

Observational Studies

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Everyday living with pain – reported by patients with multiple myeloma

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Abstract

Objectives: The prevalence and impact of pain among patients with multiple myeloma (MM) in their everyday life require renewed attention. MM patients' survival has increased considerably over the last decades and active disease episodes are interrupted by longer periods with disease inactivity. The aim with this study is to explore pain intensity and pain interference with daily activities during periods of stable or inactive MM disease.

Methods: In a cross-sectional study from September 2017 to May 2019, self-reliant MM patients in stable disease filled a comprehensive selection of validated questionnaires regarding pain, other symptoms and quality of life, which they experienced in their daily living. Patient reported pain intensity and interference with daily activities were analyzed for associations with several clinical and demographic factors and discussed from a total pain perspective. The two outcomes, pain intensity and pain

interfering with daily activities, were analyzed in two age groups (<65 years or ≥65 years).

Results: Among 92 participants, 80% experienced pain to interfere with their daily activities (equal in both age groups), and 63% reported moderate to severe pain intensity; (75% ≥65 years, and 49% <65 years). Pain intensity was significantly associated with signs of depression (OR 4.0 [95% CI: 1.2–13.9]) and age ≥65 years (OR 3.3 [95% CI: 1.2–9.2]). Pain interfering with daily activities was nearly significantly associated with bone involvement (OR 3.4 [95% CI: 1.0–11.6]) and signs of depression (OR 5.9 [95% CI: 1.0–36.3]). The patients were bothered with many problems in addition to pain; fatigue (91%), bone involvement (74%), signs of depression (41%), signs of anxiety (32%), comorbidity (29%) and uncertainty in relation to employment or pension (25%). Neuropathic pain was more prevalent in the feet (33% [95% CI: 23%, 43%]) compared with pain in the hands (13% [95% CI: 7%, 22%]).

Conclusions: In periods of stable disease, many MM patients continue to live with intense pain interfering with their daily activities. Additional or associated problems are the presence of bone involvement, neuropathic pain, older age, uncertainty in relation to employment or pension, comorbidity, signs of depression, anxiety and fatigue. This highlights the importance of health professionals being receptive to the patients' experience of pain throughout their trajectories, to assess pain systematically and to interpret this experience from a total pain perspective. While pain problems in relation to diagnosing and treating MM is well known, this study brings the message that even during periods of stable or inactive MM disease, the patients experience pain with a moderate to severe intensity, that interferes with their everyday living. The improved survival and the consequential long trajectories make coherence in the pain treatment even more important for the patients, who may see different professionals in different health care settings for different reasons. The patient group requires a coordinated, holistic patient-centered pain treatment throughout the disease trajectory.

Keywords: everyday living; multiple myeloma; pain prevalence; patient reported outcomes; total pain.

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Introduction

Pain is one of the most frequently reported symptoms throughout the disease course among patients with multiple myeloma (MM) with a prevalence ranging from 54 to 99% [1–4]. However, most of the reports are based on patient reported outcomes (PRO) in specific treatment settings, whether being first-line-, consolidation-, maintenance- or relapse treatment studies [5]. This may not be representative for MM patients, who are in a stable phase of disease, with no current need for treatment. Few studies have investigated the prevalence and level of pain in this heterogeneous population of MM patients [1, 6, 7], and little is known about MM patients' pain problems in their everyday life.

MM is an incurable hematological cancer, however new treatment options and strategies have increased the survival period considerably [8]. Consequently, the trajectories of many MM patients have changed in the direction of a more chronic disease pattern, with a disease which can be brought in to remission several times or maintain stable or inactive for longer periods of time [9]. Periods of disease activity or inactivity, and periods with more or less intensive antineoplastic treatment or no treatment, brings attention to the quality of MM patients' everyday living. A body of literature has pointed to a variety of patient reported symptoms and problems compromising MM patients' health related quality of life [1–5, 10]. Approximately two thirds of the MM patients have bone pain at the time of the diagnosis [11] and neuropathic pain is also a frequent problem for the patients [12] either as chemotherapy induced and/or as pre-existing neuropathy in 10–40% of the patients at baseline [13, 14]. During periods of stable disease many patients continue to suffer from pain [1, 15]. Thorough exploration and interpretation of the different types of pain and their mechanisms are prerequisites for the right choice of pain management. Therefore, attention is required with regard to MM patients' pain types during periods with alternating disease activity. Pain treatment is feasible [16] and necessary for the optimization of quality of life among the MM patients. However, only few studies have focused on the pain conditions bothering MM patients in their everyday life. A more detailed knowledge on the prevalence and nature of pain throughout the disease trajectory is necessary for health professionals to acknowledge the problem and to deliver sufficient and relevant pain treatment.

The aim of this study was to explore pain intensity and pain interfering with daily activities as reported by self-reliant MM patients with stable disease prior to their participation in a rehabilitation course outside the hospital setting.

Methods

Participants

Patients with MM in this study were patients who were about to participate in a rehabilitation course aimed at MM patients. The course was offered as a national service to MM patients. Its' residential part took place in Nyborg, a city located in the central part of Denmark. Hematologists throughout the country could refer patients if both patients and their doctors found rehabilitation relevant. The inclusion criteria were; MM according to the International Myeloma Working Group (IMWG) criteria [17], the patient being in remission after treatment or in maintenance therapy, the patient being adults and self-reliant and able to participate in the different activities during the rehabilitation course, a signed agreement to participate in data collection for research purposes and ability to speak and understand Danish.

Data collection and measures

Prior to the residential stay, the participants completed an extensive questionnaire booklet with validated questionnaires enquiring into different domains of health related quality of life including pain, and questions covering sociodemographic data.

Data were collected from seven courses completed in the period September 2017 to May 2019. Participants from the first four courses filled a paper copy of the booklet mailed to their home address two to three weeks prior to participation. In the following courses, data were collected using an electronic booklet with a link mailed to the participants three weeks prior to the course start. Data from the paper booklets were manually fed to the electronic data capture platform (REDCap) [18] together with the electronically collected data. Participants, who had not completed the questionnaires at home, were requested to complete the booklet at the arrival of the course.

Patient reported outcome measures

Table 1 presents the PRO data used in this study, showing the measures of interest, the tools used and the cut-off values chosen. The collected PRO-data used the following validated tools; a numeric rating scale (NRS) for pain intensity [19], EORTC QLQ-C30, single item 19, for pain interfering with daily activities [20]. EORTC CIPN20, single item 5 & 6, for elements of neuropathic pain [21], Patient Health Questionnaire (PHQ-9) for signs of depression [22], The Generalized Anxiety Disorder (GAD-7) for signs of anxiety [23], The Brief Fatigue Inventory (BFI) for signs of fatigue [24].

Disease related measures

The referring hematologist reported information on time of the MM diagnosis, number of treatment lines, relapse episodes, types of previously administered anti-myeloma drugs and treatments, bone involvement and comorbidities according to the Charlson Comorbidity Index [25]. Bone involvement was reported based on the latest performed imaging modality prior to the course participation. The

Table 1: Patient reported outcomes (PRO): measurement tools, descriptions, scoring and cut-off values.

Measure of interest	Measurement tool	Description and scoring
Pain intensity	Numeric rating scale (NRS) [19]	Average pain intensity during the last 48 h. Eleven point NRS; 0=no pain and 10=worst possible pain categorized; 1–3 for mild, 4–6 for moderate, 7–10 for severe pain intensity Cut-off value: ≥ 4
Pain interfering with daily activities	EORTC QLQ-C30, single item 19, verbal rating scale (VRS) [20]	Question: ' <i>Did pain interfere with your daily activities</i> ' within a time frame of one week. Four point VRS; 1='Not at all', 2='A little', 3='Quite a bit' and 4='Very much'. Cut-off value: < 1
Peripheral neuropathic pain, elements of	EORTC CIPN20, single item 5 & 6, VRS [21]	Questions: ' <i>Did you have shooting or burning pain in your fingers or hands?</i> ' and ' <i>Did you have shooting or burning pain in your toes or feet?</i> ' within a time frame of one week. Four point VRS; 1='Not at all', 2='A little', 3='Quite a bit' and 4='Very much'. Cut-off value: > 1
Depression, signs of	Patient health questionnaire (PHQ-9), 9 items, VRS [22]	Nine items, adding up to a total score between 0 and 27 points Four point VRS; 0='Not at all', 1='Several days', 2='More than half the days' and 3='Nearly every day', within a timeframe of two weeks Cut-off value: ≥ 5
Anxiety, signs of	The generalized anxiety disorder (GAD-7), 7 items, VRS [23]	Seven items, adding up to a total score between 0 and 21 points Four point VRS; 0='Not at all', 1='Several days', 2='More than half the days' and 3='Nearly every day', within a timeframe of two weeks Cut-off value: ≥ 5
Fatigue	The brief fatigue inventory (BFI), 9 items, NRS [24]	Nine items, adding up to a total score between 0 and 10 points

Table 1: (continued)

Measure of interest	Measurement tool	Description and scoring
		Eleven point NRS; 0=no fatigue, 1–3 for mild, 4–6 for moderate, 7–10 for severe fatigue. Cut-off value: ≥ 4

variable was dichotomized in either 'no bone involvement' or 'bone involvement' if fractures and/or osteolytic lesions were reported.

Statistical analysis

No formal sample size calculation was performed prior to the study. The number of rehabilitation courses for MM-patients were planned to reach a sample size of around 100 participants. This size was considered to provide a relevant balance between the ability to recruit enough participants within a reasonable time interval and still obtaining a reasonable level of statistical confidence.

Participants fulfilling the eligibility criteria and who completed the baseline questionnaires were included for analyses. Patient characteristics and prevalence of the symptoms at baseline were presented using descriptive statistics. Data were stratified according to age; < 65 or ≥ 65 years, as the pension age in Denmark is 65 years. We compared characteristics of patients according to age group either using Wilcoxon ranksum test, chi-square test or Fisher's exact test (if counts below five where present) depending on the type of data compared.

Logistic regression analysis was used to explore the associations between the two primary pain outcomes and possible explanatory factors. The two primary outcomes were; (1) moderate to severe pain intensity and (2) pain interfering with daily activities. The possible explanatory factors were chosen a priori from what is acknowledged to be clinically relevant for the pain experience, but also from investigating univariate associations in the present dataset and reported as both crude and mutually adjusted models. The Hosmer-Lemeshow test was used to test for goodness of fit of the logistic regression analysis.

Throughout the analyses, we applied a 5% significance level corresponding to 95% confidence intervals and analyses were performed using Stata statistical software (Stata/IC 16.0).

Results

Ninety-two MM patients participated in the seven rehabilitation courses held at REHPA during September 2017 to May 2019. All participants completed the baseline questionnaire. Moderate to severe pain intensity (mean over 48 h) was reported by 63% ($n=58$) and pain was reported to interfere with daily activities for 80% ($n=74$) of the participants prior to the course. Table 2 shows demographic and

disease related data for all participants, stratified according to age below or ≥ 65 years.

The frequency and severity of symptoms are shown in Figure 1. The prevalence of moderate to severe pain intensity seemed higher among the older participants (72% [95% CI: 58%, 83%]) compared with the younger (49% [95% CI: 31%, 66%]). In both age groups, the degree of pain interfering with daily activities appeared almost equal. The prevalence of elements of neuropathic pain was higher for pain in the feet (33% [95% CI: 23%, 43%]) compared to pain in the hands (13% [95% CI: 7%, 22%]).

Table 3 shows the associations between the two outcomes, pain intensity and pain interfering with daily

activities, with selected explanatory factors. Higher pain intensity was significantly associated with older age and with signs of depression in the adjusted odds-ratios, though only one patient showed signs of severe depression. Pain interfering with daily activities was significantly associated with bone involvement (according to the latest imaging modality performed prior to referral) and signs of depression in the crude odds-ratios. The odds-ratios for both explanatory factors showed stronger association in the adjusted analyses, though the associations were only nearly statistically significant.

From this analysis, the higher prevalence of intense pain among the older participants did not appear to translate into higher odds for pain interfering with the daily activities.

Despite the presence of elements of neuropathic pain (shooting and burning pain) reported by one third of the patients, this type of pain did not appear to be associated with an experience of higher pain intensity or pain interfering with daily activities.

Figure 1 also shows a high prevalence of mild to moderate fatigue. Fatigue was considered a potential explanatory factor, but no associations were found in relation to pain intensity ≥ 4 (OR: 0.88 [95% CI: 0.25–3.11]) or to experiencing pain interfering with daily activities (OR: 3.02 [95% CI: 0.66–15.44]), for that reason fatigue was not included in the adjusted analysis. Years from diagnosis were a priori considered to be a possible explanatory factor for pain, but no associations with pain intensity ≥ 4 (OR: 1.01 [95% CI: 1.00–1.02]) or pain interfering with daily activities (OR: 1.02 [95% CI: 1.00–1.04]) were identified. Experience of one or several relapse episodes were also explored without identification of significant associations with pain intensity ≥ 4 (OR: 1.42 [95% CI: 0.52–3.86]) or pain interfering with daily activities (OR: 1.07 [95% CI: 0.34–3.42]).

Discussion

This study explores the presence and meaning of pain in self-reliant, home-living patients with MM, who experienced a need to participate in a rehabilitation course. Eight out of 10 participants reported pain to interfere with their daily activities at home, and more than half of the course participants reported the pain to be of moderate to severe intensity. Signs of depression were associated with both pain intensity and pain interfering with daily living. Bone involvement showed a trend towards a significant association with pain interfering with daily function, whereas no significant association with pain intensity could be demonstrated. Bone involvement was registered by the

Table 2: Characteristics of the course participants.

	<65 years n=35	≥ 65 years n=57	All n=92
Age (years), median (IQR), [range]	59 (53–62) [33–64]	70 (68–75) [65–85]	67 (61–72) [33–85]
Months from diagnose, median (IQR) [range]	30.5 (16–65) [8–125]	24 (13–45) [5–187]	26 (14–57) [5–187]
Sex, male	12 (34%)	29 (51%)	41 (45%)
Employment status			
1 – Pension	11 (31%)	55 (96%)	66 (72%)
2 – Sick leave	14 (40%)	0	14 (16%)
3 – Flex job	3 (8%)	0	3 (3%)
4 – Unemployed	1 (3%)	0	1 (1%)
5 – Part time work	2 (6%)	0	2 (2%)
6 – Full time work	1 (3%)	1 (2%)	2 (2%)
7 – Other	1 (3%)	0	1 (1%)
Missing	2 (6%)	1 (2%)	3 (3%)
Cohabitation status			
Living alone	9 (26%)	19 (33%)	28 (30%)
Disease status			
Patients without relaps	17 (49%)	25 (44%)	42 (46%)
Patients with ≥ 1 relaps	17 (49%)	31 (54%)	48 (52%)
Missing	1 (2%)	1 (2%)	2 (2%)
Myeloma therapies			
ASCT	31 (89%)	23 (40%)	54 (59%)
Bortezomib	14 (40%)	32 (56%)	46 (50%)
Lenalidomid	28 (80%)	41 (72%)	69 (75%)
Thalidomide	2 (6%)	3 (5%)	5 (5%)
Bone involvement^a			
Yes	23 (66%)	45 (79%)	68 (74%)
No fractures, no osteolytic lesions	12 (34%)	11 (19%)	23 (25%)
Missing	0	1 (2%)	1 (1%)
Charlson comorbidity index			
0	26 (74%)	39 (68%)	65 (71%)
1	4 (11%)	9 (16%)	13 (14%)
≥ 2	5 (14%)	9 (16%)	14 (15%)

^aBone involvement included osteolytic lesions or fractures in the latest performed imaging modality.

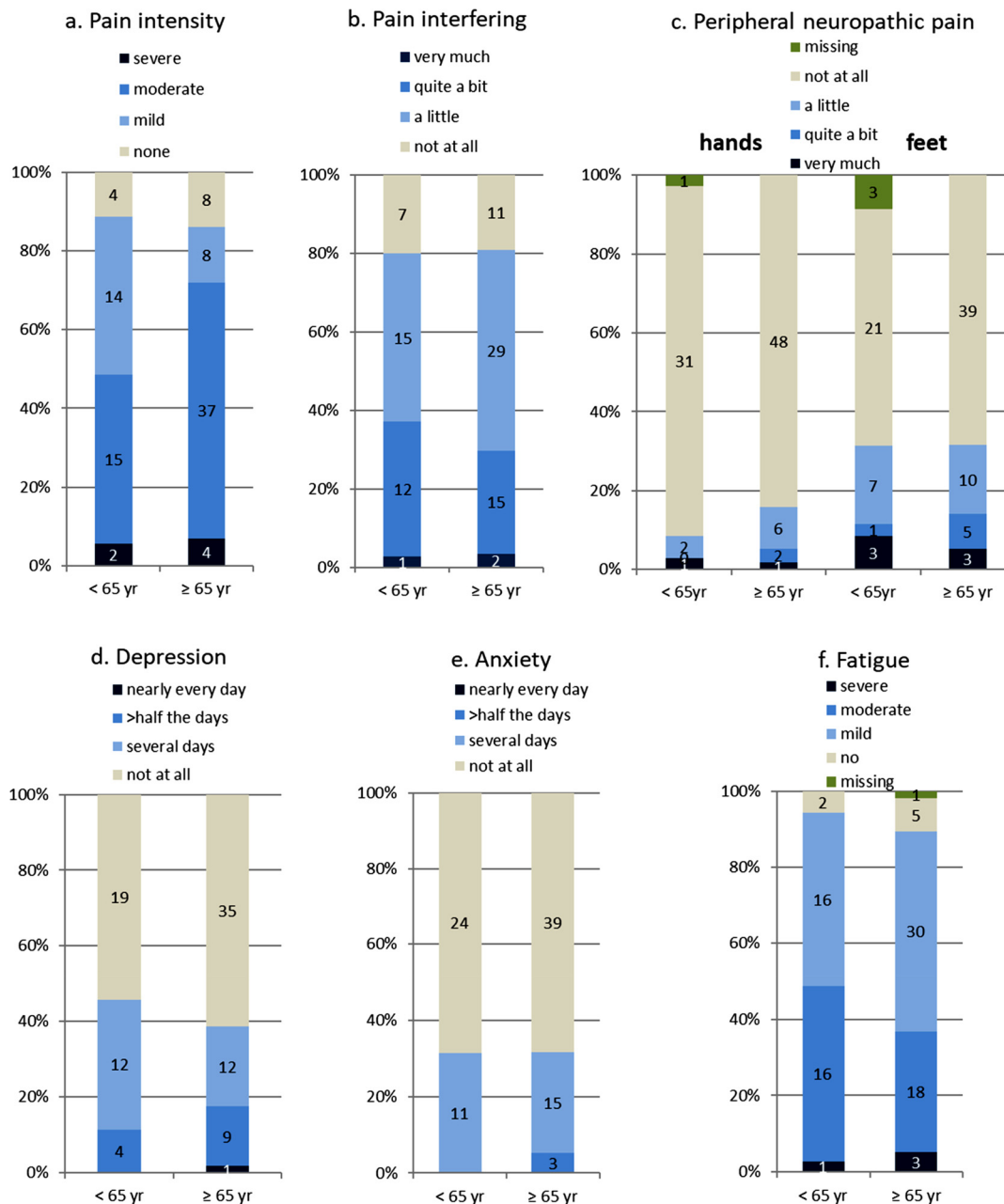


Figure 1: Prevalence and severity of everyday symptoms in participants with MM, according to age group (<65 years: n=35 and ≥65 years: n=57).

The six bar charts show the prevalence and severity of selected symptoms.

referring hematologist on the basis of the latest performed imaging modality, which not necessarily needed to be performed immediately before the referral. Participants in the older age group reported more intense pain compared to the younger group. Contrary to our expectations, the presence of elements of neuropathic pain showed no significant association with pain intensity or pain interference and neither did comorbidity.

Depression is generally well known to be associated with the subjective experience of pain [26], and this has recently been confirmed to be the case for MM patients also [27]. In this regard our results fit well with the concept of total pain [28], recognizing the importance of the interplay between the physiological components of pain and psychosocial, cognitive, cultural and existential conditions and experiences.

Table 3: Associations between the two outcomes; ‘pain intensity’ and ‘pain interfering with daily activities’, and explanatory factors (shown as crude and adjusted ODDs ratios).

	Pain intensity ^a				Pain interfering with daily activities ^b			
	ODDs ratio		ODDs ratio		ODDs ratio		ODDs ratio	
	Crude (95% CI)	p-Value	Adjusted ^c (95% CI)	p-Value	Crude (95% CI)	p-Value	Adjusted ^c (95% CI)	p-Value
Age								
≥65 years (n=57)	2.7 (1.1–6.5)	0.026	3.3 (1.2–9.2)	0.025	1.0 (0.4–3.0)	0.934	0.8 (0.2–2.7)	0.686
<65 years (n=35)	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Bone involvement ^{d,e}								
Yes (n=68)	2.3 (0.9–6.0)	0.093	1.6 (0.5–5.0)	0.397	3.1 (1.0–9.2)	0.042	3.4 (1.0–11.6)	0.051
None (n=23)	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Peripheral neuropathic pain ^e								
Symptoms (n=33)	1.9 (0.7–4.8)	0.181	1.9 (0.7–5.5)	0.217	2.3 (0.7–7.7)	0.174	2.6 (0.7–9.9)	0.156
No symptoms (n=58)	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Depression, PHQ-9								
Mild/moderate/severe (n=38)	4.4 (1.7–11.8)	0.003	4.0 (1.2–13.9)	0.027	4.5 (1.2–16.8)	0.026	5.9 (1.0–36.3)	0.055
None-minimal (n=54)	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Anxiety, GAD-7								
Mild/moderate/severe (n=29)	3.1 (1.1–8.6)	0.032	1.6 (0.4–6.3)	0.517	1.8 (0.5–6.0)	0.348	0.5 (0.1–3.2)	0.496
None-minimal (n=63)	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Charlson comorbidity index								
≥1 Comorbidities (n=27)	2.0 (0.8–5.5)	0.162	2.2 (0.7–6.7)	0.184	1.1 (0.3–3.5)	0.870	1.1 (0.3–3.7)	0.936
No comorbidity (n=65)	1 (ref)		1 (ref)		1 (ref)		1 (ref)	

^a Pain intensity, average during the last 48 h n=58 (63%) with ≥4 on NRS. ^b Pain interfering with daily activities during last week. n=74 (80%) with ≥2 on verbal rating scale. ^c Adjusted for age, bone involvement, peripheral neuropathic pain, depression, anxiety and comorbidity. ^d Bone involvement included osteolytic lesions or fractures in the latest performed imaging modality. ^e One missing in each of the two categories.

The association between pain interfering with daily activities and bone involvement identified in this heterogeneous group of MM patients could be explained by persistent bone pathology despite stable or inactive disease status in the patients [7, 29]. We hypothesize that such bone pathology could cause the same symptom characteristics as reported by patients with degenerative bone diseases, and thereby give rise to similar chronic non-malignant pain conditions. If so, the pain mechanisms in MM patients may fluctuate in parallel with alternating periods of active and inactive disease in the patients’ trajectories. This would imply that MM patients’ pain may change between acute or chronic pain characteristics and malignant or non-malignant pain characteristics. There is an increasing awareness, that cancer patients may suffer from different pain conditions, and there is a call for guidelines to treat non-malignant pain in cancer patients [30]. To our knowledge, it remains to be investigated whether active myeloma cells in the bones are more closely associated with higher pain intensity compared to more chronic pathological changes in the bones.

The association between pain intensity and older age might be explained by age related changes in pain modulation processes as mentioned in a recent meta-analysis

which demonstrated a strong quantitative evidence of an age-related increase in temporal summation and a decline in conditional pain modulation [31]. In contrast, a study of patient reported pain in patients seeking physical therapy for musculoskeletal pain found no association between pain intensity and age [32]. Selection bias cannot be ruled out as an explanation for the age related difference in pain intensity, if pain was a more frequent reason to apply for a rehabilitation course among the older participants compared to the younger. We could not verify this as there were no specific requirements to mention pain conditions in the text from the referring hematologist.

With respect to the prevalence of the MM disease our sample of self-reliant MM patients is large, and only few recent studies of patient reported pain symptoms in the heterogeneous group of MM patients living their everyday lives in the community were identified. These studies concentrate on quality of life and symptoms in a broader sense, and not specifically on pain. In these studies, pain was found to be significantly associated with quality of life [1, 6, 7]. To our knowledge, only Ramsenthaler et al. have investigated a larger cohort of MM patients comparable with ours [4, 6], and quality of life was the outcome in that study. Moderate to overwhelming pain was reported by

around 47% of the participants at baseline in the first study of the cohort [4], and this prevalence was reduced to 40% of the patients at baseline in the follow-up study [6], while moderate to overwhelming pain was reported by 63% of the participants in our study. One explanation could be that the MM patients in our sample felt a need for rehabilitation, while no such need was addressed in the other study. In another recent study of MM patients measuring the impact of autologous stem-cell transplantation (n=89) or non-transplantation consolidation (n=85) [7] on patient reported symptoms, pain was shown to interfere with daily living for up to two years post transplantation. However, only 46 patients in all completed the two-year questionnaires, and the prevalence of pain was not reported in the paper.

Strengths and limitations

Our study results cannot be directly extrapolated to cover the whole heterogeneous group of MM patients living their daily lives in the community. On one hand, the resulting prevalence of pain may be too high, as our sample consists of MM patients, who experienced a need for rehabilitation. On the other hand, due to the inclusion criteria, we only included MM patients, who were self-reliant and ready to comply with the rehabilitation program. This could imply that our sample's pain prevalence was lower compared to MM patients' general prevalence when living at home. The use of PRO data in the MM REHPA courses was not planned with the sole purpose of studying pain and pain treatment, and it is a limitation that the patients' histories of pharmacological pain treatment were not collected and included in our analyses. However, due to the sample size and the systematically collected PRO-data the analyses have revealed a robust picture of pain as a prominent problem in this heterogeneous group of MM patients.

In conclusion, we find it thought-provoking that so large a proportion of MM patients with inactive or stable disease experience moderate to severe pain intensity and that an even larger proportion experience that pain interfere with their daily activities. Having the MM pathology and the long disease trajectories in mind, the phenotypes of the MM patients' pain problems may well change in accordance with periods of active, stable or inactive MM disease. This may challenge the strategy for pain treatment if some periods are characterized by cancer-related pain due to disease activity, while other periods are dominated by treatment-related pain or chronic non-malignant pain due to persistent bone pathology. Furthermore, the experience of pain can be significantly influenced by the

suffering caused by the experience of living with an incurable cancer. So, management of MM patients' pain conditions demand receptiveness, knowledge, systematic pain assessment and a holistic approach among the professionals in the health care system [33].

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Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Conflict of interest: EJ, RFL, SM and LJ declare no conflicts of interest.

Informed consent: Informed consent has been obtained from all individuals included in this study.

Ethical approval: The study was registered at the Danish Data Protection Agency by number 19/19123. No approval from the Danish Ethic Committee was necessary, since no invasive elements were included and since the rehabilitation courses in REHPA are established as a public rehabilitation service in Denmark. The study was performed in accordance with the tenets of the Helsinki Declaration.

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