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ORIGINAL ARTICLE

Health-related quality of life in patients with multiple myeloma participating in a multidisciplinary rehabilitation program

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Abstract

Patients with multiple myeloma (MM) report high symptom burden and functional disabilities resulting in impaired health-related quality of life (HRQoL). Effective evidence-based rehabilitation guidelines are needed for patients with MM to improve HRQoL. The primary aim of this study was to investigate HRQoL in patients with rehabilitation needs living their everyday life. Patients with MM in remission attended a 12-week multidisciplinary rehabilitation program including a 5-day residential course, home-based exercise and a 2-day follow-up course. The patients were referred by the treating haematologist and completed a booklet of validated HRQoL questionnaires at baseline and before arriving for the 2-day follow-up course. The proportion of participants with moderate to severe symptoms and functional problems were assessed at the two time points and multivariate logistic regression was used to investigate explaining factors of impaired HRQoL at baseline. Ninety-two patients participated with a follow-up compliance rate of 90%. Median age was 67 years and median time since diagnosis was 26 months (ranged 5 months to 15.6 years). The most frequently reported symptoms were global quality of life, role functioning, fatigue, pain, peripheral neuropathy and physical functioning. Pain and fatigue were both highly coherent with impairment in physical functioning and those two symptoms explained most HRQoL impairments. Overall, the participants reported no change in HRQoL after the 12-week rehabilitation program. The study supports the need for an evidence-based guideline for rehabilitation and palliative care to patients with MM in remission living their everyday life.

Keywords Multiple myeloma · Health-related quality of life · Rehabilitation and patient-reported outcomes

Introduction

Multiple myeloma (MM) is a chronic malignancy of the plasma cells in the bone marrow and the second most common haematological malignancy with a median age at diagnosis of 70 years [1]. The median overall survival for patients with MM has improved over the last decade and is still improving due to therapeutic enhancements [2–4]. Patients with MM experience variable morbidity caused by bone destruction/fractures, renal dysfunction, bone marrow failure, high infection rates and potential physical disability [5]. Eighty percent of patients with MM develop osteolytic skeletal lesions resulting in bone pain and risk of pathologic fractures [6]. The most prevalent symptoms across the disease pattern from

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diagnosis to advanced MM disease stage are fatigue, pain, insomnia and peripheral neuropathy resulting in decreased physical, cognitive and role functioning [7–11]. In addition, one-quarter of MM patients report symptoms of anxiety and depression [12–16]. As a result, patients with MM report impaired health-related quality of life (HRQoL).

However, most of the existing knowledge on HRQoL has emerged from studies in hospital settings with MM patients during anti-myeloma treatments [9, 17]. As the disease trajectories of many patients with MM have changed in direction of a more chronic pattern, with stable or inactive disease periods, attention is brought to the quality of everyday living with MM. The disease and the treatment of disease might leave the MM patients with symptoms and problems that call for professional help and support. Thus, the field for rehabilitation and palliative care need to know what is on stake in the everyday living with MM, to provide healthcare services targeting the symptoms and problems most prevalent and disabling in this group of patients.

The Danish Knowledge Centre for Rehabilitation and Palliative Care (REHPA) is a national knowledge centre that contributes to the development of evidence-based practices focusing on rehabilitation and palliative care to patients with life-threatening diseases [18]. REHPA runs multidisciplinary rehabilitation programs, covering aspects of physical, psychological, social and existential needs [18, 19]. The primary aim of this study was to investigate HRQoL among MM patients with rehabilitation needs outside the hospital setting participating in a 12-week multidisciplinary rehabilitation program.

Methods

The study was an observational study of HRQoL in self-reliant patients with MM with rehabilitation needs living their everyday life outside the hospital setting. The patients attended a 12-week rehabilitation program organized and conducted by a multidisciplinary team which included medical doctors (haematologist and oncologist), physiotherapists, psychologists, nurses, social workers, data managers and patient representatives. The course professionals participated in an educational session prior to study start, learning about the MM disease, treatment and the possible consequences for patients with MM and their ability to perform physical activities.

Participants

Participants were recruited from all 10 departments of Haematology in Denmark, all joining the collaboration of Danish Myeloma Study Group and REHPA. Inclusion criteria were a diagnosis of MM according to the International Myeloma Working Group (IMWG) criteria [5] and needs for rehabilitation due to the disease or its treatment and the patients being self-reliant. The myeloma disease should be in remission defined as minimal response or better according to the IMWG criteria for response [20] after primary or relapse treatment. Exclusion criteria were inability to participate for mental or physical reasons or inability to speak and understand Danish. All participation criteria are listed in the online supplementary appendix 1. The treating haematologist referred eligible patients to REHPA by completing a referral form with the patients' contact information and the patients' rehabilitation needs. Clinicians at REHPA reviewed the referral form, contacted the patients and invited the patients to participate in the rehabilitation program. In case the allocated 5-day residential course was not filled up, the participants were allowed to invite a relative. Data from the participating relatives are not included in this analysis.

The rehabilitation program

The rehabilitation program was divided into three phases. Phase 1 was a 5-day residential course located at the REPHA rehabilitation centre in Denmark in groups of maximum 20 participants. The multidisciplinary rehabilitation program included patient education in smaller groups taught by a haematologist (the MM disease and its treatment), a psychologist (psychological reactions), a priest (spirituality), a dietitian (diet), physiotherapists (physical activity), a pain specialist (pain and pain treatment), sessions with individual physical testing, individual conversations with a professional, mindfulness, massages, walk-and-talk and singing. Phase 2 was a 12-week home program including individual adjusted physical training and working with individual rehabilitation goals, and phase 3 was a 2-days' residential follow-up course at REHPA, scheduled 12-weeks after phase 1, including physical retesting and more patient education. Participation was free of charge. The 5-day as well as the 2-day follow-up schedule is provided in the online supplementary appendix 2 and 3.

Health-related quality of life assessment

Prior to phase 1 and prior to phase 3, the participants completed a booklet of validated HRQoL questionnaires. The booklet was either mailed to the patients' home addresses for completion on paper or electronically by a link sent to the patient's email. Participants, who did not complete the questionnaires prior to the residential stays, were asked to complete the questionnaire at the start of the stays.

We choose to focus our analysis on 12 patient-reported HRQoL symptoms and functional problems frequently reported by patients with MM, in published cross-sectional HRQoL studies. The symptoms are fatigue [7–9, 13, 21–25], pain [7–9, 13, 21–26], insomnia [7, 8, 24, 25], peripheral neuropathy [8, 9, 13, 26], dyspnoea [9, 23, 24], anxiety [7, 12] and depression [7, 12]. The functional problems are physical [7, 21, 22, 24, 27], role [7, 21, 22, 24], emotional [7, 21, 25] and cognitive functioning [9, 24, 25] and global QoL [21, 23]. The four validated HRQoL questionnaires used to assess the symptom and functional domains of interest are presented in Table 1.

We used the 18-item sum score to estimate the symptom burden from peripheral neuropathy [32]. Association has been found between peripheral neuropathy adverse events grading reported by clinicians and the European Organization for Research and Treatment of Cancer Quality of life Questionnaire (EORTC QLQ) chemotherapy-induced peripheral neuropathy (CIPN20) scores [34]. In contrast, the EORTC QLQ-CIPN20 subscale structure has shown low psychometric properties to assess peripheral neuropathy and the 18-item sum score has been tested and found more reliable, valid and sensible [32, 35, 36]. Information on loneliness was reported by the participants at the Three-Item Loneliness scale (T-ILS), which is scored from 3 to 9 [37]. A high score means high degree of loneliness.

Grading of symptoms and functional problems and changes

Grading of severe, moderate and mild symptoms and functional problems for each patient assessed by EORTC QLQ-C30 was adapted from previous research in patients with haematological malignancies and MM [7, 24]. No consensus of grading or severity of peripheral neuropathy based on the 18-item EORTC QLQ-CIPN20 sum score has been developed. Based on sensory and motor peripheral neuropathy mean sum scores from Kieffer et al. [32], we graded a sum score of 16.2–19.7 points to be mild, 19.8–32.6 points to be moderate and ≥ 32.7 points to be severe peripheral neuropathy. The number of patients having anxiety was identified as reported ≥ 10 points on the Generalized Anxiety Disorder (GAD-7) scale and likewise the number of patients having depression was identified as reported ≥ 10 points on the Patient Health Questionnaire (PHG-9) scale [38, 39]. Participants scoring 6 or above on the T-ILS were defined as lonely [40]. Further information of grading of symptoms and functional problems are provided in the online supplementary appendix 4.

To investigate the number of participants with either an improvement or deterioration in a HRQoL domain, changes in the participants' symptoms and function domains before and after the 12-week rehabilitation program were evaluated. Therefore, we defined *a responder* and calculated the number of responders [41]. A responder of a symptom domain was a participant that had reported a symptom reduction either from severe to moderate *or* from moderate to mild symptoms. In the same way, a responder in a functional domain was defined as a participant that reported improvement in a functional domain from either severe to moderate *or* from moderate to mild functional problems. Further information can be found in the supplementary appendix 5.

Table 1 The 12 investigated symptom and functional domains and the four health-related quality of life questionnaires

Symptom and functional domains	Health-related quality of life questionnaires	Description and scoring
Global quality of life Physical functioning Role functioning Emotional functioning Cognitive functioning Fatigue Pain Dyspnoea Insomnia	EORTC QLQ-C30 [27]	A 30-item, 15 domain cancer-specific questionnaire validated in patients with multiple myeloma [28] The answers were scored from 0 to 100 [29] For the functional domains, a high score means low degree of problems, and for the symptom domains, a high score means high degree of symptoms
Peripheral neuropathy	EORTC QLQ-CIPN20 [30]	A 20-item questionnaire to assess peripheral neuropathy The 18-item sum score was used experienced by the participants [31] The answers to the 18 questions were scored from 0 to 100 [27] A high score means higher degree of peripheral neuropathy
Depression	The Patient Health Questionnaire (PHQ-9) [32]	A 9-item questionnaire to assess symptoms of depression The answers to the questions are added to a total score between zero and 27 points [32]. A high score means more symptoms of depression
Anxiety	The Generalized Anxiety Disorder (GAD-7) [33]	A 7-item questionnaire to assess symptoms of anxiety The answers to the questions are added to a total score between zero and 21 points [33]. A high score means more symptoms of anxiety

EORTC QLQ-C30 European Organization for Research and Treatment of Cancer Quality of life Questionnaire C30, *EORTC QLQ-CIPN20* European Organization for Research and Treatment of Cancer Quality of life Questionnaire Chemotherapy-induced peripheral neuropathy

Clinical data collection

At the referral form, the haematologist reported information of rehabilitation needs, comorbidities according to the Charlson Comorbidity Index [42] and number of and type of previously administered anti-myeloma drugs in previous lines of treatments. In addition, the haematologist completed a systematic skeleton risk assessment based on the latest diagnostic imaging modality. The result of this assessment together with the information of the patient's level of pain in femoral bone, humeral bone, pelvis, lumbar spine, thoracic spine and/or ribs was used to determine whether the patient had substantial skeletal involvement with restrictions in physical testing and exercise [43]. During phase 1, the training program was adjusted according to the individual participant based on the skeleton risk assessment and the results from physical testing. Self-assessed Activity of Daily Living (ADL) and Instrumental Activity of Daily Living (IADL) were obtained during phase 1 and used for the calculation of the IMWG Myeloma Frailty score [44–46].

Statistical methods

Patient characteristics and baseline mean and median scores were presented using descriptive statistics. Associations between symptoms or problems and possible explanatory factors were explored by univariate and multivariate logistic regressions. The possible explanatory factors were chosen a priori from acknowledged risk factors and from investigating univariate associations in the present dataset. We used substantial skeletal involvement, moderate/severe pain, fatigue, loneliness, depression, anxiety and age and gender as possible explanatory factors for the univariate and multivariate logistic regression analysis. To investigate whether the moderate to severe symptoms and functional problems come in clusters, an analysis was performed to investigate coherent moderate to severe symptoms and problems by determining pairwise concordance percentages between symptoms and problems.

For the longitudinal data on changes in HRQoL scores, only participants who filled out both the baseline and follow-up questionnaires were included in analysis. Changes in symptoms and problems were explored for each participant and presented with frequency and percentage of participants experiencing improvement, deterioration or no change in the symptoms of interest, respectively. Improvements would thus be changes crossing above, respectively, below the cut-offs and vice versa in case of deterioration. No change meant staying either above or below the cut-offs.

Confidence intervals with 95% significance level were reported and the analyses were performed using Stata statistical software.

Results

Participants and compliance

Between September 2017 and May 2019, 92 MM patients participated in one of the seven multidisciplinary rehabilitation programs provided by REHPA. All participants completed the baseline questionnaires and 83 participants completed the follow-up questionnaires (90% response rate) (Fig. 1). Seventy-one participated in the 2-day follow-up course (phase 3). Nine patients did not participate in the 2-day follow-up course; six of them were due to disease-related causes, and three of them since they had to discontinue the 5-day residential course for physical or mental reasons. The median age of the participants was 67 years and time since diagnoses ranged from 5 months to 15.6 years. The majority (71%) of patients were "fit" according to IMWG Myeloma Frailty score, 52% of the participants had experienced their first relapse and 59% were treated with high-dose therapy in relation to stem cell support previously. Baseline demographic and HRQoL scores are presented in Table 2 and the online supplementary appendix 6.

Moderate and severe HRQoL problems

The six most frequently reported moderate to severe symptoms or functional problems were global QoL (51%), role functioning (51%), fatigue (50%), pain (49%), peripheral neuropathy (44%) and physical functioning (42%). The number of participants and percentages of all participants are presented in Table 3. Physical functioning was the most coherent, which was to patients with moderate to severe symptoms of fatigue (82%) and pain (77%). The percentage of participants with coherent moderate to severe symptoms and problems of the six most frequently reported are presented in Fig. 2. Only

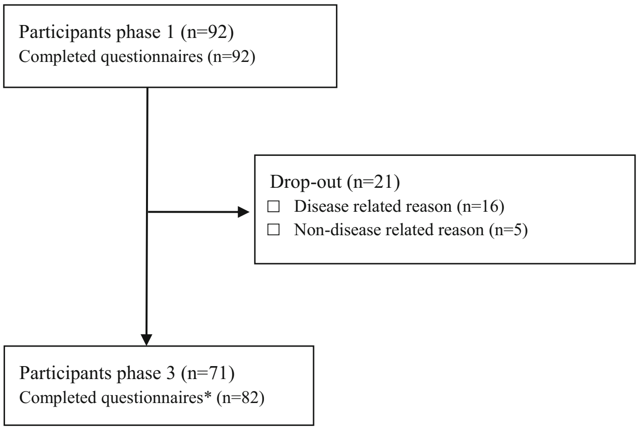

Fig. 1 Consort flow diagram of participating patients in phase 1 and 3. *The questionnaires were completed by the patients before arriving at phase 3. Due to late cancelling of participation in phase 3, some questionnaires were completed by patients that was prevented when the course as held

Table 2 Patient characteristics for the participating patients

	Multiple myeloma patients *N* = 92
Age, median (IQR), [range]	67 (61–72) [33–85]
Male sex, *N* (%)	41 (44.6%)
Months from diagnosis, median, (IQR]), range	26 (14–57) [5–187]
Course of disease	
Patients without relapse	42 (46%)
Patients with ≥ 1 relapse	48 (52%)
Missing	2 (2%)
Previously or ongoing anti-myeloma therapies, *N* (%)	
ASCT	54 (59%)
Bortezomib containing	46 (50%)
Lenalidomide containing	69 (75%)
Thalidomide containing	5 (5%)
Charlson Comorbidity Index, *N* (%)	
0	65 (71%)
1	13 (14%)
≥ 2	14 (15%)
IMWG Myeloma Frailty score, *N* (%)	
Fit	65 (71%)
Intermediate fitness	15 (16%)
Frail	7 (8%)
Missing	5 (6%)
Skeletal fractures or osteolytic lesions, *N* (%)	
Yes	68 (74%)
Spine	40 (44%)
Pelvis	36 (39%)
Humerus	17 (19%)
Femur	18 (20%)
No fractures or osteolytic lesions	23 (25%)
Missing	1 (1%)

N number of patients, *IQR* interquartile range, *ASCT* autologous stem cell transplantation, *IMWG* International Myeloma Working Group

eight (8.7%) participants did not experience any moderate or severe symptoms or functional problems of the 12 domains of interest (Fig. 3). A median of three (range 0–10, interquartile range 1–6) moderate or severe symptoms or functional problems were reported (not displayed in figures or tables).

In the multivariate analyses testing for possible explaining factors, pain was a statistically significant explaining factor of problems in global QoL, physical and role functioning and fatigue. This means that patients with moderate or severe pain have 4.1 higher risk of moderate or severe global QoL impairment, 3.5 higher risk of physical and 6.3 higher risk of role functional impairments and 4.5 higher risk of experiencing moderate or severe fatigue compared to patients with mild or no pain. Fatigue was a statistically significant explaining factor of problems in physical functioning, pain and dyspnoea. Substantial skeletal involvement was an associated factor for reporting of moderate to severe problems in physical functioning. Loneliness and depression were associated with problems in emotional functioning and loneliness was associated with moderate to severe symptoms of insomnia. Age had no influence, but for gender, we found that males had a statistical significant higher odds ratio of 4.1 (1.3–13.3) for reporting moderate to severe problems in global QoL. Peripheral neuropathy could not be explained by any of the investigated factors. The results of the multivariate logistic regression analysis are presented in Table 4 and the results of the univariate logistic regression analysis are presented in the online supplementary appendix 7.

Change in symptoms and functional problems

The change in symptoms and functional problems from baseline to 12-week follow-up are shown in Table 5, together with the number of patients who reported either improvement, deterioration or no change. The majority of participants reported no change compared to baseline in the investigated domains and none of the changes were statistically significant. The most striking difference was seen for pain, where the proportion was reduced from 49 to 36% corresponding to 19 participants reported improvement. Moreover, eight participants reported increasing pain from baseline to follow-up.

Discussion

In this study, we have investigated HRQoL impairments in patients with MM in remission with rehabilitation needs and found that almost all participants had moderate to severe symptoms or problems. Only few studies have investigated HRQoL issues in MM patients outside the hospital setting. In our study, patients with substantial skeletal involvement were included, and with 92 participants it represents one of the largest cohorts studied. Patients referred to the course were self-reliant and mainly fit MM patients living their everyday life and had less comorbidity and a lower median age than the general population of patients with MM [1, 47]. Still, around half of the participants at the rehabilitation course had moderate to severe issues in global QoL, physical and role functioning, fatigue, pain and/or in relation to peripheral neuropathy. The observational design does not allow for conclusions with regard to the rehabilitation program's effect on HRQoL. However, we find that the affected HRQoL associated with the participants' symptoms and problems provides a strong argument for MM patients living their everyday life to engage in rehabilitation initiatives. The multidisciplinary rehabilitation program for MM patients outside the hospital setting was found to be feasible and with highly compliant participants.

Table 3 Number of participants with moderate or severe symptoms or functional problems of all participant ($N = 92$)

	Moderate symptoms and problems *N* (%)	Severe symptoms and problems *N* (%)	Moderate or severe symptoms or problems *N* (%)
EORTC QLQ-C30			
Global quality of life	43 (47%)	4 (4%)	**47 (51%)**
Physical functioning	38 (41%)	1 (1%)	**39 (42%)**
Role functioning	36 (40%)	11 (12%)	**47 (51%)**
Emotional functioning	12 (13%)	0	12 (13%)
Cognitive functioning	12 (13%)	1 (1%)	13 (14%)
Fatigue	36 (39%)	10 (11%)	**46 (50%)**
Pain	39 (42%)	6 (7%)	**45 (49%)**
Dyspnoea	11 (12%)	1 (1%)	12 (13%)
Insomnia	12 (13%)	5 (5%)	17 (18%)
EORTC QLQ-CIPN20			
Peripheral neuropathy	21 (22.8%)	19 (20.7%)	**40 (44%)**
Depression (PHQ-9)			
Depression	13 (13%)	1 (1%)	14 (14%)
Anxiety (GAD-7)			
Anxiety	3 (3%)	0	3 (3%)

EORTC QLQ-C30 European Organization for Research and Treatment of Cancer Quality of life Questionnaire C30, *EORTC QLQ-CIPN20* European Organization for Research and Treatment of Cancer Quality of life Questionnaire Chemotherapy-induced peripheral neuropathy, *PHQ-9* The Patient Health Questionnarie-9, *GAD-7* The Generalized Anxiety Disorder questionnaire

The six most frequent reported moderate to severe symptoms or problems are presented in bold

Our findings of MM patients impaired in HRQoL are in line with the results from earlier published cross-sectional studies. However, here we document the problems in a cohort of self-reliant MM patients in remission. This finding is novel and interesting since the investigated cohort of patients is in a period where the disease is under control and where the patients are expected to get on with their lives. In a previous study, MM patients were shown to have a higher risk of disability pension compared to patients with other haematological malignancies [48]. That study was not designed to answer the question *why*, but with the increasing survival time for MM it is of importance to investigate whether rehabilitation programs could prevent some patients from losing their employment.

MM patients' disease trajectories differ between individuals, and the patients often receive multiple lines of anti-myeloma therapies with different drug combinations with or without autologous stem cell transplantation [49]. Our findings underline the complexity of MM patients' disease pathways and HRQoL challenges. Based on the cluster mapping and association analyses, the symptoms of fatigue and pain seem to be interrelated and placed in the centre of a cascade of physical problems. As a trigger of this cascade, a significant association between participants with physical problems and substantial skeletal involvement was found. Based on the established evidence from solid cancer patients, fatigue and pain are potential modifiable symptoms with rehabilitation programs [50, 51]. In addition, our findings highlight the importance of prevention of osteolytic lesions by early detection of disease progression and sufficient treatment of, e.g. vertebral compression fractures [52]. The finding of osteolytic bone lesions being a catalyst of more symptoms and functional impairments among MM patients in remission might suggest that MM patients are additionally challenged in their remission periods compared to other cancer patients with solid tumours and bone metastases. The complexity of these patients' heterogeneous and often lengthy trajectories loaded with symptoms and problems influencing their HRQoL calls for a separate evidence-based guideline for rehabilitation and palliative care for patients with MM.

In general, the best documented intervention on cancer-related fatigue is physical exercise [53]. We targeted the intervention towards a personalized exercise-based intervention but found no change in the investigated HRQoL in the investigated cohort of patients. A possible hypothesis for this observation could be that the participants underwent a response shift effect. Responses shift is defined as a change in one's self-evaluation of a target construct and has been found as psychological consequence of rehabilitation interventions in earlier studies [54–56]. HRQoL is a dynamic concept and in response shift theory, the patients might have adapted to an impaired HRQoL before starting the rehabilitation program.

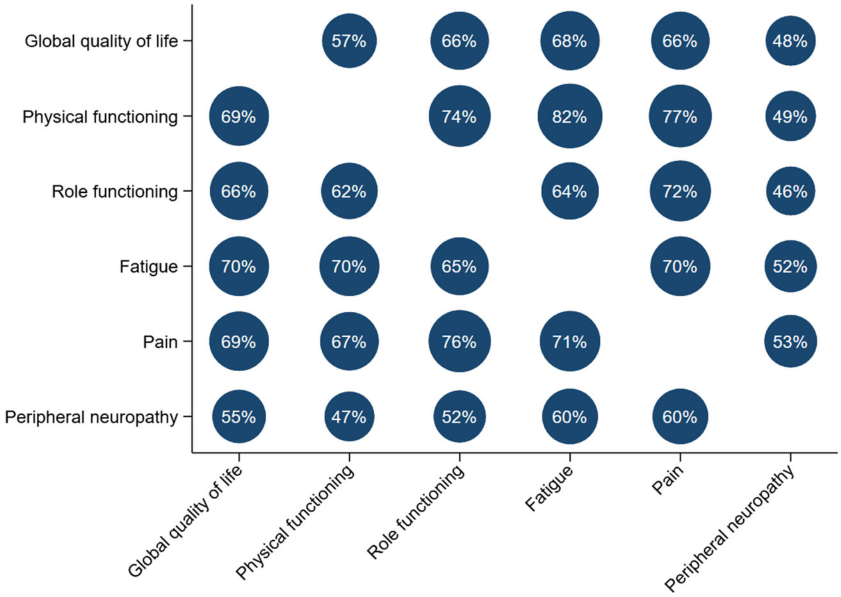

Fig. 2 The proportion of participants with cluster symptoms and problems. For the six most frequent reported moderate to severe symptoms and functional problems, the percentage of participants with coherent moderate to severe symptoms and functional problems in the other five domains are presented in this figure. In the example, for the participants experiencing moderate to severe problems in global quality of life, a proportion of 57% also experienced moderate to severe problems in physical functioning, whereas for the participants experiencing moderate to severe problems in physical functioning, a proportion of 69% also experienced moderate to severe problems in global quality of life

As a result of the rehabilitation program, some participants might have experienced that they can increase the expectations towards their HRQoL levels leading to underestimation of the change in HRQoL before and after rehabilitation [57–59]. Self-management and learning to cope with a chronic disease is a desired goal of a rehabilitation intervention [60]. The result of increased coping among the participant might lead to underestimation of the effect of the rehabilitation intervention on HRQoL [61]. The role of response shift in rehabilitation needs further investigation [62].

Strengths and limitations

The strength of this study is the systematic collection of symptoms and functional problems based on validated questionnaires in a large cohort of self-reliant MM patients. The cohort

Fig. 3 Number of participants reporting zero to ten moderate to severe symptoms and problems of the 12 domains investigated

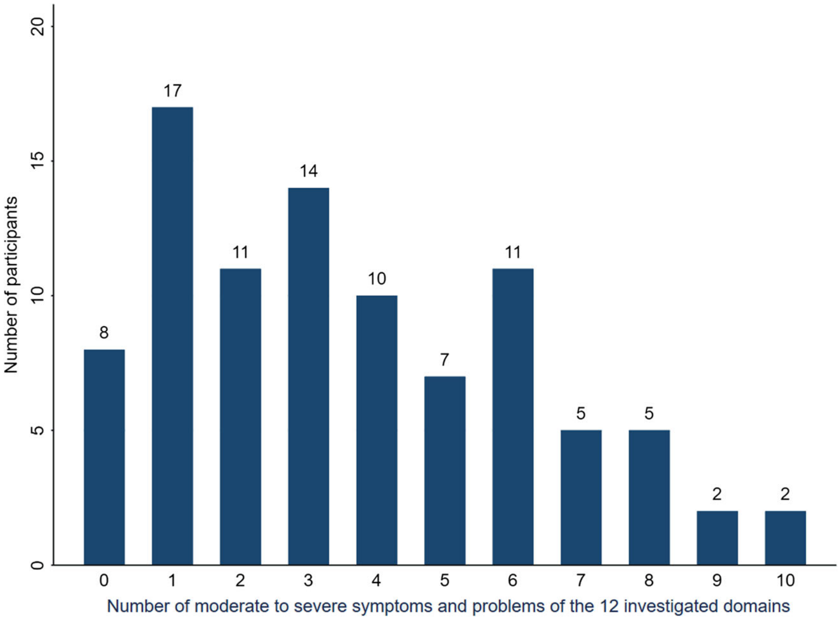

Table 4 Baseline associations between participants with severe and moderate health-related quality of life outcomes and explanatory variables using multivariate logistic regression analysis

	Global quality of life (n = 47)	Physical functioning (n = 39)	Role functioning (n = 47)	Emotional functioning (n = 12)	Cognitive functioning (n = 13)	Fatigue (n = 46)	Pain (n = 45)	Insomnia (n = 17)	Dyspnoea (n = 12)	Peripheral neuropathy (n = 40)	Depression (n = 14)
Explanatory variables	Odds ratio (95% CI)[1]										
Age											
≥ 65 years (n = 57)	**0.3 (0.1–0.8)**	1.0 (0.3–3.6)	0.9 (0.3–2.5)	0.4 (0.0–3.0)	0.9 (0.2–3.7)	0.6 (0.2–1.9)	1.6 (0.6–4.6)	0.7 (0.2–2.4)	0.6 (0.1–2.8)	2.1 (0.8–5.5)	1.3 (0.3–6.2)
Gender											
Male (n = 41)	**3.1 (1.1–9.1)**	1.7 (0.5–5.6)	1.8 (0.6–4.9)	0.9 (1.1–6.4)	0.6 (0.2–2.3)	0.8 (0.3–2.4)	1.2 (0.4–3.2)	2.0 (0.6–7.0)	1.8 (0.4–8.1)	1.1 (0.4–2.8)	1.5 (0.3–7.3)
Substantial skeletal involvement[2]	1.5 (0.5–4.7)	**5.1 (1.4–18.7)**	1.3 (0.5–3.7)	0.9 (0.1–6.6)	1.0 (0.2–3.9)	1.8 (0.6–5.4)	2.4 (0.9–6.6)	1.3 (0.4–4.7)	2.3 (0.5–11.0)	0.9 (0.3–2.3)	1.1 (0.2–5.6)
Yes (n = 46)											
Pain											
Moderate/severe (n = 45)	**4.1 (1.3–12.8)**	**3.5 (1.0–11.9)**	**6.3 (2.1–18.3)**	2.9 (0.1–58.0)	1.4 (0.3–6.0)	**4.5 (1.5–13.1)**	—	1.8 (0.4–7.2)	0.7 (0.1–3.3)	1.8 (0.7–4.8)	5.4 (0.6–50.1)
Fatigue											
Moderate/severe (n = 46)	2.4 (0.8–7.5)	**5.1 (1.5–17.7)**	1.2 (0.4–3.7)	1.1 (0.0–36.5)	2.8 (0.6–14.4)	—	**4.6 (1.6–13.2)**	0.6 (0.1–2.9)	**14.0 (1.5–133.9)**	1.5 (0.5–4.2)	Not estimable[5]
Loneliness											
Lonely (n = 17)	2.2 (0.5–9.2)	2.4 (0.5–12.2)	1.8 (0.5–7.3)	**13.6 (1.1–168.4)**	0.2 (0.2–2.0)	3.0 (0.7–12.3)	0.9 (0.2–3.5)	**5.3 (1.2–23.5)**	1.0 (0.2–6.1)	0.7 (0.2–2.7)	0.7 (0.1–4.7)
Depression											
Moderate/severe (n = 14)	3.8 (0.4–38.3)	Not estimable[3]	1.8 (0.3–11.3)	**42.0 (2.8–635.0)**	3.5 (0.6–19.3)	Not estimable[5]	4.9 (0.5–44.9)	3.7 (0.7–20.9)	0.8 (0.1–5.4)	2.4 (0.5–11.6)	—
Anxiety											
Moderate/severe (n = 3)	0.3 (0.0–7.4)	Not estimable[4]	Not estimable[4]	2.9 (0.1–72.2)	0.9 (0.0–19.3)	Not estimable[4]	0.1 (0.0–3.1)	Not estimable[4]	Not estimable[4]	0.8 (0.0–14.3)	Not estimable[4]

The number of patients with moderate and severe symptoms of anxiety was too small to perform the multivariate logistic regression analysis

Odds ratios in bold; p value of < 0.05

[1] An odds ratio above 1 reflects more functional problems or more symptoms, except for age and gender

[2] Substantial: Skeletal involvement with impact on and possibly limiting physical activity and training

[3] Not estimable because 12 out of 14 patients with depression symptoms also had moderate/severe physical function problems

[4] Not estimable because all 3 patients with anxiety symptoms also had moderate/severe physical and role function problems and moderate to severe fatigue, insomnia, dyspnoea and depression

[5] Not estimable because all 14 patients with depression symptoms also had moderate/severe fatigue symptoms

Table 5 Number of participants experiencing moderate/severe symptoms and problems at baseline and follow-up and number of participants experiencing improvement, deterioration or no change for the 12 domains of interest from EORTC QLQ-C30, EORTC QLQ-CIPN20, PHG-9 and GAD-7 questionnaires

	Number of participants with moderate/severe symptoms and problems at baseline (%)	Number of participants with moderate/severe symptoms and problems at follow-up (%)	Number of participants improving* (%)	Number of participants deteriorating** (%)	Number of participations with no change (%)
EORTC QLQ-C30					
Global QoL (=81)	42 (52%)	40 (49%)	10 (12%)	8 (10%)	63 (78%)
Physical functioning ($n = 82$)	34 (42%)	31 (38%)	10 (12%)	7 (9%)	65 (79%)
Role functioning ($n = 83$)	42 (51%)	37 (45%)	14 (17%)	9 (11%)	60 (72%)
Emotional functioning ($n = 83$)	10 (12%)	16 (19%)	5 (6%)	11 (13%)	67 (81%)
Cognitive functioning ($n = 83$)	13 (16%)	16 (19%)	7 (8%)	10 (12%)	66 (80%)
Fatigue ($n = 83$)	41 (49%)	39 (47%)	12 (15%)	10 (12%)	61 (73%)
Pain ($n = 83$)	41 (49%)	30 (36%)	19 (23%)	8 (10%)	56 (67%)
Dyspnoea ($n = 82$)	11 (13%)	10 (12%)	9 (11%)	8 (10%)	65 (79%)
Insomnia ($n = 81$)	16 (20%)	21 (26%)	5 (6%)	10 (12%)	66 (82%)
EORTC QLQ-CIPN20					
Peripheral neuropathy ($n = 69$)	28 (41%)	27 (39%)	6 (9%)	5 (7%)	58 (84%)
Depression					
PHQ-9 ($n = 82$)	12 (15%)	13 (16%)	5 (6%)	6 (7%)	71 (87%)
Anxiety					
GAD-7 ($n = 83$)	2 (2%)	6 (7%)	0	4 (5%)	79 (95%)

EORTC QLQ-C30 European Organization for Research and Treatment of Cancer Quality of life Questionnaire, *n* number of patients

*Improving: Reduction from severe to moderate symptoms/functional problems or a reduction from moderate to mild symptoms/functional problems

**Deteriorating: Increase from mild to moderate symptoms/functional problems or an increase from moderate to severe symptoms/functional problems of patients in remission is relatively heterogeneous in terms of stages of disease. A strength of the study is the compliance rate of 90%, which is acceptable for this group of cancer patients with high risk of disease-related complications of infections and disease progression. An additional strength of this study is that patients with skeletal lesions were included and participated on equal terms with those without bone involvement. This has been a limitation in earlier exercise intervention studies including patients with MM [63].

In light of our findings of skeletal lesions being a trigger of physical impairment, pain and fatigue, information regarding applied prevention and treatment strategies of skeletal lesions would have been relevant. All patients were treated according to the Danish Myeloma Study Group Guidelines for Diagnosis and Treatment of Multiple Myeloma, where it is recommended that all newly diagnosed treatment-demanding patients are treated with bisphosphonate every fourth week for 2 years and reinitiation during treatment for progressive disease or relapse. In addition, local radiotherapy is highlighted as an important treatment for acute pain relief or prevention of fracture as complication to an osteolytic lesion [64]. However, previously administered bisphosphonate, radiotherapy and current use of analgesic therapies were not systematically collected as part of the study.

The proportion of patients in our study with an IWMG frailty score of “fit” and patients without comorbidities is higher in our cohort than the general MM population [47, 65]. This could be caused by selection bias due to the inclusion criteria of being self-reliant. When comparing our findings of psychological distress symptoms to previous findings, we learned that patients with symptoms of depression and anxiety are underrepresented in the investigated cohort [12]. This might have caused underestimation of the results of symptom and functional burden since anxiety and depression symptoms have been found as predictors for poor or deterioration of QoL in patients with MM [13]. Therefore, the multidisciplinary rehabilitation program must to some extent still be considered unexplored in frail MM patients, patients with comorbidities and patients with symptoms of anxiety and/or depression. This aspect should be considered in future studies and in implementation of multidisciplinary rehabilitation programs in patients with MM.

Conclusions

This study showed that self-reliant people with MM in remission to a large extent suffer from impaired HRQoL due to many disease- and treatment-related symptoms and problems. Fatigue and pain are core symptoms, and in this study we demonstrated that these symptoms are closely related to impaired physical functioning, which again is related to substantial skeletal involvement. These findings support a proactive strategy of patients with MM to prevent skeletal lesions and fractures, and reduction of pain and fatigue and improvement of physical functioning should be targeting points in future rehabilitation and palliation intervention studies. Despite heterogeneity among the participants, it is possible and feasible to offer group-based multidisciplinary rehabilitation programs including considerations to the individual patients’ osteolytic skeleton lesions, the patients’ motivation and preferences for physical training. The study presents as a model for multidisciplinary rehabilitation program capable of comprising considerations to individual differences in needs and goals. It supports the need for a separate evidence-based guideline for rehabilitation and palliative care to patients with MM in remission living their everyday life.

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Authors’ contributions LKN, RFL, LJ and EJ participated in designing the study and writing the statistical analysis plan and manuscript. SM participated in making the statistical analysis plan and the analyses. LKN taught the rehabilitation staff before study start and the patient educational sessions as part of the multidisciplinary rehabilitation intervention. RFL developed the “Level of osteolytic skeleton lesions” form, taught the rehabilitation staff in physical activity in patients with multiple myeloma and participated in establishing the individual training programs and in physical testing of the patients. LJ taught the patient educational sessions in pain and pain management. EJ participated in establishing the individual training program for each patient, in physical testing, built the database and participated in the data analysis. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest LKN received research funding from the University of Southern Denmark, Celgene, Takeda, Amgen and Janssen. RFL received funding from Amgen. LJ, EJ and SM declare that they have no conflict of interest.

Ethical approval Oral and written consent for participation was a requirement for participation in the study. The research was conducted in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments. According to Danish regulations, approval from The Danish National Committee on Health Research Ethics was not necessary. The study was registered at the Danish Data Protection Agency by number 19/19123.

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