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Assessment of the psychometric properties of the Spanish version of EORTC QLQ-MY20 and evaluation of health-related quality of Life outcomes in patients with relapsed and/or refractory multiple myeloma in the real-world setting in Spain: results from the CharisMMa study

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ORIGINAL ARTICLE

Assessment of the psychometric properties of the Spanish version of EORTC QLQ-MY20 and evaluation of health-related quality of Life outcomes in patients with relapsed and/or refractory multiple myeloma in the real-world setting in Spain: results from the CharisMMa study

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ABSTRACT

We evaluated the psychometric properties of the Spanish version of the European Organization for Research and Treatment of Multiple Myeloma (MM) specific quality-of-life (QoL) questionnaire module (QLQ-MY20) in relapsed/refractory MM (RRMM) patients. This was an observational, cross-sectional, multicenter study using EORTC QLQ-C30 and QLQ-MY20 in RRMM patients (ClinicalTrials.gov ID NCT03188536). We assessed the non-response rate, ceiling/floor effects, internal consistency, test-retest reliability, and validity. The study included 276 patients (53.3% males, mean [SD] age of 67.4 [10.5] years). The EORTC QLQ-MY20 showed a low non-response rate, very low ceiling and floor effects, and good internal consistency. The test-retest reliability assessment revealed good temporary stability, the construct validity analysis stated four main factors similar to the ones of the original version, and the criterion validity assessment showed no differences between groups. In conclusion, the Spanish version of EORTC QLQ-MY20 is a reliable and valid tool for assessing QoL in RRMM patients.

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Introduction

Multiple myeloma (MM) is a malignant proliferative disorder of plasma cells [1]. It is the second most common hematologic cancer and accounts for more than 10% of all blood cancers [2,3], with an incidence in Europe of around 4.5–6.0 per 100,000 cases a year [4]. MM is a recurrent and progressive disease that remains incurable today and most MM patients, including those who maintain prolonged response to first-line treatment, will eventually relapse [5]. The disease becomes more aggressive with each relapse, and remissions achieved with successive lines of treatment tend to be shorter[6].

However, the recent development of new drugs with different mechanisms of action has led to significant improvements in the treatment of relapsed or refractory patients and an expansion of effective options [7–9]. The management of the relapsing and/or refractory MM (RRMM) patient is a persisting clinical challenge, as MM evolves into a more long-term disease. Thus, a key focus becomes how to preserve the quality of life in these patients [5,7].

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Quality of Life (QoL) in MM patients is impacted both by the severe symptoms of the disease as well as the toxicity associated with treatment [10,11]. Clinical trials are increasingly using patient-reported QoL questionnaires, such as the European Organization for Research and Treatment of Cancer (EORTC) core questionnaire (EORTC QLQ-C30) and the MM module (EORTC QLQ-MY20), because they correlate well with prognosis and survival [12,13]. Further, these evaluations have reflected positively on the response to treatment in RRMM patients [10]. Despite the fact that QoL assessments are often incorporated into clinical trials [14–16], they are rarely implemented in routine clinical practice [17].

Considering that RRMM patients often face long periods of treatment with drugs that entail the risk of adverse events and that treatment outcomes can depend on previous treatment choices, physician's treatment options should take into consideration the inclusion of patient preferences to implement a more holistic, integrated approach. Therefore, the implementation of QoL assessments in routine clinical practice seems a fundamental step toward improving the standard of care for the RRMM patient.

The EORTC QLQ-C30 questionnaire and the EORTC QLQ-MY20 module are self-administered tools commonly used in the evaluation of Health-Related QoL (HRQoL) in MM clinical trials. The Spanish versions of EORTC QLQ-C30 and QLQ-MY20 have been previously validated, except for the psychometric properties of reliability and validity of the EORTC QLQ-MY20 module [18,19].

Therefore, the aim of this study was to evaluate the reliability and validity of the psychometric properties of the Spanish version of the EORTC QLQ-MY20 for RRMM patients together with an assessment of the HRQoL of these patients.

Methods

Study design and patients

This was an observational, cross-sectional, multicenter study involving RRMM patients treated in 27 public hospitals in Spain (ClinicalTrials.gov ID. NCT03188536). From June 2017 to November 2018, RRMM patients with at least one prior line of treatment were consecutively recruited after experiencing a relapse in the six months prior to the study visit [20]. Data were either extracted from the medical record or collected in the single visit interview. Patients included in the study were informed and signed the corresponding consent before starting data collection. All data were processed according to 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.

Data collection and measures

Patients were asked to complete EORTC QLQ-C30 and the QLQ-MY20 module in a single visit and, for the test-retest reliability assessment, 40 participants (the first two patients enrolled in each center until reaching 40) were asked to complete again both questionnaires at home, seven days post-visit, and return them by mail.

The EORTC-C30 is a cancer-specific questionnaire including 30 items to assess the quality of life in cancer patients. It consists of five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status/QoL scale, and six single items (dyspnea, loss of appetite, sleep disturbance, constipation, diarrhea, and economic difficulties) [21]. It has been translated into several languages. The Spanish version of EORTC QLQ-C30 has been shown to be valid and reliable when used in Spanish cancer patients [19,21,22].

The EORTC QLQ-MY20 is an additional module specifically keyed to MM patients [23]. It is a 20-item questionnaire that includes four scales assessing: future perspectives (3 items), disease symptoms (6 items), side effects of the treatment (10 items), and body image (1 item). Multiple choice answers to items range from "not at all" (1) to "very much" (4) on a four-point scale [24]. The EORTC QLQ-MY20 questionnaire is shown in Appendix 1.

The scoring of the EORTC QLQ-C30 and EORTC QLQ-MY20 was performed according to the EORTC scoring manual [25] and the resulting scores were standardized to 0–100. High scores on the body image and future perspective scales represent better outcomes, while higher scores on the symptoms and side effect scales represent poorer outcomes. The Spanish version of EORTC QLQ-MY20 has been validated, except for the psychometric properties of reliability and validity [19].

Analysis and statistical Methods

Based on the assumption of maximum variability, a sample size of 350 patients was considered appropriate

to achieve a 95% confidence interval (CI) and a precision of 5%. This estimation was also considered sufficient to assess the psychometric properties of reliability and validity of the EORTC QLQ-MY20 module.[19,24,26] In addition, according to a previous study on the validation of the EORTC QLQ-MY20 module in the Mexican-Spanish language, 20 patients were sufficient for test-retest analysis. [19] However, considering the possibility of receiving questionnaires with invalid data or after the 7-day period, 40 patients were asked to complete EORTC QLQ-C30 and the QLQ-MY20 module again.

Categorical variables were described as the frequency and percentage over available data, whereas continuous data were presented as the mean and standard deviation (SD) and the median and interquartile range (IQR, 25th and 75th percentiles).

EORTC QLQ-C30 and EORTC QLQ-MY20 scale scores were examined to identify any possible associations with other key factors, such as age at study visit, sex, number of prior lines of treatment (1, 2 or more), prior number of relapses (1, 2 or more), ISS stage at last relapse (I, II or III), CRAB features at last relapse (including hypercalcemia [serum Ca >0.25 mmol/L above the upper limit of normal or >2.75 mmol/L], renal insufficiency [creatinine clearance < 40 mL/min or serum creatinine > 117 µmol/L], anemia [reduction of Hb > 2 g/dL below the 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]). In addition, comorbidities at last relapse, presence of plasmacytomas (yes or no), osteopathy (yes or no), fractures (yes or no) neurologic symptoms related to MM (yes or no), infections (yes or no), and the determination of lactate dehydrogenase [LDH], paraprotein and heavy/light chain concentration) were also assessed for possible correlations. To assess the influence of these demographic and clinical factors on each EORTC QLQ-30 scale score, we performed a bivariate analysis, using a Student's t-test, an ANOVA, or the non-parametric tests of Wilcoxon or Kruskal-Wallis, as appropriate. Subsequently, we developed multivariable regression models for each scale, with each scale score as the dependent variable and those variables with a statistically significant association with each scale in the bivariate analysis as the independent variables. The effect size was presented as the mean difference for categorical variables or the beta coefficient for continuous variables, together with the corresponding 95% confidence interval (95% CI).

Further, to evaluate the psychometric properties of EORTC QLQ-MY20, we assessed the non-response rate, ceiling/floor effects for each of its items, internal consistency, test-retest reliability, and validity (construct, criterion, convergent). The non-response rate of EORTC QLQ-MY20 was calculated and score distributions were examined to evaluate ceiling and floor effects. In terms of reliability, Cronbach's coefficient alpha (α), equal to or greater than 0.7 was considered acceptable in the assessment of internal consistency. Also, temporal stability (test-retest reliability) was assessed with a test-retest estimation of the intraclass correlation coefficient (ICC). [27] For construct validity, a principal component analysis (varimax rotation) was conducted to identify the relationships among the questionnaire's items. To establish criterion validity, the possible association between the questionnaire scores of each scale and ISS stage (I-II vs. III) or fractures (present vs. absent) was assessed with a bivariate analysis using Student's *t*, ANOVA, Wilcoxon, or Kruskal-Wallis tests, as appropriate. Finally, convergent validity was evaluated by calculating Spearman's correlation coefficients between EORTC QLQ-MY20 scores and the global health status/QoL scores of EORTC QLQ-C30.

The threshold of statistical significance was established at a two-sided alpha value of 0.05, with no adjustment made for multiple comparisons. Data analyses were conducted with SAS® software v9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics at relapse

A total of 282 patients were enrolled. Of them, one declined to participate, another one had missing data in the inclusion criteria, and five had not experienced relapse or refractoriness within the last six months. Thus, the study included 276 patients: 147 (53.3%) male and 129 (46.7%) female, with a mean (SD) age of 67.4 (10.5) years at last relapse. Table S1 (Supplementary file 1) includes the clinical characteristics of patients in the study at last relapse. These data have recently been published in a separate article. [28]

Health-related quality of life outcomes

Table 1 summarizes the scores of EORTC QLQ-MY20 and the global health status/QoL scale of EORTC QLQ C-30. Overall, the mean (SD) score of the EORTC QLQ C-30 global health status/QoL scale was 53.5 (23.9). The items with higher scores were cognitive function, social functions, and emotional state, functional scales, fatigue and pain, for symptom scales and items. Regarding the EORTC QLQ-MY20 module, body image

Table 1. Global health status/QoL scale (EORTC QLQ-C30) and Multiple Myeloma module (EORTC QLQ-MY20) scores.

	n	Mean (SD)	Median (Q1, Q3)
EORTC QLQ-C30	273	53.5 (23.9)	58.3 (33.3, 66.7)
Functional Scales			
Physical functions	273	64.2 (26.6)	66.7 (46.7, 86.7)
Daily functions (role)	274	58.6 (35.8)	66.7 (33.3, 100.0)
Emotional state	273	66.7 (25.4)	66.7 (50.0, 83.3)
Cognitive function	273	76.4 (26.3)	83.3 (66.7, 100.0)
Social functions	271	67.4 (31.5)	66.7 (33.3, 100.0)
Symptom Scales and Items			
Fatigue	271	47.2 (28.4)	44.4 (22.2, 66.7)
Nausea and vomiting	273	8.4 (18.4)	0.0 (0.0, 0.0)
Pain	273	40.0 (31.8)	33.3 (16.7, 66.7)
Dyspnea	274	23.1 (28.5)	0.0 (0.0, 33.3)
Insomnia	274	32.5 (32.3)	33.3 (0.0, 66.7)
Loss of appetite	274	28.1 (32.2)	33.3 (0.0, 33.3)
Constipation	274	27.4 (31.8)	33.3 (0.0, 33.3)
Diarrhea	272	17.4 (27.2)	0.0 (0.0, 33.3)
Economic difficulties	273	16.0 (27.0)	0.0 (0.0, 33.3)
EORTC QLQ-MY20			
Functional Scales and Items			
Future perspective	274	58.4 (27.7)	66.7 (44.4, 77.8)
Body image	273	72.9 (34.4)	100.0 (66.7, 100.0)
Symptom Scales			
Symptoms of the disease	262	30.7 (23.2)	27.8 (11.1, 44.4)
Treatment side-effects	267	25.4 (17.2)	23.3 (13.3, 36.7)

n: number of patients included in each specific analysis.
The EORTC QLQ-C30 and EORTC QLQ-MY20 scores range is 0–100. High scores on the body image and future perspective scales represent better outcomes, while higher scores on the symptoms and side effect scales represent poorer outcomes.

was the item with the maximum score, whereas the scores of symptom scales were predominantly low.

With respect to the results of the multivariable analyses, the only factor with a statistically significant association to the global health scale status/QoL scores was the presence of medullary or extramedullary plasmacytomas, which was associated with a lower QoL. Furthermore, the presence of plasmacytomas was related to the scores of almost all scales, except for cognitive functions, nausea and vomiting, dyspnea, insomnia, and diarrhea. In addition, the stage of the disease (ISS) showed a relationship with physical function and fatigue, whereas the presence of comorbidities was associated with the physical and cognitive functions and loss of appetite scales (Table 2).

Reliability and validity of the EORTC QLQ-MY20 Spanish module

Almost all the patients completed all items of the questionnaire ($n = 254$, 92.7%). Table 3 summarizes EORTC QLQ-MY20 ceiling and floor effects, as well as internal consistency. Items 41 and 42 presented a considerable floor effect ($n = 198$, 78.0% and $n = 230$, 90.6%, respectively). The questionnaire showed good internal consistency, with Cronbach's α higher than 0.7 for all scales. Of the 40 patients selected for the test-retest analysis, 36 (90%) completed the questionnaire correctly. All scales had test-retest and showed temporal stability with ICC values similar to or greater than 0.8. The disease symptoms scale had the highest test-retest reliability (ICC = 0.89).

Regarding construct validity, the relation of the factors to each of the questionnaire items is graphically represented in Figure 1. The principal component analysis showed that the Spanish version of the questionnaire consisted of four factors. Factor 1 showed a relation to items 31, 32, 33, 34, 35, 36, and 39. Factor 2 was related to items 48, 49, and 50 and slightly related to other items (i.e. 36, 37, 39, 44, and 47). Factor 3 was associated with items 38, 40, 43, 45, and 46, and to some extent with items 37, 39, and 44. Finally, factor 4 was related to items 42 and 41 and slightly related to item 47. Thus, factors 1, 2, and 3 may indicate symptoms, future perspectives, and side effects of the treatment, respectively, whereas factor 4 may indicate the side effects of the treatment and body image. The assessment of criterion validity showed no differences between groups according to ISS stage and the presence of fractures (Table 4). Convergent validity assessment showed a mild association between the scales of EORTC QLQ-MY20 and the global health status/QoL scale of EORTC QLQ-30, especially regarding symptom scales (correlation coefficients of 0.40, 0.25, −0.40, and −0.43 for future perspective, body image, symptoms of the disease, and treatment side-effects scales, respectively, Table 5).

Discussion

In this observational, cross-sectional, multicenter study, we assessed the psychometric properties of the Spanish version of the EORTC QLQ-MY20 module. Additionally, we evaluated the HRQoL of patients with RRMM treated in the context of routine clinical practice in Spain.

Given the current improved survival outcomes in RRMM patients due to new therapeutic alternatives recently incorporated to the treatment paradigm, the management of this disease increasingly requires a holistic evaluation of the outcomes considering all previous treatments received. These outcomes include effectiveness, toxicity effects, and prognostic assessments, but also the impact of all of them on the HRQoL of RRMM patients [9,29]. Generally, MM patients have more symptoms and problems compared to other cancer patients [11,14]. In addition, they tend to be older and frail, thus generally having their HRQoL affected [30,31]. Hence, HRQoL tools can be implemented in clinical practice to measure the

Table 2. Multivariable regression models: significant associations of EORTC QLQ-C30 scales scores and factors.

	Mean difference in scores (IC 95%)	*p*
Global health status/QoL Scale (*n* = 266)		
≥ 1 medullary or extramedullary plasmacytoma		<0.0001
No vs. Yes	13.91 (7.68, 20.14)	
Physical functions (*n* = 202)		
Stage of disease at last relapse and/or refractoriness according to the ISS		0.0427
I vs. II	3.51 (-4.19, 11.21)	
I vs. III	11.34 (2.51, 20.17)	
II vs. III	7.83 (-0.93, 16.60)	
Comorbidities at last relapse and/or refractoriness		0.0006
≥1 vs. None	−13.09 (−20.42, −5.76)	
≥ 1 medullary plasmacytoma		0.0002
No vs. Yes	19.70 (9.57, 29.82)	
Role functions (*n* = 267)		
≥ 1 extramedullary plasmacytoma		0.0002
No vs. Yes	22.26 (10.68, 33.84)	
Emotional functions (*n* = 266)		
Interaction between sex and ≥ 1 CRAB		0.0413
Male (interaction vs. no interaction)	18.04 (8.65, 27.43)	
Female (interaction vs. no interaction)	4.09 (−5.59, 13.77)	
≥ 1 extramedullary plasmacytoma		0.0008
No vs. Yes	14.30 (6.07, 22.54)	
Cognitive functions (*n* = 225)		
Comorbidities at last relapse and/or refractoriness		0.0296
≥ 1 vs. None	−7.62 (−14.45, −0.79)	
Free light chain concentration in serum (g/L)		0.0229
100 g/L	−0.27 (−0.51, −0.04)	
Social function (*n* = 264)		
≥ 1 extramedullary plasmacytoma		0.0025
No vs. Yes	16.00 (5.74, 26.27)	
Fractures		0.0417
No vs. Yes	10.60 (0.44, 20.76)	
Fatigue (*n* = 200)		
Stage of disease at last relapse and/or refractoriness according to the ISS		0.0243
I vs. II	−0.49 (−9.24, 8.25)	
I vs. III	−12.70 (−22.54, −2.85)	
II vs. III	−12.21 (−22.16, −2.25)	
≥1 extramedullary plasmacytoma		0.0003
No vs. Yes	−21.41 (−32.97, −9.86)	
Nausea and vomiting (*n* = 273)		
Anemia		0.0073
No vs. Yes	−6.31 (−10.89, −1.73)	
Pain (*n* = 266)		
≥ 1 extramedullary plasmacytoma		0.0102
No vs. Yes	−14.36 (−25.24, −3.47)	
Anemia		0.0436
No vs. Yes	−8.12 (−15.99, −0.26)	
Dyspnea (*n* = 274)		
Anemia		0.0253
No vs. Yes	−8.15 (−15.27, −1.04)	
Infections		0.0409
No vs. Yes	−9.71 (−18.98, −0.44)	
Loss of appetite (*n* = 267)		
Comorbidities at last relapse and/or refractoriness		0.0359
≥1 vs. None	8.47 (0.59, 16.34)	
≥1 extramedullary plasmacytoma		0.0074
No vs. Yes	−14.51 (−25.07, −3.95)	
Constipation (*n* = 252)		
≥1 extramedullary plasmacytoma		0.0038
No vs. Yes	−16.01 (−26.77, −5.26)	
Combination of treatments[a]		0.0442
IMIDs vs. PI	13.93 (1.67, 26.18)	
IMIDs vs. PI + IMIDs	14.61 (3.44, 25.77)	
IMIDs vs. mAb	11.34 (1.15, 21.54)	
Economic difficulties (*n* = 266)		
Age (years) at study visit	−0.50 (−0.80, −0.20)[b]	0.0010
≥1 extramedullary plasmacytoma		0.0041
No vs. Yes	−12.74 (−21.37, −4.12)	

Note: Insomnia and diarrhea scales did not retrieve significant associations with factors.
[a]Only shown the combinations of treatments with significant association
[b]Beta (IC 95%).
CRAB: calcium, renal insufficiency: anemia or bone lesions; IMiDs, immunomodulatory drugs; ISS: international staging system; mAb: monoclonal antibodies; PI: proteasome inhibitors; QoL: quality of life.

Table 3. Ceiling and floor effects and internal consistency of EORTC QLQ-MY20.

	N	Floor Effect, *n* (%)	Ceiling Effect, *n* (%)	Cronbach's Alpha
Functional Scales and Items				
Future perspective	254	15 (5.9)	28 (11.0)	0.8195
Body image	254	24 (9.4)	138 (54.3)	–
Symptom Scales				
Disease symptoms	254	27 (10.6)	1 (0.4)	0.8223
Treatment side- effects	254	10 (3.9)	0 (0.0)	0.7799

n: number of patients included in each specific analysis.
The EORTC QLQ-C30 and EORTC QLQ-MY20 scores range is 0–100. High scores on the body image and future perspective scales represent better outcomes, while higher scores on the symptoms and side effect scales represent poorer outcomes.

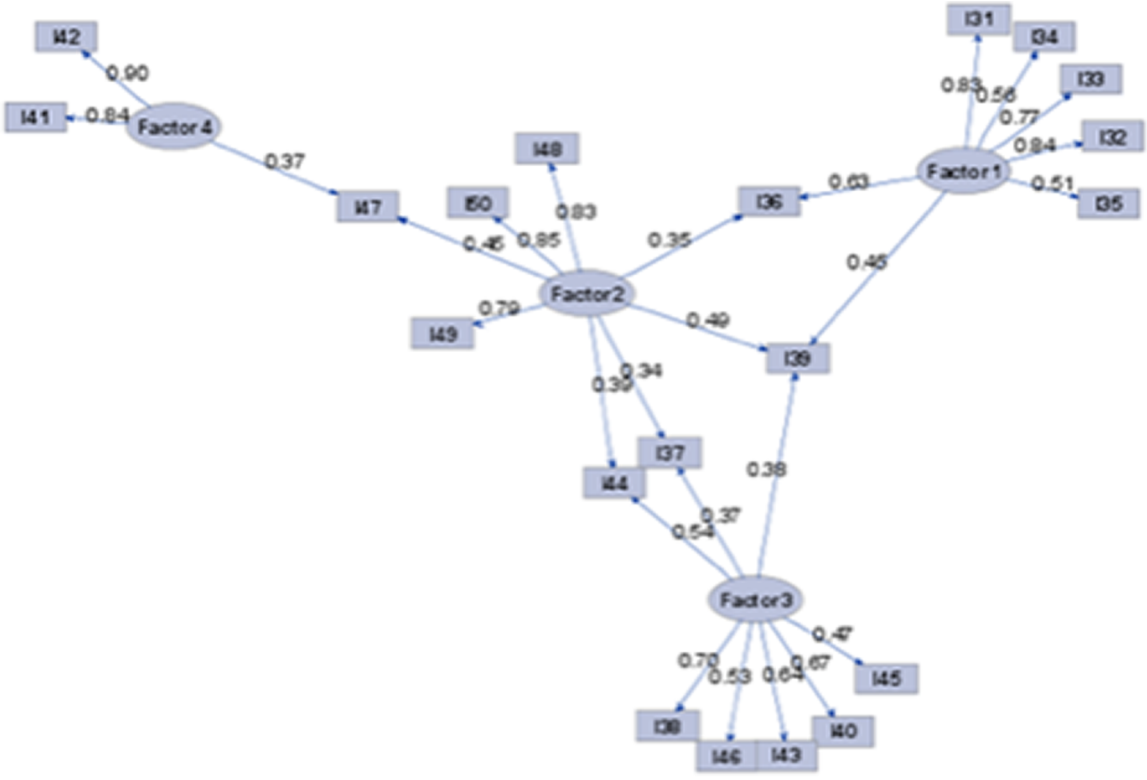

Figure 1. Construct validity of EORTC QLQ-MY20. Diagram of principal components.
Each item of the EORTC QLQ-MY20 questionnaire is represented as the letter I followed by the item number (see Appendix 1). The values on the arrows represent the correlation coefficients between the questionnaire items and the identified factors.

treatment response. Also, the use of these instruments has proved to contribute to improving the HRQoL of RRMM patients.[17,32] Here we present for the first time the evaluation of the psychometric properties of the Spanish version of the EORTC QLQ-MY20.

Previously, the EORTC QLQ-MY20 module has been fully validated in other languages, and the Spanish version has been used in Spanish patients. [22,26,33] In our study, the Spanish version of the EORTC QLQ-MY-20 module showed a low rate of non-response, a very low ceiling and floor effect, only present in two items, and good internal consistency, with a Cronbach's α higher than 0.8 for the whole questionnaire, or near, for its individual scales. In addition, the test–retest analysis revealed good temporary stability for all the scales of the questionnaire, with an ICC of around 0.8. The construct validity analysis stated four main factors similar to the ones of the original version. Factors 1 and 2 were almost coincident with symptoms and future perspectives scales, respectively, whereas factors 3 and 4 together grouped all the items in the scales of side effects of the treatment and body image. Precisely, the item on body image (item 47) was associated with factor 2 (together with the items related to future perspectives) and factor 4 (items 41 and 42, associated with hair loss, which may also be related to body image). Finally, the criterion validity

Table 4. Criterion validity: assessment of possible associations between EORTC QLQ-MY20 module scores and ISS stage or fractures.

	n	Mean (SD)	Median (Q1, Q3)	*P*
ISS Stage				
Functional Scales and Items				
Future perspective				0.1494
I-II	142	60.3 (28.2)	66.7 (44.4, 77.8)	
III	53	53.9 (24.9)	55.6 (33.3, 66.7)	
Body image				0.6005
I-II	142	73.9 (35.5)	100.0 (33.3, 100.0)	
III	53	73.0 (32.7)	100.0 (66.7, 100.0)	
Symptom Scales				
Symptoms of the disease				0.2157
I-II	142	31.9 (23.6)	27.8 (16.7, 44.4)	
III	53	27.3 (22.1)	22.2 (5.6, 44.4)	
Treatment side-effects				0.0876
I-II	142	24.3 (16.9)	20.0 (10.0, 36.7)	
III	53	29.0 (17.5)	30.0 (16.7, 40.0)	
Fractures				
Functional Scales and Items				
Future perspective				0.1034
Fractures present	39	52.7 (30.8)	55.6 (33.3, 77.8)	
No fractures	215	60.5 (26.6)	66.7 (44.4, 77.8)	
Body image				0.5543
Fractures present	39	70.1 (37.3)	100.0 (33.3, 100.0)	
No fractures	215	74.6 (32.9)	100.0 (66.7, 100.0)	
Symptom Scales				
Symptoms of the disease				0.6258
Fractures present	39	28.9 (20.3)	27.8 (16.7, 38.9)	
No fractures	215	30.9 (23.5)	27.8 (11.1, 44.4)	
Treatment side-effects				0.7685
Fractures present	39	24.7 (17.7)	20.0 (10.0, 40.0)	
No fractures	215	25.6 (17.1)	23.3 (13.3, 36.7)	

n: number of patients included in each specific analysis.
ISS: international staging system.

Table 5. Convergent validity: correlation between EORTC QLQ-MY20 and the global health status/QoL scale of EORTC QLQ-C30 scale scores.

	QLQ-C30 Global Health Scale
EORTC QLQ-MY20 ($N = 254$)	
Functional Scales and Items, Correlation	
Future perspective	0.4008
Body image	0.2525
Symptom Scales, Correlation	
Symptoms of the disease	−0.3977
Treatment side-effects	−0.4330

assessment showed no statistical differences between groups according to ISS stage and the presence of fractures. Even though the variables chosen to perform this evaluation (i.e. ISS and the presence of fractures) could not discriminate between groups of patients with different clinical situations, there might be other variables that can. However, the rest of the psychometric properties consistently showed that the Spanish translation of the EORTC QLQ-MY20 module is a reliable tool to assess the HRQoL of RRMM patients, as had already been proven in other languages.[24,26,33]

The HRQoL of RRMM patients may vary greatly between individuals depending on many factors. In our study, the presence of plasmacytomas significantly influenced the HRQoL and was associated with almost all scales, except for those evaluating cognitive functions, nausea and vomiting, and dyspnea. It is well established that plasmacytomas are a bad prognostic factor for MM patients, which is consistent with our findings; [1,34] all patients with some sort of plasmacytoma showed worse HRQoL than patients without them. The stage of the disease, another factor typically associated with a poorer prognosis of MM, was related to the physical functions and fatigue scales, indicating that advanced stages of MM have a significant impact on QoL, particularly in terms of physical performance. In addition, the presence of comorbidities showed a significant impact on the loss of appetite, cognitive functions, and physical function scales, showing the burden of comorbidities on the overall QoL of RRMM patients. After the last relapse or refractoriness, most patients received a pharmacological treatment including immunomodulatory drugs (IMiDs), alone or combined with proteasome inhibitors, as recommended by the ESMO guidelines.[4] However, the combination of treatments only showed a significant impact on the constipation scale, suggesting that patients treated with IMiDs were more prone to constipation than patients who received other drugs.

It has been widely demonstrated that the assessment of HRQoL in cancer patients has an important value in complementing clinical trial endpoints such as disease-free survival, progression-free survival, overall survival, or toxicity, and improving communication between patients and physicians.[19,35,36] Despite the potential power of these tools to guide the physician's decision-making in a patient-centered manner, their implementation is still scarce in routine clinical practice. Our results present the QoL picture of RRMM patients in Spain and highlight the importance of translating such assessments to clinical practice.

The results of this study must be read in the context of its nature and design. Data collection was limited to the information included in the medical record and the single visit interview. Also, although the study sample included only RRMM patients, it was heterogeneous, especially regarding health status, stage of the disease, and prior treatments received. Remarkably, although the number of prior lines of treatment and the number of previous relapses were significant

determinants of treatment choice,[28] they were not associated with QoL. The heterogeneity of the sample and the study design may have precluded some existing association between the patients' QoL and factors such as the number of prior treatments or the number of prior relapses.

To conclude, the evaluation of the psychometric properties of the Spanish version of the EORTC QLQ-MY20 module showed that it is a reliable and valid instrument suitable for HRQoL assessments in Spanish RRMM patients. Furthermore, data concerning the QoL of RRMM patients may help physicians to assess patients' evolution and make decisions regarding their treatment approach.

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Appendix

Appendix 1. EORTC QLQ- MY20 questionnaire, instructions, and scoring

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:

	Scoring			
Items	Not at all	A little	Quite a bit	Very much
31. Have you had bone aches or pain?	1	2	3	4
32. Have you had pain in your back?	1	2	3	4
33. Have you had pain in your hip?	1	2	3	4
34. Have you had pain in your arm or shoulder?	1	2	3	4
35. Have you had pain in your chest?	1	2	3	4
36. If you had pain did it increase with activity?	1	2	3	4
37. Did you feel drowsy?	1	2	3	4
38. Did you feel thirsty?	1	2	3	4
39. Have you felt ill?	1	2	3	4
40. Have you had a dry mouth?	1	2	3	4
41. Have you lost any hair?	1	2	3	4
42. Answer this question only if you lost any hair: Were you upset by the loss of your hair?	1	2	3	4
43. Did you have tingling hands or feet?	1	2	3	4
44. Did you feel restless or agitated?	1	2	3	4
45. Have you had acid indigestion or heartburn?	1	2	3	4
46. Have you had burning or sore eyes?	1	2	3	4
47. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
48. Have you been thinking about your illness?	1	2	3	4
49. Have you been worried about dying?	1	2	3	4
50. Have you worried about your health in the future?	1	2	3	4

Source: EORTC Myeloma Module QLQ-MY20 [Internet]. [cited 2021 May 10]. Available from: https://www.eortc.org/app/uploads/sites/2/2018/08/Specimen-MY20-English.pdf.