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ARTICLE

Predictors of return to work after autologous stem cell transplantation in patients with multiple myeloma

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Return to work (RTW) is a marker of functional recovery in cancer patients, with quality of life, financial and social implications. We investigated frequency and factors associated with RTW in a cohort of patients younger than 66 years, with newly diagnosed multiple myeloma (MM), uniformly treated with a bortezomib-based induction followed by autologous stem cell transplantation (ASCT). Socio-economic and working status data were collected by a self-administered questionnaire. One hundred and eighty-six patients entered the study. Of whom, 145 (78%) where employed at diagnosis, which was more frequent in younger (median 55 vs. 60 years, $p < 0.001$), men (59.3% vs. 34.2%, $p = 0.004$), and with college studies (44.8% vs. 24.4%, $p = 0.008$). Forty-three (30%) of the 145 patients who had a job at diagnosis, RTW after ASCT in a median of 5 (range 1–27) months. Factors independently associated with RTW were having three or more children (HR 2.87, 95% CI 1.33–6.18), college studies (HR 2.78, 95% CI 1.21–6.41), and a family income >40 × 10^3€/year (HR 2.31, 95% CI 1.12–4.78). In conclusion, the frequency of RTW herein reported in MM patients seems lower than reported in other malignancies. The risk factors observed may guide the design RTW programs.

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INTRODUCTION

Return to work (RTW) among cancer survivors is a marker of functional recovery [1] and is associated with quality of life [2] and financial security [3]. Furthermore, in the context of ageing societies, to resume employment may become an economic and social necessity [4]. Nevertheless, about one third of cancer survivors will not RTW after treatment [4, 5] due to long-lasting physical and psychological late effects, often including fatigue [6, 7] and depression [6, 8].

Multiple myeloma (MM) accounts for ~1.8% of all cancers [9] and 15% of hematologic malignancies [10]. Although it is considered a disease of the elderly, one third of patients are younger than 65 years at diagnosis [9]. The main clinical features include anemia, osteolytic bone disease that can result in pain and pathologic fractures, renal insufficiency, fatigue, and hypercalcemia [11]. Treatment consists of an induction of 4–6 months of duration; with a triple combination of an immunomodulatory drug, a proteasome inhibitor, and steroids; followed by a high-dose melphalan-based autologous stem cell transplantation (ASCT), and a long-term maintenance usually based on lenalidomide. After the ASCT, most patients achieve a response and can enjoy a period of disease control that can exceed 5 years [12, 13]. However, relapses are common and, although subsequent treatments are becoming increasingly effective, responses tend to be shorter. In the last decades, an increase in overall survival has been noted, especially in younger patients, due to the introductions of several families of new drugs [14–17]. Nowadays about one third of patients live 10 years or more and survival is projected to further improve in the near future [17, 18]. Nevertheless, MM remains an incurable disease with a significantly inferior outcome compared to other curable hematologic cancers like diffuse large B-cell lymphoma or Hodgkin lymphoma, in which patients who survive 3 years achieve a life expectancy similar to the background population [19].

A Danish nationwide register-based study found that patients with MM are at higher risk of not returning to work than patients with other hematologic malignancies, such as lymphoma [20]. However, most studies examining RTW in survivors of hematological malignancies have focused on stem cell transplant populations rather than in specific diseases, and patients with MM have been underrepresented [21–25]. The aim of the present study is to analyze in a systematic manner, the frequency and factors associated with RTW in a cohort of patients with MM

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homogeneously treated with a bortezomib-based induction followed by ASCT.

PATIENTS AND METHODS

Participants and procedures

The study was conducted in seven hospitals included in the GEMMAC (Group for the Study of Myeloma and Amyloidosis of Catalonia) group. It was approved by the Ethics committees of all the participating centers and patients signed an informed consent form. Eligibility criteria were: (1) confirmed diagnosis of MM, (2) to have been treated with an ASCT in first line between January 2013 and May 2019, and (3) to be younger than 66 years old (the average age of retirement in Spain) at the time of ASCT. Potential participants were recruited from local transplant registries. The treating hematologist was responsible for explaining the study to candidates in their regular follow-up visits.

Study variables

Basal demographic and clinical data were collected from electronic medical records and included: gender, date of birth, date of diagnosis, Charlson's comorbidity index, psychiatric treatment (excluding benzodiazepines), heavy and light chain, hemoglobin, calcium, creatinine, significant bone disease (defined as requiring antalgic radiotherapy, surgery, or opioids for pain control), bone marrow plasma cell infiltration, international staging system (ISS), and induction treatment. Follow-up variables included: date of ASCT, response to ASCT, maintenance regimen, progression status, and date, as well as survival status and date. Socio-economic data were self-reported by participants in a questionnaire developed for the study (Appendix 1) based on previous publications [26] and included: working status, education, marital status, number of children, and family income. The questionnaire examined working status before the diagnosis of myeloma and after ASCT (i.e., occupation status, working hours and kind of job, working capacity, and date of RTW), as well as reasons for not RTW after ASCT, the impact of the disease and its treatment on work-related physical and mental activities and the workplace characteristics (i.e., flexibility to adapt, satisfaction with support received from work).

Statistical design and analysis

Baseline demographic and clinical characteristics according to the working status (working vs. not working) before the diagnosis of MM were compared. Two-sided Fisher's exact tests were used to test for differences between categorical variables. Cramer's V was used to test correlation between groups of ordinal variables. Two-sided Wilcoxon rank sum test was used to test for differences between continuous variables. The analysis of factors affecting RTW was restricted to patients who had a job before the diagnosis. Kaplan–Meier curves were plotted considering time 0 the date of transplant and followed until the date of RTW, the date of relapse, or up to 36 months (censor variables). Differences between curves were tested for statistical significance using the two-sided log-rank test. Variables with a two-sided p value < 0.1 at univariate analysis were dichotomized and included in a multivariate analysis using the Cox proportional hazards model. All statistical analysis was performed using the of R software version 4.0.3.

RESULTS

Employment status at diagnosis

One hundred and eighty-six patients who fulfilled the inclusion criteria agreed to participate in the study. Demographic, clinical, and socio-economic data of the overall cohort and according to the working status before the diagnosis of MM are summarized in Table 1. One hundred and forty-five of the 186 (78%) patients had a paid job when they were diagnosed of MM, while 41 (22%) did not. Of the 145 patients who had a paid job, 81 (55.9%) were salaried employed by others, 34 (23.4%) self-employees, 17 (11.7%) intermediate managers, 12 (8.3%) executives or academics, and one (0.6%) patient did not report his type of job. One hundred and thirty (89.7%) individuals had a full-time job and the remaining 15 (10.3%) a part-time job.

Comparison of baseline characteristics showed that women (65.8% vs. 40.7%, $p = 0.004$), older patients (median age 65 vs. 55 years, $p < 0.001$), and individuals without university studies (24.4% vs. 44.8%) were less likely to have a job at the time of diagnosis. The household income in families where the patient did not have a job at diagnosis was lower (<40.000 €/year 85.3% vs. 70.3%, $p = 0.003$).

Frequency and factors associated with RTW

Forty-three (30%) of the 145 patients who had a job before diagnosis RTW after ASCT. Of them, 36 (84%) returned full-time and 7 (16%) part-time. Median time from transplant to RTW was 5 (range 1–27) months. Thirty-five (81%) of the 43 patients who RTW were still working on the date they completed the questionnaire while 9 (19%) patients have worked for a median of 12 (extremes 2–36) months after ASCT. Ninety-one (89%) of the 102 patients who did not RTW had a disability pension or a long-term sick leave. Detailed working status of the overall cohort before and after transplantation is shown in Table 2. None of the patients who did not have a paid job before being diagnosed of MM were employed after ASCT.

Five variables showed an association with RTW at 3 years post-ASCT in the univariate analysis: male gender, type of job (not being employed by others), having three or more children, having college or university studies, and having a yearly higher family income. In additions, a trend towards association ($p = 0.059$) was observed for ISS (Fig. 1). These variables were dichotomized and included in the multivariate analysis. Three of them maintained significance: having college/university studies, household income higher than 40×10^3 €/year, and having three or more children (Table 3).

Working capacity before diagnosis and after transplantation

Patients were asked about their subjective perception of working capacity before the diagnosis of myeloma and 3–6 months after transplantation. Specifically, to the question: "before being sick, how do you rate your working capacity in a scale from 0 indicating invalidity to 9 indicating the highest capacity ever had?," none of the 182 patients who answered scored their working capacity from 0 to 3, 1 (0.5%) patient scored 4, 6 (3.3%) scored 5, 4 (2.2%) scored 6, 7 (3.8%) scored 7, 25 (13.7%) scored 8, and 139 (76.4%) scored 9. To the question: "between 3 and 6 months after transplant, how do you rate your working capacity in a scale from 0 indicating invalidity to 9 indicating the highest capacity ever had?," 44 (24.7%) of the 178 patients who answered scored their working capacity as 0, 10 (5.6%) scored 1, 19 (10.7%) scored 2, 17 (9.6%) scored 3, 12 (6.7%) scored 4, 22 (12.4%) scored 5, 15 (8.4%) scored 6, 11 (6.2%) scored 7, 15 (8.4%) scored 8, and 13 (7.3%) scored 9 (Fig. 2). Patterns of responses were similar between patients with and without a paid job before the diagnosis of myeloma (data not shown).

Impact of myeloma on physical and mental activities

Patients were asked about their subjective perception of the impact of myeloma in physical and mental activities. Responses of patients with a paid job at diagnosis grouped according to the RTW status are shown in Fig. 3.

To the question: "did the disease and its treatment affect your working capacity to perform physical activities?" 53 (51.9%) of the 102 patients who did not RTW, answered "a lot," 40 (39.2%) "pretty much," 7 (6.8%) "somewhat," 1 (1%) "a little," and 1 (1%) "not at all." Within the patients who RTW, 6 (13.9%) of the 43 patients answered "a lot," 5 (11.6%) "pretty much," 6 (13.9%) "somewhat," 12 (27.9%) "a little," and 14 (32.5%) "not at all." Patterns of responses between patients who did and did not RTW were strongly associated (Cramer's V 0.711).

To the question: "did the disease and its treatment affect your working capacity to perform mental activities?" 11 (%) of the 102 patients who did not RTW, answered "a lot," 30 (29.4%) "pretty much," 22 (21.6%) "somewhat," 15 (14.7%) "a little," and 24 (23.5%) "not at all." Within the patients who RTW, 1 (2.3%) of the 43 patients answered "a lot," 2 (4.6%) "pretty much," 6 (13.9%) "somewhat," 3 (6.9%) "a little," and 31 (72.1%) "not at all." Patterns of responses between patients who did and did not RTW were moderately associated (Cramer's V 0.471).

Table 1. Baseline demographic, clinical, and socio-economic characteristics.

Variable	Overall	Working	Not working	*p*
N	186	145	41	
Female, *n* (%)	86 (68.2)	59 (40.7)	27 (65.8)	0.004
Age, median (range)	56 (32–65)	55 (32–65)	60 (38–65)	<0.001
Heavy chain, *n* (%)				
–G	108 (58.1)	84 (57.9)	24 (58.5)	n.s
–A	35 (18.8)	27 (18.6)	8 (19.5)	
–D	5 (2.7)	5 (3.4)	0 (0.0)	
–Light chain only	38 (20.4)	29 (20.0)	9 (22.0)	
Light chain, *n* (%)				
–Kappa	112 (60.2)	86 (59.3)	26 (63.4)	n.s
–Lambda	74 (39.7)	59 (40.7)	15 (36.6)	
Bone disease, *n* (%)	100 (53.7)	77 (53.1)	23 (56.1)	n.s
Creatinine >2 g/dL, *n* (%)	24 (12.9)	20 (13.8)	4 (9.7)	n.s
Bone marrow PC, median (extremes)	35 (0–99)	35 (0–99)	35 (0–90)	n.s
ISS, *n* (%):				
–I	69 (37.1)	58 (40)	11 (26.8)	n.s
–II	68 (36.6)	47 (32.4)	21 (51.2)	
–III	45 (24.2)	36 (24.8)	9 (21.9)	
–NA	4 (2.1)	4 (2.7)	0	
Charlson score, *n* (%):				
–0	142 (76.3)	114 (78.6)	28 (68.3)	n.s
–1	26 (13.9)	20 (13.8)	6 (14.6)	
–>1	18 (9.7)	11 (7.6)	7 (17.1)	
Psychiatric treatment, *n* (%)	39 (20.9)	28 (19.3)	11 (26.8)	n.s
Education, *n* (%):				
–Primary school	48 (25.8)	30 (20.7)	18 (43.9)	0.008
–Secondary	55 (29.6)	43 (29.6)	12 (29.3)	
–University	75 (40.3)	65 (44.8)	10 (24.4)	
–NA	8 (4.3)	7 (4.8)	1 (2.4)	
Marital status, *n* (%):				
–Never married	14 (7.5)	12 (8.3)	2 (4.9)	n.s
–Married/living w. couple	134 (72.0)	102 (70.3)	32 (78.0)	
–Separated/divorced	25 (13.4)	23 (15.9)	2 (4.9)	
–Widowed	10 (5.4)	7 (4.8)	3 (7.3)	
–NA	3 (1.6)	1 (0.7)	2 (4.9)	
Number of children, *n* (%):				
–None	27 (14.5)	24 (16.6)	3 (7.3)	n.s
–1	41 (22.0)	34 (23.4)	7 (17.1)	
–2	89 (47.8)	67 (46.2)	22 (53.7)	
–>2	29 (15.6)	20 (13.8)	9 (21.9)	
Household income ($\times 10^3$ €/year):				
–<20	64 (34.4)	48 (33.1)	16 (39.0)	0.003
–>20–40	73 (39.2)	54 (37.2)	19 (46.3)	
–>40–60	29 (15.6)	27 (18.6)	2 (4.9)	
–>60	11 (5.9)	11 (7.6)	0	
–NA	9 (4.8)	5 (3.4)	4 (9.8)	

Causes, flexibility, and support

Of the 91 patients who answered the question: "In the case you are not working, specify if it is due to" with two possible choices: "health status" or "not finding a job although would like to work," 85 (93%) selected the first option, 4 (4.4%) the second option, and 2 (2.2%) both statements.

Of the 100 patients who answered the question: "Have you had the flexibility to adapt your work to your illness?", 43 (43%) persons answered yes and 57 (57%) no. In the 42 patients who RTW, 30

Table 2. Working status in the overall group.

	At diagnosis, *N* (%)	After transplant, *N* (%)
Working	145 (78.0)	43 (23.1)
Retired	14 (7.5)	20 (10.7)
Unemployed	9 (4.8)	6 (3.2)
Homemaker	9 (4.8)	11 (5.9)
Disability	8 (4.3)	89 (47.8)
Sick leave	1 (0.5)	17 (9.1)

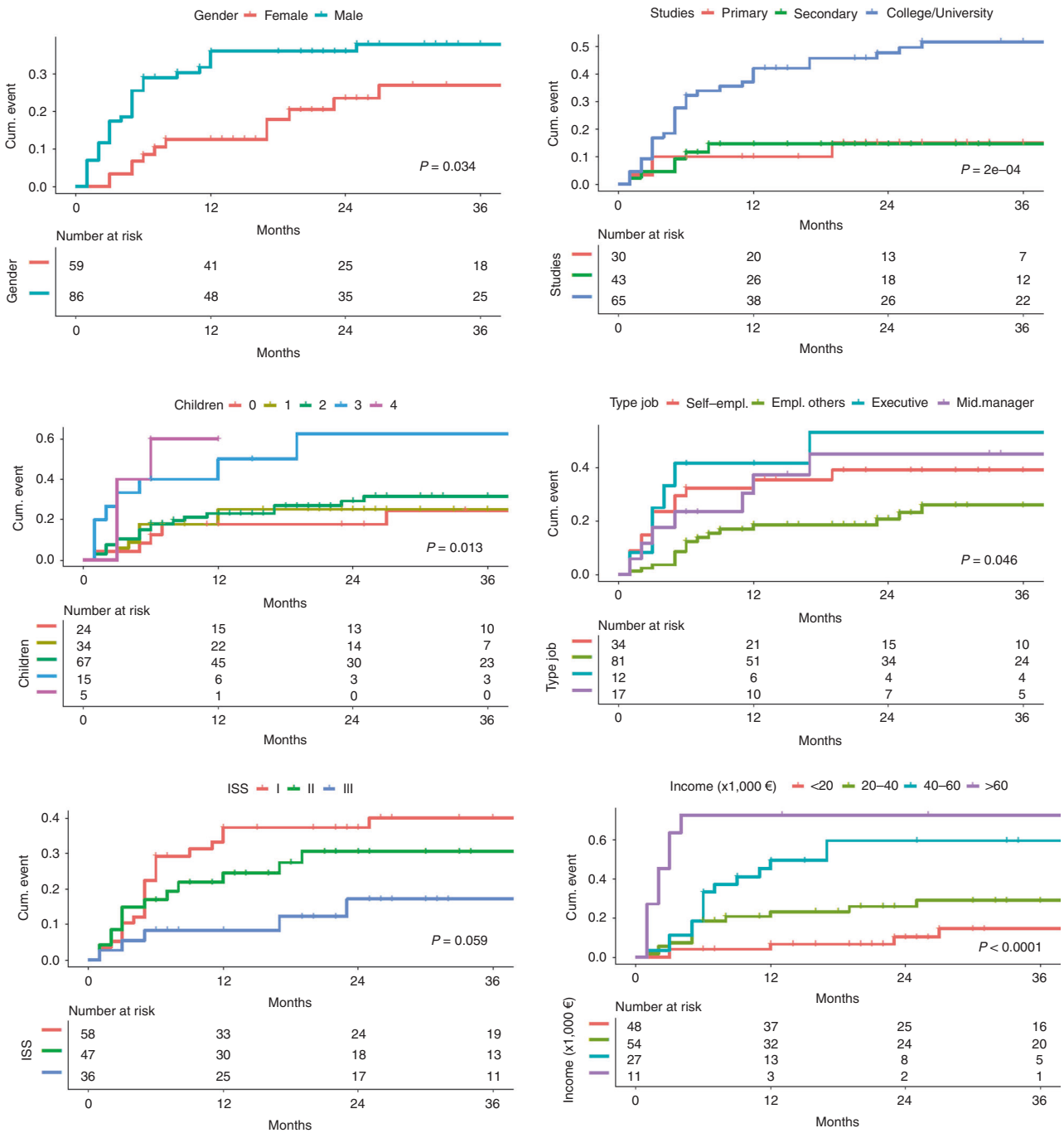

Fig. 1 Cumulative incidence of RTW. Significant variables in univariate analysis.

(71%) answered yes, and 12 (29%) no; whereas in the 58 patients who did not RTW, 13 (22%) answered yes and 45 (88%) no.

Of the 94 patients who answered the question: "Is the support you receive from your work environment satisfactory?", 62 (66%) persons answered yes and 32 (34%) no. In the 42 patients who RTW, 37 (88%) answered yes and 5 (12%) no; whereas, in the 52 patients who did not RTW, 25 (48%) answered yes and 27 (52%) no.

DISCUSSION

In the present study, 30% of patients with myeloma who had a paid job before diagnosis returned to work after a standard induction treatment followed by an ASCT. Such frequency is clearly lower than the three-quarters observed in other cancer populations [4], and the 50–58% reported in populations undergoing ASCT for diffuse large B-cell lymphoma [27, 28]. To our knowledge, only one previous study has addressed the issue of RTW exclusively in MM [29]. In this study, Jackson el al. found a frequency of RTW of 39.1% after ASCT in a series of 115 patients from five European countries. Our results support the observation of a lower likelihood of RTW in patients with MM compared to other hematologic malignancies reported by Horsboel et al. [20]. Some specific features of myeloma might explain such differences: (1) median age of myeloma patients at diagnosis is 65–70 years [11], similar the age of retirement in many western countries. Age is the factor most consistently associated with RTW both in solid

Table 3. Variables associated with RTW.

Variable	Univariate			Multivariate		
	HR	95% CI	*p*	HR	95% CI	*p*
Male	2.03	1.04–3.96	0.03	1.82	0.89–3.77	0.095
ISS II/III	0.51	0.27–0.96	0.04	0.71	0.35–1.43	0.337
>2 children	3.21	1.61–6.41	5×10^{-4}	2.87	1.33–6.18	**0.006**
University studies	3.99	1.96–8.12	4×10^{-5}	2.78	1.21–6.41	**0.016**
Not employed by others	2.32	1.26–4.29	0.005	1.27	0.60–2.67	0.521
Income > 40 × 10e3 €	4.42	2.40–8.15	2×10^{-7}	2.31	1.12–4.78	**0.022**

Statistically significant *p* values are in bold.

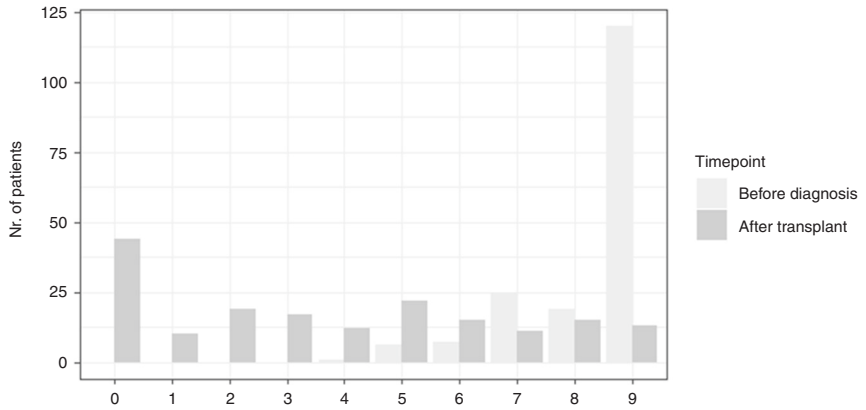

Fig. 2 Patient-reported perception of working capacity.

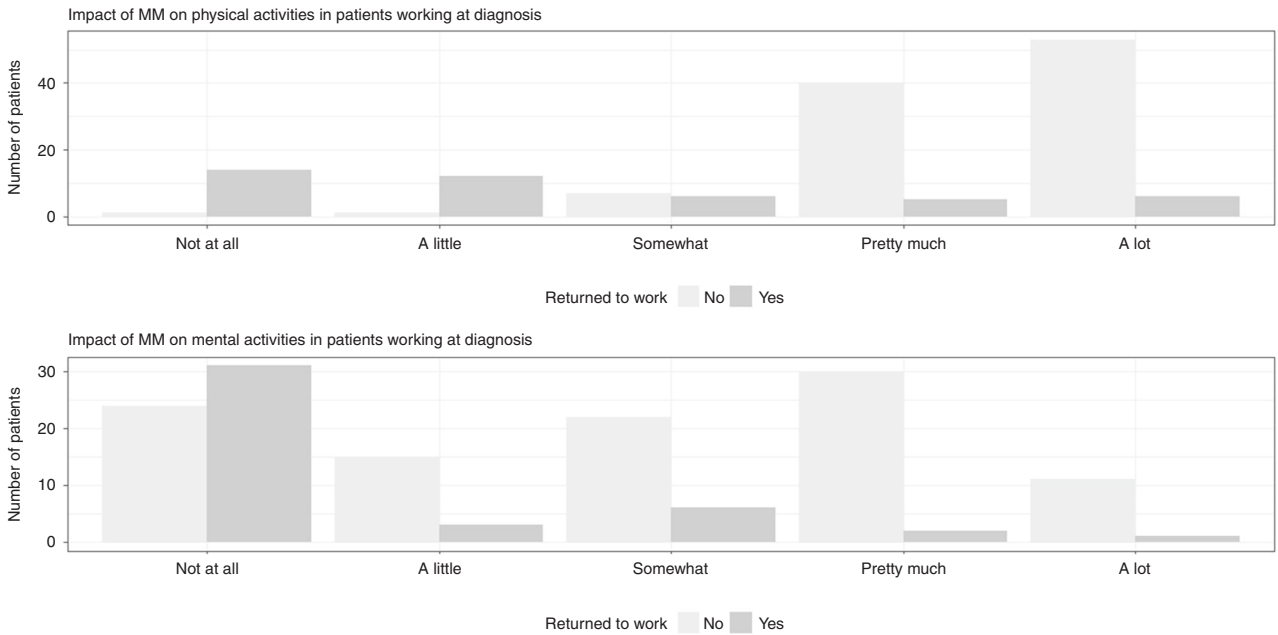

Fig. 3 Patient-reported impact of MM on physical and mental activities.

[30, 31] and hematologic [22, 23] cancers. In the present study, only five (3.4%) patients retired after transplantation. (2) Bone pain, secondary to lytic bone lesions and pathologic fractures, is present in 58% of patients at diagnosis [11], frequently becomes chronic and requires management with opioids that can affect the ability to resume work. (3) Although the survival of myeloma is improving and is expected to become a chronic condition, it remains an incurable disease and almost all patients experience relapses that impact their physical and emotional quality of life [32]. It is possible that the perspective of dealing with an incurable disease may impact patient's decision to resume work.

In the present cohort, higher family income, college/university education, and three or more children are predictive of RTW in the multivariate analysis. Lower income has been associated with RTW

in studies of breast [33, 34] cancer as well as education level has been associated with RTW in head and neck [35] cancer and lymphoma [23]. By contrast, the number of children has not been previously associated with RTW. It should be noted that in the present study, RTW was not independently linked to any of the variables related to the aggressiveness of the myeloma (i.e., significant bone disease, renal insufficiency, other prognostic markers, etc.) in patients who received an ASCT in first remission. These results highlight the key importance of social rather than medical factors in the process of RTW.

Patient-reported outcomes included in the questionnaire indicate that most patients feel a drop in their capacity to work related to the diagnosis and treatment of the myeloma, mostly due to physical activities, although mental activities are also affected. Within the patients who did not RTW, more than 90% stated than their health status rather than not finding a job was the main reason for not RTW. On the other hand, most patients who RTW reported that, after being diagnosed with MM, they had flexibility to adapt their work and received support from their working environment.

The absence of a non-cancer comparator group in our study is a limitation that prevents analyzing the impact of being diagnosed of MM in the general labor market. Furthermore, the unemployment rate in the general population of Catalonia in the study period ranged from 10 to 24% [36] and this may impact the external validity of our results since RTW of cancer patients in populations with lower unemployment rates is expected to be higher. By contrast, the homogeneity of the present cohort, including only newly diagnosed MM patients treated with a bortezomib-based triplet followed by and an ASCT in first response, represents a more realistic picture of the myeloma population than studies focused on stem cell transplantation for different hematologic malignancies with different clinical characteristics and outcome.

The high cost of MM treatments impacts patient and health systems finances. Thus, to analyze the effects of the disease and its treatment on employment seems suitable, especially as the survival of myeloma patients increases and most of them can enjoy extended periods of disease-free symptoms. RTW could be viewed as a surrogate marker of quality of life in the real-world setting when it is impossible to perform serial prospective questionnaires. The results of this study bring some ideas that could guide the design of onco-revalidation programs to increase the RTW rate: considering the importance of education in RTW and the impact of MM in physical activities, to promote professional training of patients with MM, could enable the adaptation of the workplace, especially in patients with a physical work. On the other hand, given the relationship between income and RTW, one might consider the possibility of tax incentives in patients returning to work, especially in those with lower income.

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AUTHOR CONTRIBUTIONS

MGr and AB designed the study. MGr, AS, M-TC, MGi, JL-P, CM, AG-G, EA, RB-A, J-MM, JS, CFL, AO, and LR identified candidates to the study, obtained informed consent, and collected data. MGr and RM analyzed and interpreted data and wrote the manuscript. All the authors reviewed the manuscript and approved the final version.

COMPETING INTERESTS

The authors declare no competing interests.

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