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# Quality of life gains in frail and intermediate-fit patients with multiple Myeloma: Findings from the prospective HOVON123 clinical trial

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ABSTRACT

*Background:* Frailty in newly-diagnosed multiple myeloma (NDMM) patients is associated with treatment-related toxicity, which negatively affects health-related quality of life (HRQoL). Currently, data on changes in HRQoL of frail and intermediate-fit MM patients during active treatment and post-treatment follow-up are absent.
*Methods:* The HOVON123 study (NTR4244) was a phase II trial in which NDMM patients $\geq$ 75 years were treated with nine dose-adjusted cycles of Melphalan-Prednisone-Bortezomib (MPV). Two HRQoL instruments (EORTC QLQ-C30 and -MY20) were obtained before start of treatment, after 3 and 9 months of treatment and 6 and 12 months after treatment for patients who did not yet start second-line treatment. HRQoL changes and/or differences in frail and intermediate-fit patients (IMWG frailty score) were reported only when both statistically significant ($p < 0.005$) and clinically relevant (>MID).

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*Results:* 137 frail and 71 intermediate-fit patients were included in the analysis. Compliance was high and comparable in both groups. At baseline, frail patients reported lower global health status, lower physical functioning scores and more fatigue and pain compared to intermediate-fit patients. Both groups improved in global health status and future perspective; polyneuropathy complaints worsened over time. Frail patients improved over time in physical functioning, fatigue and pain. Improvement in global health status occurred earlier than in intermediate-fit patients.
*Conclusion:* HRQoL improved during anti-myeloma treatment in both intermediate-fit and frail MM patients. In frail patients, improvement occurred faster and, in more domains, which was retained during follow-up. This implies that physicians should not withhold safe and effective therapies from frail patients in fear of HRQoL deterioration.

## 1. Introduction

Multiple myeloma (MM) mainly affects elderly people. [1] The current therapeutic armamentarium provides important progression-free survival (PFS) and overall survival (OS) benefits and reduces disease-specific symptoms, also for older patients. [1,2] However, treatment is associated with an ongoing risk of side effects. As many treatment regimens are provided continuously, this risk is becoming increasingly prevalent. [3].

This may be even more pronounced in intermediate-fit and frail patients. This is specifically relevant to patients with MM, since approximately 60 % of older patients with newly diagnosed (ND)MM are intermediate-fit or frail, as assessed by the International Myeloma Working Group (IMWG) frailty score. [4–6] Such defined frailty is associated with a higher incidence of non-haematological toxicity and discontinuation of therapy, which subsequently leads to an inferior PFS and OS. [6] As health-related quality of life (HRQoL) can be negatively affected by toxicity during treatment, [7–9] it is reasonable to hypothesize that the level of frailty is also associated with HRQoL. However, longitudinal data on whether and to what extent HRQoL is affected by the level of frailty, defined by the IMWG frailty score, are lacking. Furthermore, it is currently unknown whether a period without any treatment improves HRQoL. [7,8] As especially older MM patients prefer HRQoL over length of life, [9,10] these data are necessary for sensible shared treatment decision making in intermediate-fit and frail patients.

In the HOVON123 trial, mainly intermediate-fit and frail patients aged 75 years or older were treated with dose-adjusted Melphalan-Prednisone-Bortezomib (MPV). In this trial, we showed that frail patients were indeed more functionally frail, had a higher risk of treatment discontinuation as well as an inferior OS as compared to intermediate-fit patients. [11] We here present HRQoL data from the HOVON123 trial, differentiated by IMWG frailty score. We investigated whether frailty status is associated with HRQoL outcomes during treatment and post-treatment follow-up.

## 2. Methods

### 2.1. Study design

The HOVON123 (Netherlands Trial Registry number [NTR]4244) was a prospective, phase II multicentre trial. Patients with symptomatic NDMM and who were 75 or older were eligible and were treated with a dose-adjusted MPV regimen. The in- and exclusion criteria reflect a real-world population,(**Supplemental** Table 1). Patients were treated with nine cycles of dose-adjusted MPV: melphalan (orally) 6 mg/m$^2$ and prednisone (orally) 30 mg/m$^2$ on days 1–4; and bortezomib (subcutaneously) 1.3 mg/m$^2$ on days 1, 8, 15, and 22 of a 35-day cycle. The present HRQoL assessment between frailty subgroups was a secondary analysis of the HOVON123 trial.

### 2.2. Frailty assessment

Frailty was assessed using the IMWG frailty score. The score incorporates age (1 point for age 76 - 80 years, 2 points for age $\geq$ *81 years*), the Charlson Comorbidity Index (CCI, 1 point for CCI $\geq$ 2) and (instrumental) Activities of Daily Living ([i]ADL, 1 point for ADL $\leq$ 4 and 1 point for iADL $\leq$ 5) (Supplemental table 2**).** Fit patients (based on age [exactly 75 years] without co-morbidities and independent in [i]ADL) were excluded because of the limited number, precluding meaningful analyses. Based on the IMWG frailty score, the remaining patients were stratified into intermediate-fit (score = 1) and frail (score $\geq$ 2). [6].

### 2.3. Health-related quality of life assessment

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 and the EORTC QLQ-MY20 questionnaires were used for HRQoL assessment. [12–15] The outcome of question 13 of the EORTC QLQ-MY20 (“tingling hands/-feet”) was used as a proxy for peripheral neuropathy (PNP). [16] Scores in both questionnaires are transformed to a scale ranging from zero to 100, with higher scores indicating either better functioning on functional scales or global health status (better HRQoL), versus more symptoms on symptom scales, indicating a worse HRQoL. [12,17].

**Table 1**
Mean baseline HRQoL scores and differences between frail and intermediate-fit.

| Outcome | Frail | | | Intermediate-fit | | | Difference between groups | P-value | Relevance |
|---|---|---|---|---|---|---|---|---|---|
| | Estimate | 95 % CI | | Estimate | 95 % CI | | | | |
| Global health status | 54.4 | 50.8 | 58.1 | 66.8 | 61.7 | 71.8 | 12.3 | < 0.001 | Medium |
| Physical functioning | 51.2 | 47.1 | 55.3 | 74.9 | 70.6 | 79.2 | 23.7 | < 0.001 | Large |
| Fatigue | 50.7 | 46.0 | 55.3 | 33.6 | 28.4 | 38.9 | -17.0 | < 0.001 | Medium |
| Pain | 50.6 | 45.1 | 56.1 | 32.4 | 25.6 | 39.1 | -18.2 | 0.001 | Medium |
| Constipation | 19.2 | 14.8 | 23.6 | 15.0 | 9.9 | 20.1 | -4.2 | 0.29 | Trivial |
| Diarrhoea | 11.7 | 8.0 | 15.4 | 5.6 | 1.2 | 10.1 | -6.0 | 0.072 | Medium |
| MM – Side effects of treatment | 21.9 | 19.3 | 24.6 | 16.8 | 13.8 | 19.7 | -5.2 | 0.022 | NA |
| MM - Future perspective | 54.0 | 49.5 | 58.6 | 62.1 | 56.7 | 67.6 | 8.1 | 0.046 | NA |
| MM - Peripheral neuropathy | 10.5 | 6.0 | 14.9 | 8.1 | 3.3 | 12.8 | -2.4 | 0.40 | NA |

Abbreviation: NA = The relevance of the EORTC-QLQ-MY20 subscales have not been established by previous studies

HRQoL was assessed at start of treatment (SoT, start of first MPV dosing), after 3 and 9 months of treatment (3MoT and 9MoT), and 6 and 12 months after treatment (6MaT and 12MaT), for those patients who did not yet start second-line treatment. Only patients who at least completed a SoT questionnaire were included in the HRQoL analysis. A subset of nine subscales being clinically relevant to older intermediate-fit and frail patients were analysed: global health status, physical functioning, future perspective, fatigue, pain, constipation, diarrhoea, treatment side effects, and PNP. [17–19].

### 2.4. Statistical analyses

Differences in HRQoL between frailty groups were analysed with independent t-tests, and linear mixed models over time, with a random intercept for patient and fixed effects for time, group and their two-way interaction. HRQoL changes over time within groups were also analysed with a linear mixed model, with a fixed effect for time. We used linear mixed models to mitigate bias within groups caused by drop-outs and missing data as much as possible. [20] Moreover, we assessed whether compliance and the timing of going off protocol differed between groups to ensure that bias between groups was minimised. Changes in HRQoL from baseline within each group were defined clinically relevant using

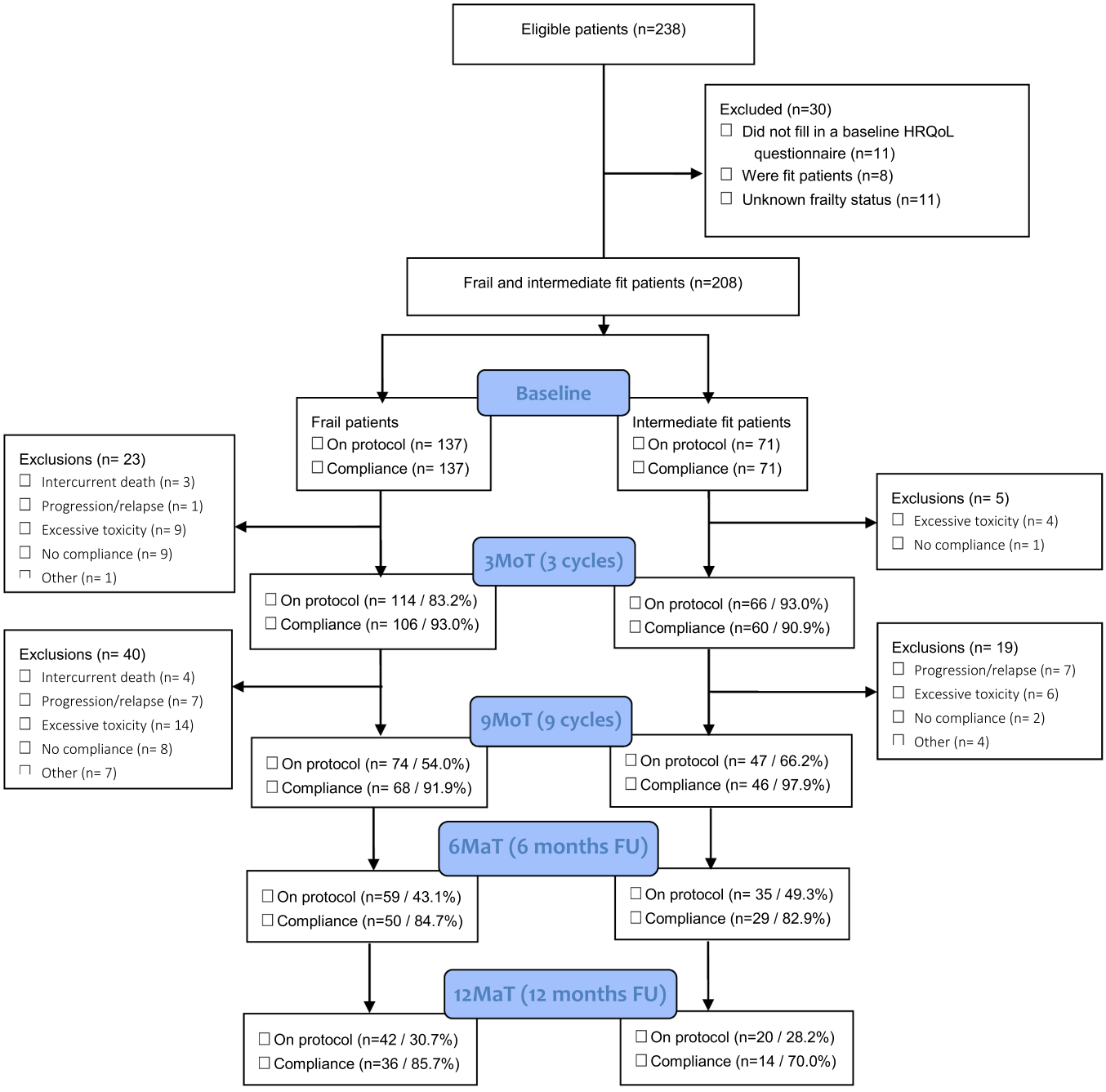


**Fig. 1.** Consort diagram. P-values for differences in compliance per time point: p = 0.62 (3MoT), p = 0.11 (9MoT), p = 0.86 (6MaT), p = 0.14 (12MaT). The overall difference in timing of exclusion between groups: p = 0.20. Differences between timing of going off protocol and compliance per time point are calculated using chi-square tests. Abbreviations: 3MoT= 3 Months of Treatment, 9MoT = 9 Months of Treatment (treatment completion), 6MaT = 6 Months after Treatment completion, 12MaT = 12 Months after Treatment completion, FU = Follow-Up.

minimal important difference (MID) thresholds. These were calculated by either a HRQoL score change of ≥ 1 standard error of measurement (SEM) of mean baseline HRQoL score for multi-item scales, or ≥ 0.5 times the standard deviation (SD) of mean baseline HRQoL score for single-item scales (Supplemental tables 3 and 4). [12,21] For HRQoL scores of the EORTC QLQ-MY20, the MID thresholds estimated by Sully et al. were used (Supplemental table 5). [15] Differences in percentages of patients with a clinically relevant (>MID) change in HRQoL at each time point between groups were analysed using chi-square tests. Cross-sectional clinically relevant superiority in HRQoL of one group over the other was defined as a MID score of ≥ 5 points between groups (Supplemental table 4). [21] HRQoL changes and/or differences were reported only when they were both statistically significant ($p < 0.005$, adjusted for multiple testing) and clinically relevant (>MID). Additionally, the magnitude of HRQoL changes (trivial, small, medium or large) based on Cocks et al. was investigated for cross-sectional analyses of HRQoL scales of the EORTC QLQ-C30 if these were statistically significant and clinically relevant. [13,14] All statistical analyses were performed in IBM SPSS Statistics version 26.

## 3. Results

### 3.1. Patient characteristics

In total, 238 patients were screened of whom 227 (95 %) filled in a baseline HRQoL questionnaire. We excluded eight fit patients and 11 patients with unknown frailty status. Finally, 137 frail and 71 intermediate-fit patients were included in the HRQoL analysis. Median age at diagnosis was 81 (range: 75–91) years in frail- and 77 (range: 75–80) years in intermediate-fit patients. All patient characteristics are presented in Supplemental table 6. Compliance of questionnaires and timing of going off protocol (i.e. due to treatment discontinuation, progression, starting a new therapy or death) were similar between frailty groups per time point (median compliance: 88.8 % [range: 70.0 – 97.9 %] in frail and median compliance: 86.9 % [range: 81.4 – 93.0 %] in intermediate-fit patients) (Figure 1).

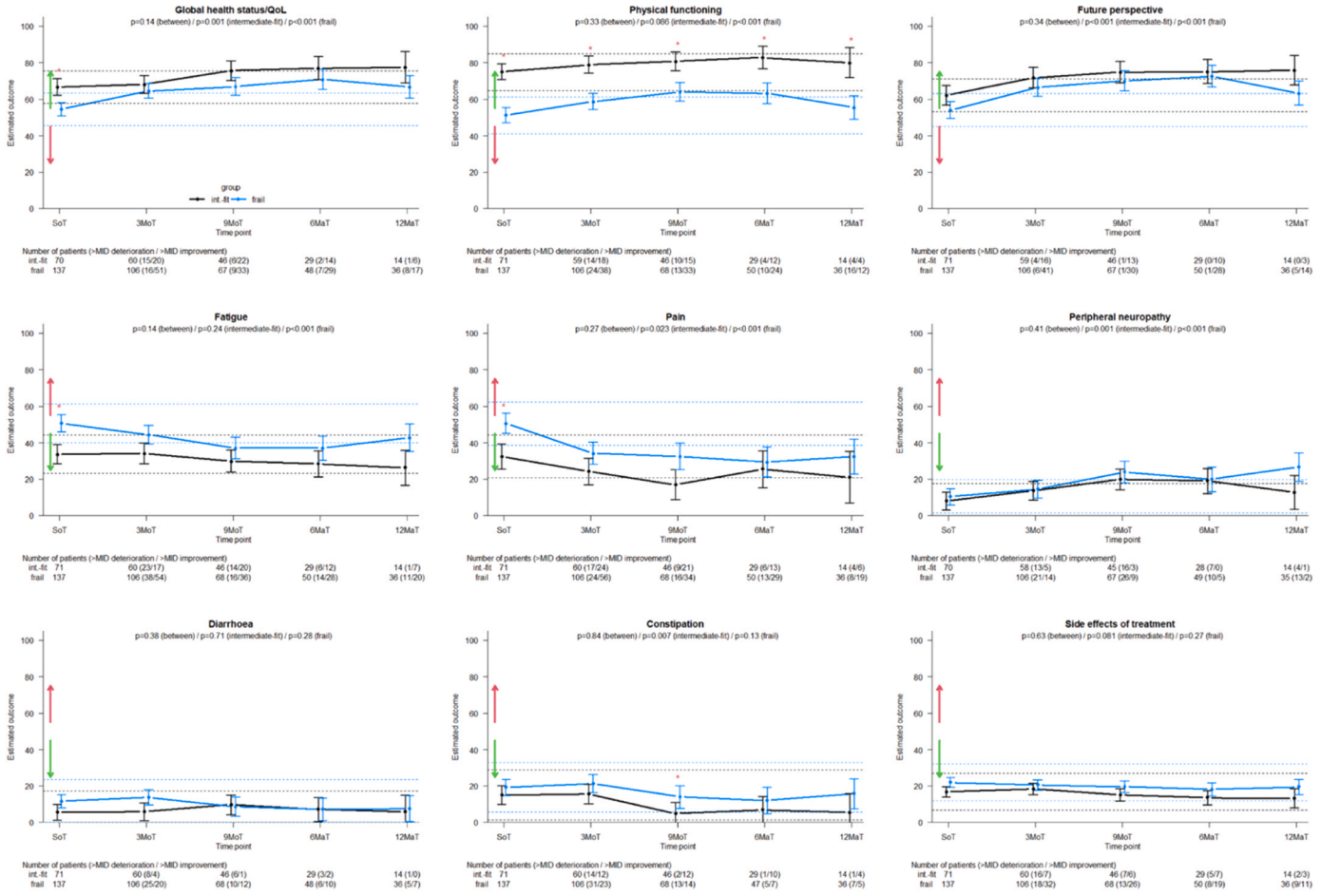


**Fig. 2.** Estimated HRQoL for nine HRQoL subscales for both intermediate-fit (black) and frail (blue) patients. Green arrows point towards improvement, red arrows point towards deterioration. Dotted lines implicate threshold for clinically relevant change from baseline (MID), red asterisks indicate a MID (>5 points) *and statistically significant ($p < 0.005$)* difference between intermediate-fit and frail patients. Abbreviations: SoT = Start of Treatment, 3MoT = 3 Months of Treatment, 9MoT = 9 Months of Treatment (treatment completion), 6MaT = 6 Months after Treatment completion, 12MaT = 12 Months after Treatment completion. 2A: Global health status, p-values over the entire course: p = 0.14 (between groups), p < 0.001 (frail) & p = 0.001 (intermediate-fit); 2B: Physical functioning, p-values over the entire course: p = 0.33 (between groups), p < 0.001 (frail) & p = 0.086 (intermediate-fit); 2 C: Future perspective, p-values over the entire course: p = 0.34 (between groups), p < 0.001 (frail) & p < 0.001 (intermediate-fit); 2D: Fatigue, p-values over the entire course: p = 0.14 (between groups), p < 0.001 (frail) & p = 0.24 (intermediate-fit); 2E: Pain, p-values over the entire course: p = 0.27 (between groups), p < 0.001 (frail) & p = 0.023 (intermediate-fit); 2 F: Peripheral neuropathy (PNP), p-values over the entire course: p = 0.41 (between groups), p < 0.001 (frail) & p = 0.001 (intermediate-fit); 2 G: Diarrhoea, p-values over the entire course: p = 0.38 (between groups), p = 0.28 (frail) & p = 0.71 (intermediate-fit); 2 H: Constipation, p-values over the entire course: p = 0.84 (between groups), p = 0.13 (frail) & p = 0.007 (intermediate-fit); 2I: Side effects of treatment, p-values over the entire course: p = 0.63 (between groups), p = 0.27 (frail) & p = 0.081 (intermediate-fit).

### 3.2. HRQoL differences between frailty groups

We investigated potential differences in HRQoL between frail and intermediate-fit patients at SoT. Frail patients had a lower baseline global health status (mean: 54.4 vs 66.8, medium effect size, $p < 0.001$), worse physical functioning (mean: 51.2 vs 74.9, large effect size, $p < 0.001$), more pain (mean: 50.6 vs 32.4, medium effect size, $p = 0.001$) and more fatigue (mean: 50.7 vs 33.6, medium effect size, $p < 0.001$) compared to intermediate-fit patients (Figure 2, Table 1 and Supplemental table 3). [14] In contrast, future perspective, constipation, diarrhoea, treatment side effects, and PNP complaints (tingling hands and/or feet) were similar between both groups at baseline (Figure 2 and Table 1). Subsequently, we investigated cross-sectional differences in HRQoL between frailty groups at each specific follow-up time point (from 3MoT to 12MaT). Only physical functioning remained inferior across all time points in frail patients, and they experienced more constipation at 9MoT (Figure 2).

### 3.3. Changes in HRQoL within each frailty group

Next, we evaluated changes in HRQoL course over time within each frailty group (SoT to 12MaT). In both groups, there was an improvement over time in global health status ($p < 0.001$ [frail] and $p = 0.001$ [intermediate-fit]) and future perspective ($p < 0.001$ [both groups]). In frail patients, we observed additional improvements in 3 HRQoL subscales; physical functioning ($p < 0.001$), fatigue ($p < 0.001$) and pain ($p < 0.001$). PNP complaints worsened over time in both groups ($p < 0.001$ [frail] and $p = 0.001$ [intermediate-fit]) (Figure 2).

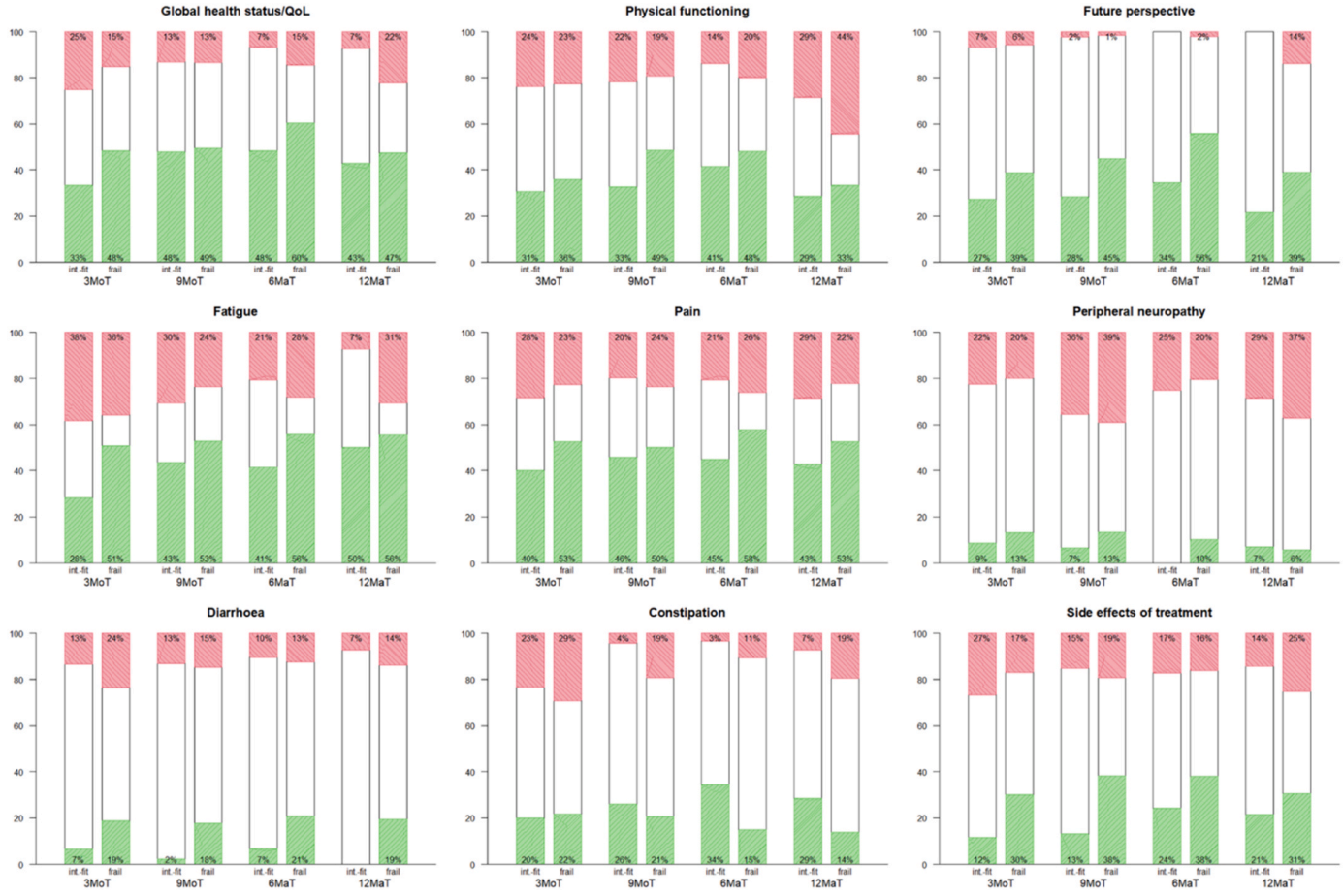


**Fig. 3.** Percentages of a minimal important difference (MID) HRQoL change from SoT (Start of Treatmen) at 3MoT (after 3 cycles of treatment), 9MoT (after 9 cycles of treatment [treatment completion]), 6MaT (after 6 months of follow-up after treatment completion) & 12MaT (after 12 months of follow-up after treatment completion). Numbers in green indicate the percentage of patients with a MID improvement at a certain time point, whereas numbers in red indicate the percentage of patients with a MID deterioration at a certain time point. 3A: Global health status, p-values of differences in percentages of HRQoL changes between frail and intermediate-fit patients at certain time points: $p = 0.12$ (3MoT), $p = 0.98$ (6MoT), $p = 0.17$ (6MaT), $p = 0.31$ (12MaT) & $p = 0.49$ (Overall); 3B: Physical functioning, p-values of differences in percentages of HRQoL changes between frail and intermediate-fit patients at certain time points: $p = 0.78$ (3MoT), $p = 0.22$ (6MoT), $p = 0.50$ (6MaT), $p = 0.33$ (12MaT) & $p = 0.35$ (Overall); 3 C: Future perspective, p-values of differences in percentages of HRQoL changes between frail and intermediate-fit patients at certain time points: $p = 0.33$ (3MoT), $p = 0.21$ (6MoT), $p = 0.11$ (6MaT), $p = 0.10$(12MaT) & $p = 0.024$ (Overall); 3D: Fatigue, p-values of differences in percentages of HRQoL changes between frail and intermediate-fit patients at certain time points: $p = 0.002$ (3MoT), $p = 0.59$ (6MoT), $p = 0.09$ (6MaT), $p = 0.045$ (12MaT) & $p = 0.041$ (Overall); 3E: Pain, p-values of differences in percentages of HRQoL changes between frail and intermediate-fit patients at certain time points: $p = 0.28$ (3MoT), $p = 0.63$ (6MoT), $p = 0.17$ (6MaT), $p = 0.81$ (12MaT) & $p = 0.35$ (Overall); 3 F: Peripheral neuropathy (PNP) complaints, p-values of differences in percentages of HRQoL changes between frail and intermediate-fit patients at certain time points: $p = 0.66$ (3MoT), $p = 0.42$ (6MoT), $p = 0.21$ (6MaT), $p = 0.85$ (12MaT) & $p = 0.26$ (Overall); 3 G: Diarrhoea, p-values of differences in percentages of HRQoL changes between frail and intermediate-fit patients at certain time points: $p = 0.012$ (3MoT), $p = 0.032$ (6MoT), $p = 0.23$ (6MaT), $p = 0.13$ (12MaT) & $p < 0.001$ (Overall); 3 H: Constipation, p-values of differences in percentages of HRQoL changes between frail and intermediate-fit patients at certain time points: $p = 0.61$ (3MoT), $p = 0.071$ (6MoT), $p = 0.098$ (6MaT), $p = 0.34$ (12MaT) & $p = 0.037$ (Overall); 3I: Side effects of treatment, p-values of differences in percentages of HRQoL changes between frail and intermediate-fit patients at certain time points: $p = 0.04$ (3MoT), $p = 0.008$ (6MoT), $p = 0.43$ (6MaT), $p = 0.44$ (12MaT) & $p = 0.003$ (Overall).

### 3.4. Timing of clinically relevant HRQoL changes

Global health status improved earlier in frail than in intermediate-fit patients: at 3MoT to 12MaT in frail patients versus from 9MoT to 6MaT in intermediate-fit patients. Likewise, improvement in pain was achieved earlier in frail patients: from 3MoT onwards in frail patients versus at 9MoT in intermediate-fit patients. Only frail patients reached an improvement in physical functioning at 3MoT to 6MaT and fatigue at 9MoT and at 6MaT. However, this returned below the MID at 12MaT in both scales. While PNP complaints worsened from 9MoT onwards in both groups, the mean score for PNP complaints returned approximately to baseline at 12MaT for intermediate-fit patients, while no recovery was observed in frail patients (Figure 2 and Supplemental tables 7 and 8).

### 3.5. Differences in the proportion of patients reaching a clinically meaningful change in HRQoL

In addition to changes in HRQoL on a group level, we assessed percentages of clinically relevant changes (>MID from baseline) during or after treatment. Over time, more frail patients had improvements and fewer had deteriorations in two subscales (diarrhoea ($p < 0.001$) and side effects of treatment ($p = 0.003$)) compared to intermediate-fit patients. Only at 3MoT, a larger proportion of frail patients exhibited an improvement in fatigue, when compared to intermediate-fit patients (50.9 % vs. 28.3 %, $p = 0.002$) (Figure 3).

At each time point, HRQoL improved from baseline in 20–60 % of patients in global health status, physical functioning, future perspective, fatigue and pain (Figure 3). However, deterioration occurred in 7–22 % in global health status, in 14–44 % in physical functioning and in 7–38 % in fatigue. Few patients (0–14 %) exhibited deterioration in future perspective. In contrast, the proportion of patients who remained stable (within MID ranges) was 43–93 % in the scales representing side effects of treatment (PNP complaints, diarrhoea, constipation and side effects of treatment), with 20–37 % of patients that deteriorated in PNP complaints.

### 3.6. Impact of HRQoL on duration of remaining on protocol

HRQoL at baseline might be better in patients with complete follow-up until 12 MaT, as compared to patients who went off protocol prematurely for reasons such as toxicity, progression or death. To check whether differences in baseline HRQoL could explain the observed HRQoL improvements over time, we investigated baseline differences between patients who did and who did not reach the last time point. Baseline HRQoL was comparable between both groups (Supplemental table 9 and 10), except for physical functioning, which was better in frail patients who completed the full protocol versus those who did not (mean score: 61.7 vs 47.6, medium effect size, $p = 0.0052$) (Supplemental table 9).

Furthermore, in order to exclude an overestimation of HRQoL, we conducted a separate analysis at each time point of patients who were still on protocol and either completed the questionnaire at the following time point and of patients who did not complete the following questionnaire due to incompliance or going off protocol in between. There were no differences in any scale at any time point during the treatment.

## 4. Discussion

In this study, we prospectively analysed HRQoL in intermediate-fit and frail NDMM patients during treatment with nine cycles of dose adjusted MPV and after completion of therapy up to one year. This study is the first comparing HRQoL courses stratified by frailty status in a study reflecting a real-world population, due to the very liberal inclusion criteria. Frail patients reported lower global health status and physical functioning and more pain at baseline. Nevertheless, global health status and future perspective improved in both groups, and only frail patients additionally reported improvements in physical functioning, fatigue and pain over time. Furthermore, global health status benefits were generally achieved earlier and sustained for a longer period of time in frail as compared to intermediate-fit patients. These data indicate that treatment should not be withheld from such patients out of concern for HRQoL deterioration.

We here demonstrate that frail patients have lower baseline scores in all EORTC-QLQ-C30 scales except for constipation, when compared to non-transplant eligible patients, included in the MAIA and ALCYONE trials. [2,22] However, we found quantitatively larger HRQoL improvements in frail patients upon treatment compared to patients aged 75 years or older in the MAIA and ALCYONE trials. [2,22] Taking into account the limitations of inter-study comparisons, a possible explanation for the inferior baseline scores in our study might be that more than half of the patients in both trials were below the age of 75 and also included fit patients using a simplified frailty score. [23,24] Nevertheless, lower baseline functioning might allow 'more room for improvement' in our frail group, exemplified by the more pronounced improvement in frail patients, as compared to intermediate-fit patients.

The potential for achieving meaningful HRQoL improvement provides an important argument to initiate treatment. In contrast, physical functioning remained lower in frail patients at each time point when compared to intermediate-fit patients, which may reflect an irreversible condition. In future studies, we propose to conduct predefined subgroup HRQoL analyses based on frailty. By identifying associations between frailty and HRQoL, more specific therapies can be developed.

Several studies have described (HR)QoL and specific scales as physical functioning as possible prognostic factors for survival in MM. [25–27] In line, we found an association in frail patients between superior baseline physical and completing the study protocol. This suggests another potential avenue for further investigation in prospective HRQoL studies.

We demonstrated that the IMWG frailty score correlates with HRQoL in intermediate-fit and frail MM patients before, during, and after discontinuation first-line treatment. It remains unclear whether other frailty scoring tools would yield similar results. A few studies reported associations between HRQoL and MM-specific [5,28,29] or non-disease-specific [30] frailty tools or risk scores. [28,31] Cross-sectional HRQoL was inferior in frail and high-risk patients, both in NDMM and RRMM, but HRQoL was not evaluated longitudinally in these studies. [5,28,31] The MAIA subanalysis showed HRQoL improvement in frail patients over time, however without comparison to other frailty subgroups. The only study investigating HRQoL in fit and frail patients longitudinally, found a more pronounced increase in HRQoL during treatment in frail patients. [30] However, the dichotomous, non-disease-specific frailty score used by Nakazato et al. impedes distinction between intermediate-fit and frail patients, [30] which may be crucial in the heterogeneous older MM population. [6,32] Finally, none of these reports assessed HRQoL after treatment discontinuation. In the current study, comparison of these frailty tools with the IMWG frailty score was hindered by missing components. Which instrument to determine frailty is best associated with HRQoL is currently unknown, making it an important subject for further research.

Although HRQoL improved on disease-related and general domains, there were no improvements in adverse event-related domains and even a worsening in PNP-related complaints. Moreover, the scores remained worse when compared to the general Dutch population of 70 years and older. [33] This underscores the necessity for strategies to enhance the tolerability of continuous therapy to further enhance HRQoL. One potential approach involves a dose reduction of proteasome inhibitors, while ensuring an acceptably effective level. [1] Importantly, we found that PNP-related complaints returned to baseline levels in intermediate-fit patients only during post-treatment follow-up. This implies that in intermediate-fit patients, higher dosages may be administered, and as an alternative tactic to mitigate PNP-associated

complaints – a treatment-free period – could be effective. [34].

Data of previous cohort studies implicated benefit of a treatment-free interval for HRQoL. [7,8] We here show that discontinuation of therapy after nine cycles did not lead to a decrease in HRQoL and all benefits persisted for at least 6 months. Accordingly, other studies reported no further HRQoL improvements after 12 months of continuous treatment. [2,17] This supports a treatment-free interval as potential strategy to mitigate toxicity while retaining or even improving HRQoL. This may not account for continuous maintenance therapy with daratumumab, as ALCYONE showed no further HRQoL changes with- and without daratumumab treatment following nine cycles of MPV. [22] Our study design does not allow for comparison of HRQoL dynamics with- and without continued treatment, especially in relation to efficacy. Such approaches should be addressed in future studies.

HRQoL studies are potentially hindered by a "survivorship bias". [35] In our study, only patients who completed the full nine cycles of MPV and who did not yet start second-line treatment were included in the follow-up analysis. These patients are in remission and therefore may have a low disease burden and potentially superior HRQoL compared to those who were excluded prematurely. To minimize bias within subgroups due to dropout, we employed a linear mixed model. [20] Furthermore, there were no HRQoL differences between patients who remained on treatment and those who subsequently went off protocol. Finally, although we found more pronounced improvements in HRQoL in frail patients as compared to intermediate-fit patients, the proportions of patients going off protocol at every time point were similar in both groups. Therefore, it is unlikely that differences are due to a survivorship bias. However, to definitely exclude survivorship bias, future studies should at least include HRQoL measurements at the time of progression or other reasons for going off protocol, and preferably collect and compare HRQoL data of subsequent lines of treatment.

## 5. Conclusion

Frail patients show faster and larger improvements in HRQoL outcomes during treatment with MPV compared to intermediate-fit patients and these improvements in HRQoL outcomes persist during post-treatment follow-up. Physicians should not withhold safe and effective therapies from frail patients in fear of HRQoL deterioration.

## Contributors

MRS, HMB, DGJC and SZ designed the study. MRS, CAMS, BILW, KN, HMB, DGJC and SZ verified and analysed data. MDL, GJT, MH, PFY, SKK, GAV, MW, LS, NDR, MADS, RJWK, ACD, AK, MHS, ES, AB, ZE, NCHPBG, MBLL, NWCJD, PS and SZ provided study materials and enrolled patients to the study.

All authors were involved in data analysis and interpretation, writing of the manuscript, and final approval of the manuscript. All authors had full access to all the data in the study and accept responsibility for the decision to submit for publication.

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## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: CAMS serves on advisory boards for Sanofi and Janssen and on speakers' bureaus for Sanofi, Celgene, BMS and Takeda. GJT served as advisor for Novartis. PFY has received payments for lectures from Janssen and Amgen and support for travel expenses from Janssen. RJWK has received support for travel expenses from Novartis and serves on an advisory board of Novartis. PS has received research support from Janssen, Amgen, BMS, Celgene and Karyopharm; and serves on advisory boards for Celgene, Janssen, Amgen, Karyopharm, BMS and Pfizer. NWCJD has received research support from Janssen Pharmaceuticals, AMGEN, Celgene, Novartis, Cellectis and BMS, all paid to their institution; and serves on advisory boards for Janssen Pharmaceuticals, AMGEN, Celgene, BMS, Takeda, Roche, Novartis, Bayer, Adaptive, and Servier, all paid to their institution. HMB serves on an advisory board for Pfizer and has received research support from BMS-Celgene, all paid to their institution. DGJC has received payments for lectures for Takeda, and received financial support for travel expenses from Servier, all outside the submitted work. SZ has received research support from Janssen and the Dutch Cancer Society, all paid to their institution; and serves on advisory boards for Janssen, BMS, Oncopeptides, and Sanofi, all paid to their institution. Others: All remaining authors have declared no conflicts of interest.

## Data availability

The data presented in this study are available upon reasonable request. Qualified researchers can request access to anonymised patient data. Details on sharing criteria and processes for requesting access to data can be obtained from the corresponding author.

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This trial was registered at www.trialregister.nl (NTR 4244), EudraCT 2013–000320-33.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.114153.

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