Seventy-four percent of patients had CRAB features at the time of study inclusion, 65.9% bone lesions, 28.7% high-risk cytogenetics, and 27.0% were at ISS stage III; 65.1% were retired and lived in urban areas (75.7%) with their relatives (85.8%); 28.7% had some dependence degree. Patients had experienced their last relapse in a median of 1.61 months before enrollment and had received a median of 2 treatment lines (range 1-10). Second-and third-line therapies were mostly based on immunomodulatory drugs, followed by proteasome inhibitors (PIs), whereas monoclonal antibodies prevailed in later treatment lines. The presence of extramedullary plasmacytomas, the absence of osteopenia, and being in the second or third treatment line (vs. later lines) significantly increased the odds of receiving PIs. **Conclusions:** RRMM treatment in the real-world setting is highly heterogeneous

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and is primarily influenced by the number of previous lines. The consideration of patients' clinical and sociodemographic characteristics may support clinicians in making therapeutic decisions.

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## Introduction

Multiple myeloma (MM) is the second most common hematological malignancy and accounts for 13% of all blood cancers.[1] It has been estimated that nearly 86,000 new diagnoses are made worldwide every year; however, the global epidemiological landscape of MM suggests an upward trend of MM incidence in developed countries, probably associated with population aging.[2] In the last decade, several advances in the understanding of the molecular basis and prognostic factors of MM, along with the advent of novel therapeutic agents, have remarkably improved the survival of these patients. Nevertheless, MM remains incurable, and most patients–including those with a durable response–will eventually experience multiple relapses that may ultimately lead to the development of refractory disease.[3,4] Patients with relapsed or refractory MM (RRMM) are faced with a remarkable, cyclical burden of symptoms and treatments that severely compromises their quality of life and that of their relatives and/or caregivers.[5]

The development of new anti-myeloma agents has expanded the therapeutic approaches to the management of MM, and clinicians may now choose from a relatively extensive repertoire of treatments based on high-level evidence and patient characteristics.[6,7] However, unlike reasonably bounded algorithms proposed for first-line treatment,[7] therapeutic decisions for the management of RRMM patients require a balanced appraisal of multiple factors, including patient characteristics (eg, age, comorbid conditions, performance status, and frailty), disease characteristics (eg, staging, cytogenetic risk, organ function, presence of extramedullary disease), and the outcome of previous therapies (eg, duration of response, toxicities).[3,6,7] Of them, the previous treatment received has been identified as one of the most important determinants of treatment success in RRMM patients.[8] In this regard, the advent of novel therapies provides clinicians with more tools for improving survival in MM patients, but it also increases the complexity of therapeutic decision-making, particularly in the context of RRMM.[9]

Regardless of the type of MM, certain patient profiles (particularly older patients with a higher comorbidity burden) and those with less advantaged socioeconomic backgrounds are often underrepresented in randomized controlled trials (RCTs).[10] Likewise, MM patients treated in routine practice tend to present poorer treatment outcomes and higher discontinuation rates than those reported in RCTs.[11,12] This discrepancy, together with budget constraints in routine practice which may limit the access to novel therapies, often challenges the use of evidence-based guidelines for making individual therapeutic decisions in the real world.[13] Therefore, there is a need to expand the knowledge of real-world RRMM patients and investigate whether clinical guidelines cover the case-mix of RRMM enough to result in common prescription trends according to patients' characteristics. In this observational study, we investigated the sociodemographic and clinical characteristics of RRMM patients treated in routine clinical practice and their impact on the prescribing patterns in this setting.

## Materials and Methods

### *Study Design and Patients*

This was an observational, cross-sectional, multicenter study on RRMM patients routinely treated in public hospitals in Spain (ClinicalTrials.gov ID. NCT03188536). Between June 2017 and November 2018, RRMM patients who had received at least one previous line of treatment and started a new treatment line because of a relapsed/refractory disease[14] in the 6 months preceding the study enrollment visit were recruited in 27 Spanish centers. All data were retrieved either from the clinical records or from a structured interview in a single visit and considering treatment guidelines available at study timeliness.[7]

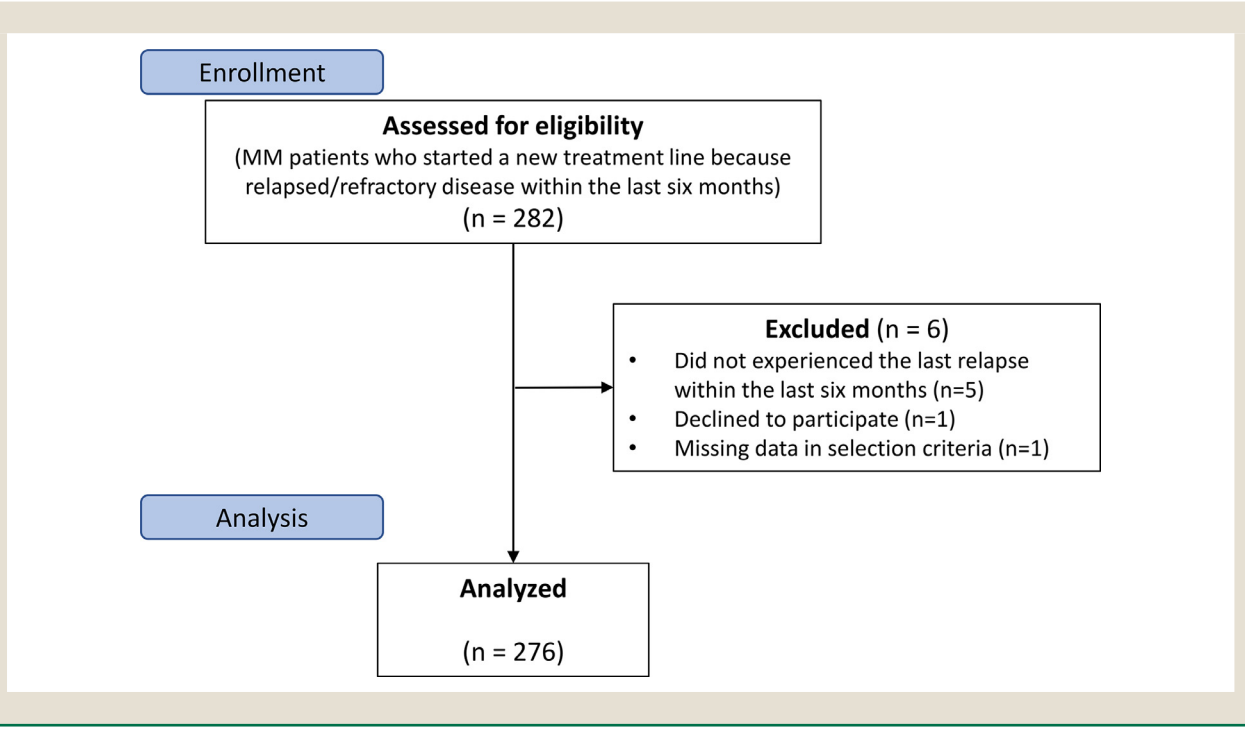
Before starting data collection, patients signed the corresponding informed consent. All data were processed according to the General Data Protection Regulation 2016/679 on data protection and privacy for all individuals within the European Union and the local data protection regulatory framework. The study protocol was approved by the local independent ethics committee.

### *Study Variables*

The sociodemographic characteristics of study patients at enrollment included age, sex, area of residence, education level, employment status, cohabitation status, the receipt of economic subsidies, and degree of dependence, classified as grade I (ie, the patient needs assistance once a day to perform daily activities), grade II (ie, the patient needs assistance more than once a day to perform daily activities, but he/she does not require constant support), and grade III (ie, the patient needs constant support because of a lack of autonomy in the physical, mental or sensorial area). The lifestyle-related behaviors of study participants included smoking, alcohol consumption (yes/no, as reported by the patient) and physical activity, classified as high (ie, playing a sport or doing intensive exercise) and moderate (ie, brisk walking and other activities such as gardening, dancing, domestic work, etc).

Clinical variables at MM diagnosis included the International Staging System (ISS) score, the Eastern Cooperative Oncology Group (ECOG) performance status, and the cytogenetic risk, determined by bone marrow fluorescence in situ hybridization (FISH) and stratified as high risk [d (17p) / t (14; 16) / t (4; 14)], standard

**Figure 1** Flow diagram of included patients. Participants may be excluded because of more than one reason.




risk (ie, presence of other genetic abnormalities not considered high risk). CRAB features at diagnosis included hypercalcemia (serum Ca >0.25 mmol/l [>1 mg/dL] above the upper limit of normal or >2.75 mmol/l [>11 mg/dL]), renal insufficiency (creatinine clearance <40 mL/min or serum creatinine >117 $\mu$mol/l [>2 mg/dL]), anemia (reduction of Hb >2 g/dL below lower limit of normal or Hb <10 g/dL), and the presence of bone lesions (one or more osteolytic lesion on a plain x-ray or computed tomography/positron-emission tomography image).

The ISS, cytogenetic risk and presence of CRAB features were also collected at relapse and at the time of the study visit (ie, in the 6 months following the last relapse). Data at that time also included the presence of plasmacytomas, comorbidities and the determination of lactate dehydrogenase, paraprotein and heavy/light chain concentration.

Treatments prescribed at the last and previous relapses were grouped according to the therapeutic class of the leading drug of each regimen and considering treatment options available as study timelines into immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), IMiDs+PIs, anti-CD38 monoclonal antibody (mAb), and other. Table S1 (Supplemental Digital Content) provides further details regarding the regimens included in each category.

### *Statistical Analysis*

Quantitative variables were described as the mean and standard deviation (SD) or the median and interquartile range (IQR, defined by the 25th and 75th percentiles). Categorical variables were described as the frequency and percentage of each category over the available data, which were specified for each variable. To assess the influence of clinical and sociodemographic characteristics on the type of pharmacological regimen prescribed for RRMM, patients were grouped according to the presence or absence of PI–currently, the gold standard in MM in the front line setting–in the prescribed regimen (ie, IMiD+PI and PI categories in our classification). For the bivariate analysis, categorical variables were compared using a Chi-squared or Fisher's exact test, whereas quantitative variables were compared using a *t* test, ANOVA or their non-parametric counterparts Wilcoxon and Kruskal-Wallis. Variables showing statistical significance in the bivariate analysis were included in a logistic regression model (multivariate analysis). The threshold of statistical significance was set at a two-sided alpha value of 0.05. All analyses were analyzed using the statistical package SAS® (version 9.4) for Windows.

## Results

### *Patient Characteristics at Relapse*

The study included 276 patients with RRMM (Figure 1), who had experienced their last relapse in a median of 1.61 months (IQR 0.74; 3.14) before entering the study. Table 1 summarizes the main clinical characteristics of RRMM patients at the time of enrollment. Most patients presented with CRAB features (n = 205; 74.3%), primarily bone lesions (n = 135, 48.9%); 57 (27.0%) were classified as ISS stage III, and 25 (28.7%) had high cytogenetic risk. The 42 patients with extramedullary plasmacytomas at enrollment had a median of 1.0 tumor (IQR 1-3; range 1-10), and those with fractures had a median of 1.0 fracture (IQR 1-3; range 1-8), most frequently located in the spine (n = 12; 28.6%). The most prevalent comorbidity was cardiovascular disease (n = 85, 30.8%), followed by diabetes (n = 43, 15.6%) and neuropathy (n = 36, 13.0%).

**Table 1** Clinical Characteristics of Patients With Relapsed or Refractory Multiple Myeloma at the Time of Last Relapse

| Characteristics of Multiple Myeloma, *n (%)* | |
|---|---|
| ISS stage (n = 211) | |
| I | 79 (37.4) |
| II | 75 (35.5) |
| III | 57 (27.0) |
| CRAB features | |
| None | 71 (25.7) |
| Some | 205 (74.3) |
| Hypercalcemia | 19 (9.3) |
| Renal insufficiency | 42 (20.5) |
| Anemia | 90 (43.9) |
| Bone lesions | 135 (65.9) |
| Cytogenetic risk[1] (n = 87) | |
| High | 25 (28.7) |
| Standard | 62 (71.3) |
| Bony plasmacytomas (n = 261) | 40 (15.3) |
| Extramedullary plasmacytomas (n = 269) | 42 (15.6) |
| Clinical presentation, *n (%)* | |
| Bone fractures (n = 276) | 42 (15.2) |
| Active infection (n = 276) | 42 (15.2) |
| Comorbidities (n = 276) | 175 (63.4) |
| Laboratory parameters, *mean (SD)* | |
| LDH (UI/l) (n = 249) | 236.3 (137.0) |
| Serum M-protein (g/L) (n = 236) | 19.8 (85.5) |
| Urin M-protein (g/L, 24h) (n = 168) | 3.6 (16.0) |
| Free light chain concentration (g/L, serum) (n = 228) | 309.6 (1386.1) |

Unless otherwise specified, the assessment corresponds to **N = 276.**
[1] High risk: d (17p) / t (14; 16) / t (4; 14). Standard risk: t (11; 14) / t (6; 14) / t (14; 20) / g (1q). Other: presence of other genetic abnormalities not considered for standard and high risk.

**Table 2** Sociodemographic Characteristics of Patients With Relapsed or Refractory Multiple Myeloma

| Age (years), *mean (SD)* | 67.4 (10.5) |
|---|---|
| Sex (male), *n (%)* | 147 (53.3) |
| BMI (Kg/m$^2$), *mean (SD)* (n = 201) | 27.5 (5.1) |
| Area of residence, *n (%)* | |
| Urban | 209 (75.7) |
| Rural | 67 (24.3) |
| Level of education, *n (%)* (n = 270) | |
| Illiteracy | 2 (0.7) |
| No formal education (only read/write) | 28 (10.4) |
| Primary education | 117 (43.3) |
| Secondary education | 92 (34.1) |
| Higher education | 31 (11.5) |
| Employment status, *n (%)* (n = 275) | |
| Unemployed | 15 (5.5) |
| Active[1] | 14 (5.1) |
| Temporary/permanent disability | 55 (20.0) |
| Retired | 179 (65.1) |
| Other | 12 (4.4) |
| Cohabitation status, *n (%)* (n = 274) | |
| Living alone[2] | 34 (12.4) |
| Living with relatives | 235 (85.8) |
| Living alone with assistance | 5 (1.8) |
| Receive financial support, *n (%)* (n = 274) | 17 (6.2) |
| Level of dependence, *n (%)* (n = 275) | |
| Independent | 196 (71.3) |
| Grade I | 40 (14.5) |
| Grade II | 35 (12.7) |
| Grade III | 4 (1.5) |
| Physical activity of the patient, *n (%)* (n = 275) | |
| High | 5 (1.8) |
| Moderate | 126 (45.8) |
| Inactive | 144 (52.4) |
| Currently smoking, *n (%)* | 10 (3.6) |
| Alcohol consumption, *n (%)* | 18 (6.5) |

Unless otherwise specified, the assessment corresponds to **N = 276.**
[1] Active patients were either full-time employed (n = 10), part-time employed (n = 3) or unknown (n = 1).
[2] Patients who lived alone with assistance had daily (n = 3), 2-3 times a week (n = 1), permanent (n = 1).

Table 2 summarizes the main sociodemographic characteristics of patients with RRMM included in the study. Roughly, the prototypical profile of RRMM patients in our cohort was a man or woman over 60 years of age (median 69; IQR 60-76), retired (n = 179; 65.1%), and living in an urban area (n = 209, 75.7%) with their relatives (n = 235, 85.8%); 79 (28.7%) patients had some degree of dependence on caregivers. Smoking and alcohol consumption were infrequent.

### *Treatment Since Diagnosis*

Study participants had received a median of 2 previous lines of treatment (1-10; IQR 1-3). Overall, 141 (51.1%) patients had received a stem cell transplant before the last relapse: 137 (97.2%) autologous and 4 (2.8%) allogeneic. The number of patients who underwent any type of transplant progressively decreased as treatment lines increased: 121 (43.8%) patients as first-line therapy, 35 (22.2%) as second-line therapy, and 11 (5.7%) as third or later lines of. Figure 2 summarizes the treatments prescribed before the last relapse, grouped by treatment line and therapeutic class/administration route. PIs were the leading agents in the first-line setting, and they were present (with or without IMiDs) in 86% of regimens prescribed in this setting. The frequency of PIs dropped in the second and subsequent lines, in which IMiDs were more frequently prescribed. Accordingly, first-line regimens were administered mostly through injected routes (eg, subcutaneous or intravenous), whereas second and subsequent lines were mainly oral.

### *Treatment at Relapse*

At study enrollment, 119 (43.3%) patients had just initiated second-line treatment, 71 (25.8%) third line, and 85 (30.9%) fourth or subsequent lines; 245 patients (88.8%) were receiving concomitant medication. Twelve (4.3%) patients underwent

**Figure 2** Treatments prescribed before the last relapse preceding study enrollment (ie, all previous treatment lines). (a) treatment categories prescribed as first line (n = 275), second line (n = 154), and third line and subsequent (n = 188). (b) administration route of treatments prescribed as first line (n = 274), second line (n = 153), and third line and subsequent (n = 186). Treatments are grouped according to the therapeutic class of the leading drug of each regimen. Abbreviations: IMiDs = immunomodulatory drugs. PIs = proteasome inhibitors. mAb = monoclonal antibodies. Details on drug types included in each treatment category are provided in Table S1 (Supplementary file 1).

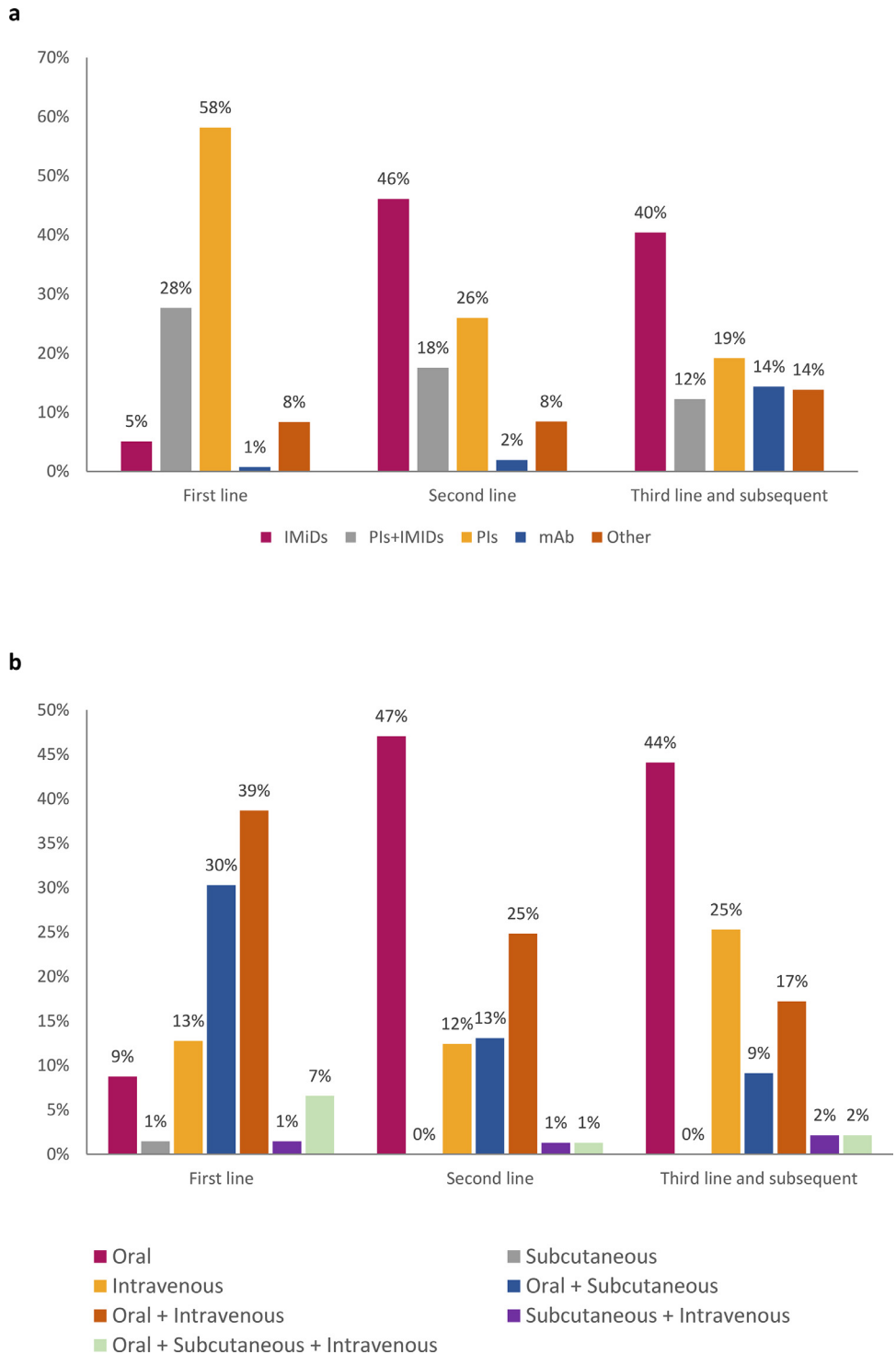


**Table 3** Adjusted Multivariate Model to Predict the Inclusion of a Proteasome Inhibitor in the Treatment Regimen for Relapsed/Refractory Multiple Myeloma (n = 276)

| | OR (95% CI) | *P* |
|---|---|---|
| Previous lines | | |
| 1 vs. 2 | 2.03 (1.03; 4.02) | 0.003 |
| 1 vs. ≥3 | 3.06 (1.52; 6.16) | |
| 2 vs. ≥3 | 1.50 (0.68; 3.35) | |
| Presence of extramedullary plasmacytomas | 2.98 (1.40; 0.71) | 0.004 |
| Absence of osteopenia | 3.52 (1.36; 9.11) | 0.004 |

**OR** = odds ratio of receiving a proteasome inhibitor vs. no proteasome inhibitor.

stem cell transplant at the last relapse before study enrollment: 9 autologous and 4 allogeneic. Figure 3 summarizes the treatments prescribed at the last relapse for the overall study sample and the subset of patients with biochemical relapse (ie, without CRAB features). Of the 61 patients treated with mAb (ie, anti-CD38), 26 (42.6%) cases were monotherapy: 1 as second-line (6.3% of all second-line treatments), 9 (50.0%) as third-line, and 16 (59.3%) as fourth and subsequent lines. Of all patients treated with PIs as the leading agent, 23 received doublet therapy (ie, a PI plus a steroid, alkylating agent or other): 11 (68.8%), 7 (63.6%), and 5 (71.4%) as second, third, and fourth/subsequent lines.

Seventy-one patients (25.7%) started therapy at biochemical relapse: 32 (45.1%) as second line, 17 (23.9%) as third line, and 22 (31.0%) as fourth or subsequent lines. Compared with the overall study sample, patients without CRAB features at relapse tended to receive IMiDs and mAb (ie, anti-CD38) in earlier lines of treatment.

### *Factors Influencing the Choice of Treatment*

The bivariate analysis comparing patients who received regimens containing PIs and those without PIs in the context of RRMM (ie, the last relapse before study enrollment) revealed significant differences in age at the time of RRMM treatment start, number of previous lines, the presence of extramedullary plasmacytomas, and osteopenia (Table S2, Supplemental Digital Content). Of these variables, the number of previous lines of treatment, the presence of extramedullary plasmacytoma and the absence of osteopenia significantly contributed to the multivariate model for predicting the presence of a PI in the regimen prescribed for the RRMM (Table 3).

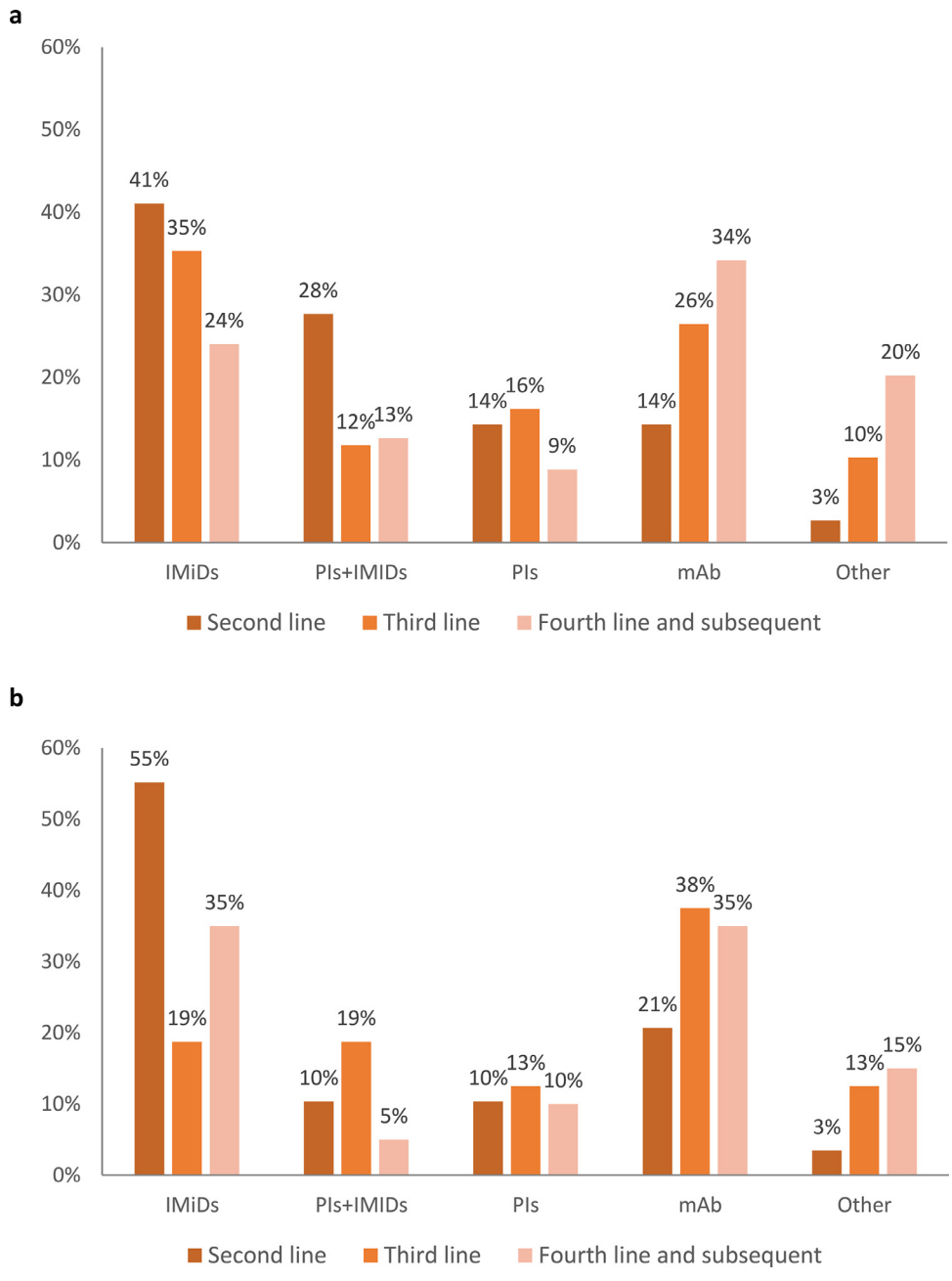
## Discussion

In this observational, cross-sectional, multicenter study, we describe the clinical and sociodemographic profile of patients with RRMM treated in the context of routine clinical practice, as well as the prescribing patterns at relapse and for each of the preceding treatment lines and how the patients' characteristics may influence the regimen prescribed.

Typically, patients with a higher comorbidity burden and less advantaged socioeconomic background are less likely to be enrolled in RCTs.[10] However, in the area of multiple myeloma–particularly in RRMM–sociodemographic characteristics of study participants (aside from sex and age) are rarely reported, even in studies investigating these patients in the real-world setting.[15-21] Furthermore, most of these studies are focused on specific therapeutic agents, thus losing sight of the general profile of RRMM. Our analysis made it possible to provide an archetypal sociodemographic profile of RRMM patients in Spain, who are mostly men or women in their 60s or 70s, retired and living in an urban area with their relatives. Of note, only 14% had grade II or III dependence, which implies the need for assistance more than once a day to perform daily activities. A qualitative research study conducted with 50 patients from various European countries showed that the ability to perform daily activities was among the features that worsened most on experiencing disease relapse, which strongly influenced the financial and logistic burden by increasing the time spent staying at and traveling to the hospital and/or the need for daily support at home.[5] The fact that 86% of patients in our cohort lived with their relatives, only 6% received financial support, and 5% were employed suggests that the economic and logistic overburden associated with disease relapse is likely to be shouldered by the patient's relatives. This assumption supports the idea that despite its moderate prevalence overall, RRMM has a remarkable direct and indirect social impact, which is often overlooked.[22]

The clinical profile of MM patients enrolled in RCTs is often more favorable than that of patients encountered in day-to-day practice.[23] However, differences between the 2 settings, particularly those regarding treatment burdens, tend to diminish in studies investigating regimens for RRMM. Patients in our study were older than those enrolled in phase 3 trials investigating the efficacy of front-line treatments such as bortezomib[24,25] or lenalidomide.[26] However, the number of previous lines in our cohort (nearly 60% had received two or more prior lines) was similar to that of most RCTs on RRMM patients[16,24-26] and even lower than in some trials, which reported up to 80% of patients with three or more previous lines of treatment.[27,28] In accordance with the therapeutic approach proposed by the ESMO guidelines,[7] the agents most frequently prescribed as second-line treatment were IMiDs, followed by a combination of IMiDs and PIs. On the other hand, refractoriness to more efficacious agents leaves clinicians with limited options for establishing therapies in later lines, which is reflected in our data by an increase in the frequency of treatments other than those based on IMiDs, PIs or combinations thereof. Our data also show how clinicians increasingly use anti-CD38 monoclonal antibodies as the patient progresses through relapses. Of note, monotherapy with anti-CD38 was approved in Spain during the time frame of our study; therefore, this trend might be explained by the progressive introduction of this agent into local therapeutic algorithms rather than the actual choice for a given line. Twelve patients received a stem cell transplant at the last relapse before study enrollment. While this therapeutic approach is limited to the context of clinical research, guidelines recommend offering patients the option to participate in clinical trials whenever allogeneic transplant is considered potentially beneficial in the event of relapse.[7] In fact, the financial barriers for optimal MM treatments often encourage clinicians to invite RRMM patients to participate in clinical trials,[6,13] suggesting that in some centers–particularly university hospitals–the line between routine practice and clinical research might be

**Figure 3** Treatments prescribed at the last relapse preceding the study enrollment, grouped by treatment line. (a) Overall study sample; data regarding the prescribed treatment were available for 112, 71, and 85 patients who initiated second, third, and fourth (and subsequent) treatment lines. (b) Patients with biochemical relapse (ie, without CRAB features); data regarding the prescribed treatment were available for 32, 17, and 22 patients who initiated second, third, and fourth (and subsequent) treatment lines. Treatments are grouped according to the therapeutic class of the leading drug of each regimen. Abbreviations: IMiDs = immunomodulatory drugs. PIs = proteasome inhibitors. mAb = monoclonal antibodies. Details on drug types included in each treatment category are provided in Table S1 (Supplementary file 1).



blurred. Interestingly, 26% of patients in our cohort initiated treatment for RRMM despite the lack of CRAB features. In these patients, PIs (either alone or combined with IMiDs) were used in a lower frequency than in the overall group in all treatment lines. Conversely, IMiDs were the dominant choice for second-line treatment, and the use of monoclonal antibodies increased in all treatment lines.

Therapeutic decisions after the first relapse should be made on a case-by-case basis and considering multiple factors related to the patient's health status and the outcome of previous lines.[7,25] Our multivariate analysis addressed the factors that may contribute to including PIs, currently considered the gold standard in MM. As expected, the number of previous lines emerged as one of the significant determinants of treatment, with patients in later lines having lower odds of receiving PIs (the odds ratio of patients initiating second-line was two times higher than those in the third line and three times higher than those in the fourth or later lines). This observation is in line with the current evidence, which points to previous treatments as one of the major predictors of treatment success [8]. Surprisingly, the multivariate analysis selected the presence of osteopenia and extramedullary disease as the only two factors with a statistical contribution to treatment choice. Despite the statistical significance, osteopenia is rarely considered per se in algorithms for therapeutic choice; therefore, the contribution of this factor has to be read with cautiousness. Likewise, the multivariate analysis did not select laboratory parameters, MM-associated neurological symptoms, renal insufficiency, and cytogenetic risk as significant contributors to the treatment decision. Although missing data in some variables (eg, cytogenetic risk) might have limited the strength of the analysis, these conflicting findings illustrate the complexity of decision-making in the RRMM context and suggest that clinical characteristics recommended for choice of treatment such as frailty, comorbidity burden, or even patient preferences[6] may outweigh other relevant factors like cytogenetic risk and neuropathy.

Our results must be read in the context of the observational design of our research, in which data collection is partially limited by the information included in the medical records. This limitation led to unbalanced numbers of available data across variables. The sociodemographic and clinical classification of our target population (ie, patients with RRMM) should also be interpreted by considering the heterogeneity of the sample, and the RRMM context, which encompasses patients who experienced the first relapse to MM therapy and refractory patients who persistently failed with various treatment lines. As discussed previously, RRMM patients evolve through different health stages as the disease progresses, so certain characteristics may vary depending on the line studied. It is also worth mentioning that the management of RRMM is constantly evolving, and our analysis illustrates how changes incorporated in the successive guidelines were progressively incorporated in routine care (eg, quadruplet combinations or monoclonal antibodies). However, owing to the rapid change experienced in the therapeutic landscape in the past few years, future studies shall investigate how the factors influencing therapeutic decisions found in our analysis have changed. Finally, although patients were recruited consecutively without exclusion criteria regarding previous lines, two thirds of them had only 1-to-2 prior lines, thus underrepresenting heavily treated, more complex, patients.

## Conclusion

Our results paint a general picture of RRMM patients that provide policymakers and physicians with helpful information regarding the clinical and societal burden of MM, particularly when the patient progresses to a refractory stage of the disease. The description of therapies prescribed at relapse and throughout the course of treatment in the routine practice setting also provides a real view of this setting and how far or close it is to the scenario in RCTs. Regardless of the actual regimens most frequently prescribed after disease relapse, our findings illustrate the complexity of making therapeutic decisions in this setting, which are primarily influenced by the number of previous lines of treatment.

### *Clinical Practice Points*

- The development of new anti-myeloma agents has expanded the therapeutic approaches in the management of MM, and clinicians may now choose from a relatively extensive repertoire of treatments and mechanism of action based on high-level evidence and patient characteristics. However, unlike reasonably bounded algorithms proposed by guidance's for first-line treatment, therapeutic decisions for the management of RRMM patients require a balanced appraisal of multiple factors, including patient characteristics, disease characteristics, and the outcome of previous therapies received.
- The complexity of the RRMM scenario challenges making therapeutic decisions in day-to-day practice, and currently there is little information regarding the prescription behavior in this setting.
- We found that regimens prescribed in real-world RRMM patients are highly heterogeneous and various factors presumably relevant for therapeutic decisions do not significantly influence the prescribed regimen. In this setting, factors with significant influence on the prescribed regiment included the number of previous lines of treatment and the presence of extramedular disease.
- Our findings raise awareness on the complexity of prescribing treatments for RRMM in day-to-day practice and the need for considering not only clinical but also demographic characteristics (eg, cohabitation status, urbanity, dependence level) of patients before making therapeutic decisions.

## Disclosure

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clml.2021.10.001.

## References

1. Raab MS, Podar K, Breitkreutz I, Richardson PG, Anderson KC. Multiple myeloma. *Lancet*. 2009;374:324–339. doi:10.1016/S0140-6736(09)60221-X.
2. Becker N. Epidemiology of multiple myeloma. *Multiple Myeloma* Springer; 2011:25–35.
3. Laubach J, Garderet L, Mahindra A, et al. Management of relapsed multiple myeloma: recommendations of the International Myeloma Working Group. *Leukemia*. 2016;30:1005–1017. doi:10.1038/leu.2015.356.
4. Palumbo A, Anderson K. Multiple myeloma. *N Engl J Med*. 2011;364:1046–1060. doi:10.1056/NEJMra1011442.
5. Hulin C, Hansen T, Heron L, et al. Living with the burden of relapse in multiple myeloma from the patient and physician perspective. *Leuk Res*. 2017;59(May):75–84. doi:10.1016/j.leukres.2017.05.019.
6. Mikhael J, Ismaila N, Cheung MC, et al. Treatment of multiple myeloma: ASCO and CCO joint clinical practice guideline. *J Clin Oncol*. 2019;37:1228–1263. doi:10.1200/JCO.18.02096.
7. Moreau P, San Miguel J, Sonneveld P, et al. Multiple myeloma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28(suppl_4):iv52–iv61. doi:10.1093/annonc/mdx096.
8. Reece DE, Leitch HA, Atkins H, et al. Treatment of relapsed and refractory myeloma. *Leuk Lymphoma*. 2008;49:1470–1485. doi:10.1080/10428190802064941.
9. Dingli D, Ailawadhi S, Bergsagel PL, et al. Therapy for relapsed multiple myeloma: guidelines from the Mayo stratification for myeloma and risk-adapted therapy. *Mayo Clin Proc*. 2017;92:578–598. doi:10.1016/j.mayocp.2017.01.003.
10. Booth CM, Tannock IF. Randomised controlled trials and population-based observational research: partners in the evolution of medical evidence. *Br J Cancer*. 2014;110:551–555. doi:10.1038/bjc.2013.725.
11. Jagannath S, Roy A, Kish J, et al. Real-world treatment patterns and associated progression-free survival in relapsed/refractory multiple myeloma among US community oncology practices. *Expert Rev Hematol*. 2016;9:707–717.
12. Richardson PG, San Miguel JF, Moreau P, et al. Interpreting clinical trial data in multiple myeloma: translating findings to the real-world setting. *Blood Cancer J*. 2018;8:109. doi:10.1038/s41408-018-0141-0.
13. Bergin K, McQuilten Z, Moore E, Wood E, Spencer A. Myeloma in the real world: what is really happening? *Clin Lymphoma, Myeloma Leuk*. 2017;17:133–144 e1. doi:10.1016/j.clml.2016.12.002.
14. Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood*. 2011;117:4691–4695. doi:10.1182/blood-2010-10-299487.
15. Katodritou E, Vadikolia C, Lalagianni C, et al. real-world" data on the efficacy and safety of lenalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma who were treated according to the standard clinical practice: a study of the Greek Myeloma Study Group. *Ann Hematol*. 2014;93:129–139. doi:10.1007/s00277-013-1841-y.
16. Pantani L, Zamagni E, Zannetti BA, et al. Bortezomib and dexamethasone as salvage therapy in patients with relapsed/refractory multiple myeloma: analysis of long-term clinical outcomes. *Ann Hematol*. 2014;93:123–128. doi:10.1007/s00277-013-1828-8.
17. Soyer N, Patir P, Uysal A, et al. Efficacy and safety of lenalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma: a real-life experience. *Turkish J Med Sci*. 2018;48:777–785. doi:10.3906/sag-1712-160.
18. Musto P, Simeon V, Cascavilla N, et al. Is re-challenge still an option as salvage therapy in multiple myeloma? The case of REal-life BOrtezomib re-Use as secoND treatment for relapsed patients exposed frontline to bortezomib-based therapies (the REBOUND Study). *Ann Hematol*. 2019;98:361–367. doi:10.1007/s00277-018-3524-1.
19. João C, Coelho I, Costa C, Esteves S, Lucio P. Efficacy and safety of lenalidomide in relapse/refractory multiple myeloma—real life experience of a tertiary cancer center. *Ann Hematol*. 2015;94:97–105. doi:10.1007/s00277-014-2164-3.
20. Salomon-Perzyński A, Walter-Croneck A, Usnarska-Zubkiewicz L, et al. Efficacy of daratumumab monotherapy in real-world heavily pretreated patients with relapsed or refractory multiple myeloma. *Adv Med Sci*. 2019;64:349–355. doi:10.1016/j.advms.2019.05.001.
21. Delforge M, Michiels A, Doyen C, et al. Lenalidomide in relapsed refractory myeloma patients: impact of previous response to bortezomib and thalidomide on treatment efficacy. Results of a medical need program in Belgium. *Acta Clin Belg*. 2011;66:371–375. doi:10.2143/ACB.66.5.2062589.
22. Robinson D, Orlowski RZ, Stokes M, et al. Economic burden of relapsed or refractory multiple myeloma: results from an international trial. *Eur J Haematol*. 2017;99:119–132. doi:10.1111/ejh.12876.
23. Shah JJ, Abonour R, Gasparetto C, et al. Analysis of common eligibility criteria of randomized controlled trials in newly diagnosed multiple myeloma patients and extrapolating outcomes. *Clin Lymphoma Myeloma Leuk*. 2017;17:575–583 e2. doi:10.1016/j.clml.2017.06.013.
24. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med*. 2005;352:2487–2498. doi:10.1056/NEJMoa043445.
25. Mikhael JR, Belch AR, Prince HM, et al. High response rate to bortezomib with or without dexamethasone in patients with relapsed or refractory multiple myeloma: results of a global phase 3b expanded access program. *Br J Haematol*. 2009;144:169–175. doi:10.1111/j.1365-2141.2008.07409.x.
26. Dimopoulos MA, Swern AS, Li JS, et al. Efficacy and safety of long-term treatment with lenalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma. *Blood Cancer J*. 2014;4:e257. doi:10.1038/bcj.2014.77.
27. Richardson PG, Barlogie B, Berenson J, et al. A phase 2 study of Bortezomib in relapsed, refractory myeloma. *N Engl J Med*. 2003;348:2609–2617. doi:10.1056/NEJMoa030288.
28. Richardson PG, Blood E, Mitsiades CS, et al. A randomized phase 2 study of lenalidomide therapy for patients with relapsed or relapsed and refractory multiple myeloma. *Blood*. 2006;108:3458–3464. doi:10.1182/blood-2006-04-015909.