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Letter
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Impact of Comorbidities on Health-related Quality of Life in Nontransplant Eligible Patients With Newly Diagnosed Multiple Myeloma

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The median age at diagnosis of multiple myeloma (MM) is 70 years.[1] As the prevalence of multimorbidity increases with age, patients with MM are more likely to be affected by comorbid chronic disease.[2] Over the last few decades, the overall survival (OS) of patients with MM improved significantly due to novel therapies, including treatment with proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies. Besides, the improvement of survival has also been attributed to intermittent or continuous treatment. However, prolonged treatment may lead to side effects that may turn the pros of prolongation of therapy into cons because of a negative effect on health-related quality of life (HRQoL).[3] In addition, the presence of comorbidities has been described to negatively affect HRQoL in patients with cancer.[4] Despite the increasing interest in HRQoL in patients with MM, data on HRQoL in MM patients with comorbidities are scarce, although needed in view of the multiplicity of valuable treatment options, also for older patients.[5,6] To the best of our knowledge, this is the first analysis using different methods to assess the impact of comorbidities on HRQoL and its clinical relevance in nontransplant eligible patients with newly diagnosed multiple myeloma (NDMM). This post hoc analysis was based on data from the HOVON87/NMSG18 trial (NTR1630).[7] In this trial, NDMM patients aged ≥65 years or nontransplant eligible <65 years were randomized between induction treatment with melphalan-prednisone with either thalidomide followed by thalidomide maintenance, or with lenalidomide followed by lenalidomide maintenance. Only patients with cardiac dysfunction (NYHA II-IV), pulmonary dysfunction, hepatic dysfunction (bilirubin ≥30 μmol/L or transaminases ≥3 times normal level) and renal dysfunction (creatinine clearance < 30 mL/min), active malignancy or HIV, were excluded from participating in this trial.

HRQoL was assessed at baseline (T0), after 3 cycles (T1) and 9 cycles (T2) of induction therapy and after 6 months (T3) and 12 months (T4) of maintenance therapy.[6,8]

We retrospectively determined comorbidities in patients who were included in the HOVON87/NMSG18 trial, by counting the comorbid conditions (excluding MM and without age adjustments) of the Charlson Comorbidity Index (CCI)[9] (Suppl. Table S1). Based on previous studies in MM,[5,10-12] we determined HRQoL focusing on the following eight scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30): global health status/quality of life (GHS/QoL), physical functioning, role functioning, cognitive functioning, social functioning, fatigue, pain, and dyspnea.

All patients with both a CCI score and a HRQoL assessment at baseline were included in the analysis and were divided into a group of patients without comorbidities (CCI = 0) and a group of patients with at least one comorbidity (CCI > 0). HRQoL was determined at baseline (T0), at the end of induction treatment (T2) and after 12 months of maintenance treatment (T4). The change in HRQoL over time of groups of patients with and without comorbidities was analyzed, using linear-mixed models both "between groups" and "within groups." Cross-sectional differences were assessed between groups at all time points using the model estimated effects. A P value of <0.05 was considered statistically significant.

Clinically relevant improvements or deteriorations in HRQoL over time were estimated using Cocks' guidelines for interpreting of mean changes over time.[13] Additionally, to provide insight into different methods of interpretation of HRQoL data, we used thresholds in HRQoL outcomes for identifying clinical important problems as described by Giesinger et al.[14] This method provides predefined HRQoL score thresholds for all subscales of the EORTC QLQ-C30 except GHS/QoL. According to this method, patients whose HRQoL score did not reach these thresholds, experienced clinically meaningful problematic functioning or symptoms ("problems") in that particular subscale, which negatively affected HRQoL (Suppl.

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Table S2). We evaluated this per time point (T0 to T4). Chi-square tests were used to assess cross-sectional differences in percentages of reported problems between patients with and without comorbidities. Generalized estimating equations were used to assess differences in percentages of problems over time, both "between groups" and "within groups" of patients with and without comorbidities.

A CCI and HRQoL score at baseline (T0) was available for 552 patients, 380 of whom had no comorbidities, whereas 172 had at least one comorbidity. Response rates to HRQoL questionnaires during treatment were high (range 71.4–86.3%). After 12 months of maintenance treatment, 168 patients (30.5%) were on protocol, 127 of whom completed an HRQoL questionnaire. Median age in both groups was 73 years. Comorbidities were

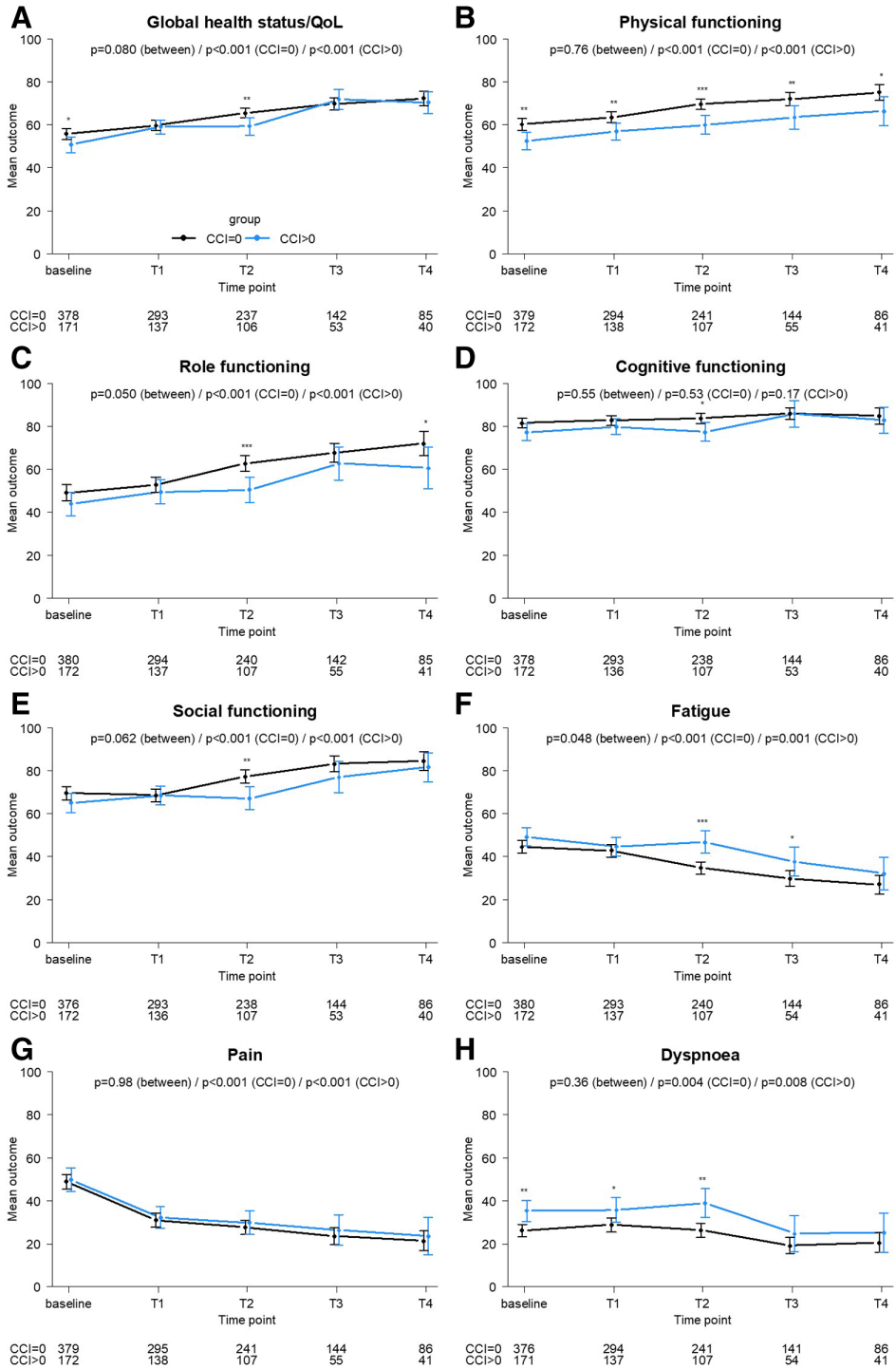

Figure 1. Course of HRQOL outcomes in patients with and without comorbidities. Cross-sectional differences between patients with (CCI > 0) and without comorbidities (CCI = 0). *P < 0.05, **P < 0.01, ***P < 0.001. Baseline: before start treatment, T1: after 3 induction cycles, T2: after 9 induction cycles, T3: after 6 months maintenance treatment, T4: after 12 months maintenance treatment, P (between): P value for differences in HRQoL course over time T0-T4 between patients with and without comorbidities. P CCI = 0, P value for change in HRQoL over time within patients without comorbidities; CCI > 0, P value for change in HRQoL over time within patients with comorbidities. Total number of patients CCI = 0 and CCI > 0 with available HRQoL score at each time point. CCI = Charlson Comorbidity Index; HRQoL = health-related quality of life.

more common among male patients (P = 0.001), and patients with comorbidities more often had a compromised World Health Organisation (WHO) performance score (P = 0.030). Patients with and without comorbidities did not differ in OS, PFS, or time to treatment discontinuation (Suppl. Table S3).

We assessed the impact of comorbidity on HRQoL at different time points, using cross-sectional analyses. At baseline, patients with comorbidities reported a statistically significant inferior GHS/QoL (P = 0.025), physical functioning (P = 0.003), and significantly more dyspnea (P = 0.001) than patients without comorbidities (Figure 1, baseline). Furthermore, after induction therapy (T2) patients with comorbidities reported statistically significant inferior HRQoL in all subscales except pain compared to patients without comorbidities (Figure 1, T2). After 12 months of maintenance treatment (T4) patients with comorbidities only reported statistically significant

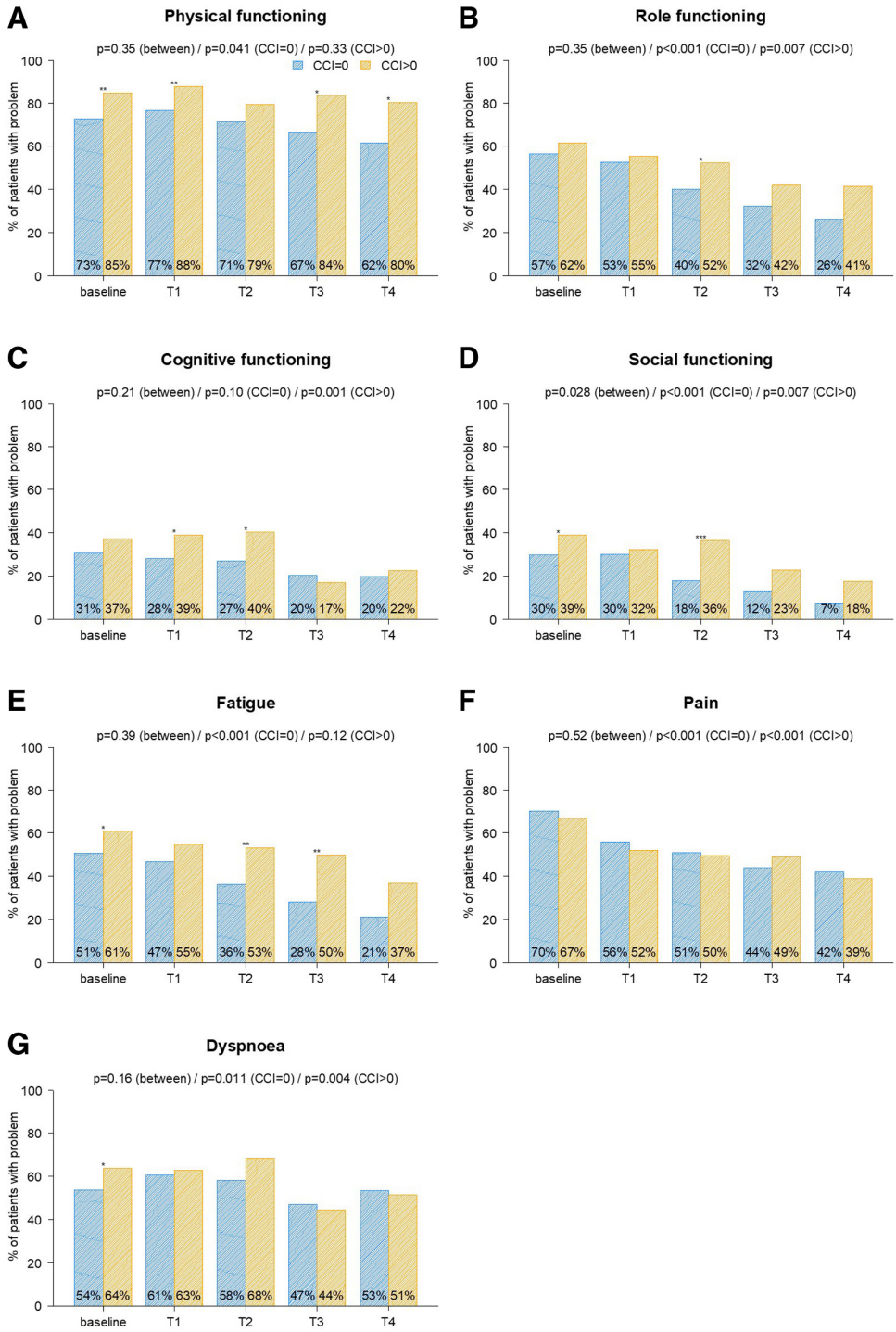

Figure 2. Percentage of patients with clinically relevant problems affecting HRQoL. P (between): P value for differences in change of percentage of patients with problems over time between patients with and without comorbidities. CCI = 0, P value for change over time within patients without comorbidities; CCI > 0, P value of change over time within patients with comorbidities. Cross-sectional differences between percentages of patients with and without comorbidities at each time point: *P < 0.05, **P < 0.01, ***P < 0.001. Baseline: at start treatment, T1: after 3 induction cycles, T2: after 9 induction cycles, T3: after 6 months maintenance, T4: after 12 months maintenance. CCI = Charlson Comorbidity Index; HRQoL = health-related quality of life.

lower physical functioning (P = 0.015) and role functioning (P = 0.037) compared with patients without comorbidities (Figure 1, T4). Interpretation of HRQoL based on Giesinger's thresholds demonstrated high percentages of clinically relevant problems in patients with and without comorbidities in most subscales at each time point. Overall, problematic functioning and symptoms were reported more often by patients with comorbidities than by patients without comorbidities, although the differences were not statistically significant in all subscales (Figure 2). After 12 months of maintenance treatment, only in physical functioning statistically significant more often "problems" were reported in patients with comorbidities as compared to those without comorbidities (62% versus 80%, P = 0.042; Figure 2, T4). Thus, although patients with comorbidities experienced more functional limitations and symptoms affecting HRQoL, the differences in HRQoL between patients with and without comorbidities became less pronounced during maintenance treatment. Based on the cross-sectional differences in HRQoL, there is no clear rationale to withhold treatment in MM patients with comorbidities. Nevertheless, the percentage of patients with comorbidities who reported problematic physical functioning was high, which underscores the importance to address the unmet need to further improve HRQoL.

Analyses of HRQoL course over time, "between groups" showed no differences between patients with and without comorbidities, except for fatigue, which was more pronounced over time in patients with comorbidities than in patients without comorbidities (P = 0.048) (Figure 1). Treatment arm did not affect the course of HRQoL between groups (data not shown). Using Giesinger's thresholds to analyze the percentage of patients who reported problems over time, no differences "between groups" were found, except in social functioning, where patients with comorbidities were more likely to experience problems over time than patients without comorbidities (P = 0.028) (Figure 2). These results corroborate our finding to not withhold MM treatment based on the presence of comorbidity.

Although cross-sectional analyses showed differences in HRQoL between patients with and without comorbidities, also in patients with comorbidities HRQoL improved over time in all subscales except cognitive functioning (Figure 1). Interpretation of HRQoL based on "Cocks" estimates' showed clinically relevant medium improvements in the HRQoL scales GHS/QoL, physical, role and social functioning, and fatigue, and large improvements in pain during treatment, irrespective of the presence of comorbidities. However, statistically significant and clinically relevant improvements in HRQoL were generally reached earlier in patients without comorbidities (already during induction therapy), than in patients with comorbidities (from maintenance treatment onward) (Suppl. Table S4). According to Giesinger's method, the percentage of patients who experienced "problems" decreased during treatment in both groups, except in cognitive functioning (in patients without comorbidities) and physical functioning and fatigue (in patients with comorbidities) (Figure 2).

In summary, these findings demonstrate that HRQoL outcomes improve over time irrespective of the presence of comorbidity, which supports MM treatment in patients with and without comorbidities. However, it must be acknowledged that although HRQoL overall improved over time in older patients with MM, many had persistent clinically relevant problems that hampered HRQoL, which highlights the need for investigating HRQoL and improvement of supportive care.

Our analyses, similar to the majority of HRQoL analyses in randomized MM trials, are limited by the fact that we only investigated HRQOL in patients on protocol. This may have led to an overestimation of HRQoL.[15] In our study, we observed an inferior GHS/QoL in patients who went off protocol, due to either disease progression or toxicity leading to discontinuation, compared with patients remaining on protocol (data not shown). However, we did not observe a difference in HRQoL between patients with and without comorbidities who went off protocol, which indicates that if bias was present, it equally affected patients with and without comorbidities.

Since in this study patients with severe comorbidities were excluded, our findings should be validated with detailed analysis of comorbidities in relation to outcome, preferably in clinical trials specifically including older and unfit patients with MM or in real world data. Additionally, using age adjusted CCI scores may provide additional insights.

In conclusion, although nontransplant eligible patients with NDMM with comorbidities overall reported an inferior HRQoL, treatment was associated with clinically meaningful improvements in HRQoL during treatment independent of comorbidities. Therefore, our findings provide evidence for not withholding treatment in MM patients with comorbidities. However, parallel to the overall improvement in HRQOL during treatment, the use of thresholds for clinical importance revealed a considerable percentage of patients with functional impairments and symptoms, that were not captured with the standard HRQoL assessment techniques. Especially, the unchanging high percentage of patients with comorbidities that reported problematic physical functioning throughout the course of treatment, requires attention in clinical practice to identify patients with impaired HRQoL.

AUTHOR CONTRIBUTIONS

CB, CS, BL, SO, PS, and SZ participated in the design of this secondary analysis. CB, CS, BL, SO, MS, and SZ participated in data analysis. All authors participated in writing the article.

DISCLOSURES

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