Comparison of the Prognostic Significance of 5 Comorbidity Scores and 12 Functional Tests in a Prospective Multiple Myeloma Patient Cohort

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Background: Because of the various therapeutic options available for multiple myeloma (MM), remarkable interest exists today in individualized therapeutic concepts based on patients’ fitness. The main objectives of this study were to compare different comorbidity scores and functional tests with respect to their impact on survival (overall survival [OS] and progression-free survival [PFS]); develop a time-efficient, MM-specific functional assessment (FA); and evaluate changes in patients’ FA during treatment. Methods: The authors performed a prospective FA in 266 consecutive patients with MM at their initial diagnosis. This included 5 comorbidity scores and 12 commonly used geriatric functional tests. To evaluate changes in the course of treatment, the authors reassessed these 17 tests after ≥6 months. The entire analysis included 7327 FA tests. Results: On the basis of univariate and multivariate Cox regression analyses, the authors identified 4 of the 17 evaluated scores and functional tests as most relevant: the Revised Myeloma Comorbidity Index (R-MCI), Activity of Daily Living (ADL), the Mini-Mental State Examination (MMSE), and the quality-of-life 12-Item Short Form Health Survey Physical Composite Scale (SF-12 PCS). These showed precise group differences for fit, (intermediate-fit), and frail patients in OS and PFS: the 3-year OS rates were 90%, 74%, and 43% via the R-MCI for fit, intermediate-fit, and frail patients, respectively (P = .0006); 80% and 66% via the ADL for fit and frail patients, respectively (P = .0159); 78% and 48% via the MMSE for fit and frail patients, respectively (P = .0001); and 86% and 66% via the SF-12 PCS for fit and frail patients, respectively (P = .0091). In follow-up analyses, 16 of 17 FA tests improved, mostly in younger patients (<70 years old) and responding patients (partial remission or better). Conclusions: Patients may recover from functional and physical limitations under applied MM therapy. The newly established MM-specific FA (via the R-MCI, ADL, MMSE, and SF-12 PCS) allows a precise evaluation of the prognosis and risk status in MM. Its use may improve treatment tolerability and should be validated to individualize MM treatment decisions in the future. Cancer 2021;127:3422-3436. © 2021 The Authors. Cancer published by Wiley Periodicals LLC on behalf of American Cancer Society This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

Lay Summary:
• The authors performed a prospective functional assessment (FA) in 266 consecutive patients with multiple myeloma at their initial diagnosis.
• On the basis of univariate and multivariate Cox regression analyses, the authors identified 4 of 17 initially evaluated scores and functional tests as most relevant: the Revised Myeloma Comorbidity Index, Activity of Daily Living, the Mini-Mental State Examination, and the quality-of-life 12-item Short Form Health Survey Physical Composite Scale.
• The authors checked the stability of the final model by applying forward and stepwise selection. To evaluate changes in the course of treatment, they reassessed these 17 tests in 165 patients after ≥6 months: 16 of the 17 FA tests improved, mostly in younger patients (<70 years old) and responding patients (partial remission or better).

KEYWORDS: abbreviated functional assessment, follow-up analysis, functional assessment (FA), multiple myeloma, quality of life.

INTRODUCTION
Multiple myeloma (MM) is a disease that occurs predominantly in elderly patients.1-3 With the introduction of novel agents (immunomodulatory drugs, proteasome inhibitors, and monoclonal antibodies), treatment options and outcomes for MM patients may recover from functional and physical limitations under applied MM therapy. The newly established MM-specific FA (via the R-MCI, ADL, MMSE, and SF-12 PCS) allows a precise evaluation of the prognosis and risk status in MM. Its use may improve treatment tolerability and should be validated to individualize MM treatment decisions in the future.

The first and last authors contributed equally to this article.
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have improved considerably. The selection of suitable MM therapies has, therefore, become considerably more complex.

The standard of care for transplant-eligible patients consists of induction therapy followed by autologous stem cell transplantation (ASCT) and/or a combination treatment with novel agents. Historically, most studies have used an upper age limit of 65 years for the indication of ASCT. However, it is known that carefully selected older patients can benefit from intensive therapy as much as younger patients. Because the health status and fitness of MM patients of the same age are heterogeneous, chronological age is no longer considered a parameter to be used alone to guide therapy decisions. Rather, it has been acknowledged as important for distinguishing which patients may benefit from more intensive approaches versus less intensive ones.

A functional assessment (FA) is a multidimensional and multidisciplinary approach to more objectively and accurately assessing the functional health status of patients. It aims to individualize treatment decisions. However, because of time- and personnel-intensive demands, FA is not widely used in clinical routines. Therefore, it seems important to identify the key scores and tests that are most important for patients with MM and have a relevant influence on their prognosis. Moreover, during the course of treatment, patients' functional status may change and can be reassessed. Functional follow-up care seems likewise important to adapt treatment recommendations. Nevertheless, whether and to what extent the functional constitution of patients with MM changes during the course of treatment has largely not been investigated.

The aim of this study was to compare the prognostic significance of 5 comorbidity scores and 12 functional tests (n = 17) for their distinction of overall survival (OS) and progression-free survival (PFS) in a prospective MM patient cohort. We intended to develop a time-efficient, MM-specific FA. A verification of FA tests for use in clinical decision support was not a subject of this analysis, but it will be addressed in future MM trials. Additionally, we performed a follow-up analysis to determine possible changes in patients' functional constitution during the course of treatment.

MATERIALS AND METHODS

Patient Population and Study Design

The study was based on a prospective FA in 266 consecutive patients with MM at the time of their initial diagnosis and first presentation at the University of Freiburg Medical Center between 2011 and 2017. This involved 4522 baseline FA tests for the patients (266 × 17 = 4522). Furthermore, the assessment was repeated in 165 patients ≥6 months after the baseline assessment with 2805 FA tests (165 × 17 = 2805; Fig. 1A-C). The entire analysis included 7327 FA tests (4522 + 2805 = 7327). This comprised the careful recording of patient- and disease-specific data, the collection of 5 comorbidity scores ([1] the Revised Myeloma Comorbidity Index [R-MCI], [2] the International Myeloma Working Group [IMWG] frailty score, [3] the Charlson Comorbidity Index [CCI], [4] the Hematopoietic Cell Transplantation–Specific Comorbidity Index [HCT-CI], and [5] the Kaplan-Feinstein Index [KF]), and the standardized examination of 12 functional tests ([1] patient-rated fitness, [2] physician-rated fitness, [3] the Timed Up and Go Test [TUGT], [4] the Mini-Mental State Examination [MMSE], [5] Activity of Daily Living [ADL], [6] Instrumental Activity of Daily Living [IADL], [7] the Pain Scale, [8] the Geriatric Depression Scale [GDS], [9] the Karnofsky Performance Status [KPS], [10] the 12-Item Short Form Health Survey Physical Composite Scale [SF-12 PCS], [11] the 12-Item Short Form Health Survey Mental Composite Scale [SF-12 MCS], and [12] the Malnutrition Checklist by Suter; Fig. 1A).

The functional tests were selected after a detailed literature search in PubMed. This was based on the following search terms: elderly, frailty, geriatric assessment, quality of life, and fitness. Fitness was assessed according to the German school grading system on a scale from 1 to 6. On this scale, 1 is considered very good, 2 is considered good, 3 is considered satisfactory, 4 is considered sufficient, 5 is considered deficient, and 6 is considered extremely poor. The quality of life of the patients was evaluated with the SF-12 questionnaire, which is used to provide easily interpretable scales for physical and mental health (PCS and MCS). The results range from 0 to 100, where 0 indicates the lowest level of health and 100 indicates the highest.

For each of the FA tests, the frequency of uncompromised (fit) patients versus compromised (frail) patients was determined, and their ability to show differences in OS and PFS was determined via Kaplan-Meier analysis. The analysis was performed according to the guidelines of the Declaration of Helsinki and Good Clinical Practice. All patients gave their written informed consent for institutionally initiated research studies and analyses of clinical outcome studies conforming to the institutional review board guidelines. The study protocol was reviewed and approved by the ethics committee of the University of Freiburg (EV, 81/10). Data were analyzed with SAS 9.2 (SAS Institute, Inc, Cary, North Carolina).
Figure 1. Consolidated Standards of Reporting Trials flow diagram: study design. (A) Detailed functional assessment of 5 comorbidity scores and 12 functional tests. (B) Development of an abbreviated assessment consisting of only 4 tests. (C) Prospective 6-month follow-up analysis. KPS indicates Karnofsky Performance Status; MM, multiple myeloma; NRS, numeric rating scale; SF-12, 12-Item Short Form Health Survey.
Survival Analysis, Univariate and Multivariate Cox Regression, Brier Scores, and Age/Treatment Subgroups

Data were analyzed as of April 2017. OS was calculated from the date of the initial assessment to the date of death from any cause, whereas PFS was calculated from the date of the initial FA to the date of progression, relapse, or death from any cause. When no event of interest occurred, observations were censored at the time when the patient was last seen alive/without a documented event. OS and PFS rates were estimated with the Kaplan-Meier method and compared with the log-rank test. The relevance of the different comorbidity scores and functional tests was compared with univariate Cox regression analyses. The results were expressed as hazard ratios (HRs) with 2-sided 95% confidence intervals and associated P values.

To develop an abbreviated FA, a multivariate Cox regression analysis was performed for OS; the R-MCI was included a priori, and those functional tests in addition to the R-MCI that had prognostic relevance were determined via variable selection (backward elimination, selection criterion: \( P \leq .1 \)). Variable selection was applied to eliminate redundant information and to select only those FAs that provided independent, additional information. The stability of the selection procedure was checked by investigating whether other approaches (forward selection and stepwise procedure) led to the same model. We used dichotomized variables: for the FA variables, cutoffs had already been suggested (Table 1). Thus, we analyzed the variables in the way in which they would be applied in practice. The categorization of continuous variables may lead to a loss of information but is a more robust approach. The loss of information is compensated by the use of a more generous selection criterion (P value).

Subsequently, the selected comorbidity score and functional tests were combined in a final assessment (Fig. 1B). Brier scores were used to compare prediction errors of the newly developed assessment versus a single FA score/test alone.\(^3\) To identify differences in R-MCI status and therapy between younger and older patients, a subgroup analysis was conducted for patients \( \leq 70 \) years old and patients \( > 70 \) years old. Additionally, those patients who might have been overtreated or undertreated on the basis of their R-MCI results were evaluated.

Follow-Up Analyses

To determine possible assessment changes during the course of treatment, we reassessed all comorbidity scores and functional tests in 165 of our patients (62% of the total cohort) after \( \geq 6 \) months of follow-up (Fig. 1C). The test results

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**TABLE 1. Risk Group Definitions for Fit, Intermediate-Fit, and Frail Patients With References**

| No. | Scores and Functional Tests | Fit | Intermediate-Fit | Frail | References |
|-----|-----------------------------|-----|-----------------|-------|------------|
| 1.  | Comorbidity scores (n = 5)  |     |                 |       |            |
| 2.  | R-MCI \( \leq 3 \)          | 4-6 | \( \geq 7 \)     |       | 1, 2       |
| 3.  | IMWG frailty score          | 0   | 1               | \( \geq 2 \) | 18         |
| 4.  | CCI \( \geq 2 \)            |     |                 | \( \geq 2 \) | 19         |
| 5.  | HCT-Cl \( \geq 2 \)         |     |                 | \( \geq 2 \) | 19         |
| 6.  | IMWG frailty score          | \( \geq 2 \) | \( \geq 2 \)   |       | 20         |
| 7.  | Functional tests (n = 12)   |     |                 |       |            |
| 8.  | Patient-rated fitness       | \( \leq 4 \) | \( \geq 4 \)   |       | Analogous to German school gradings (1-6)\(^a\) |
| 9.  | Physician-rated fitness     | \( \leq 4 \) | \( \geq 4 \)   |       | Analogous to German school gradings (1-6)\(^a\) |
| 10. | TUGT \( \geq 11 \)          | \( \geq 11 \) |       |       | 22         |
| 11. | MMSE \( \geq 24 \)          | \( \leq 24 \) |       |       | 23         |
| 12. | ADL \( \geq 4 \)            | \( \leq 4 \) |       |       | 24         |
| 13. | IADL \( \geq 5 \)           | \( \leq 5 \) |       |       | 25         |
| 14. | Pain (NRS) \( \leq 4 \)     | \( \geq 4 \) |       |       | 26         |
| 15. | GDS \( \leq 5 \)            | \( \geq 5 \) |       |       | 27, 31     |
| 16. | KPS \( \geq 70 \)           | \( \leq 70 \) |       |       | 28         |
| 17. | SF-12 PCS \( \geq 3 \)     | \( \geq 3 \) |       |       | 30         |
| 18. | SF-12 MCS \( \geq 3 \)     | \( \geq 3 \) |       |       | 30         |
| 19. | Malnutrition Checklist by Suter | \( \leq 3 \) | \( \leq 3 \)   |       | 30         |

Abbreviations: ADL, Activity of Daily Living; CCI, Charlson Comorbidity Index; GDS, Geriatric Depression Scale; HCT-Cl, Hematopoietic Cell Transplantation-Specific Comorbidity Index; IADL, Instrumental Activity of Daily Living; IMWG, International Myeloma Working Group; KF, Kaplan-Feinstein Index; KPS, Karnofsky Performance Status; MMSE, Mini-Mental State Examination; NRS, numeric rating scale; R-MCI, Revised Myeloma Comorbidity Index; SF-12 MCS, 12-Item Short Form Health Survey Mental Composite Scale; SF-12 PCS, 12-Item Short Form Health Survey Physical Composite Scale; TUGT, Timed Up and Go Test.

\(^a\)1 = very good, 2 = good, 3 = satisfactory, 4 = sufficient, 5 = deficient, and 6 = extremely poor.

\(^b\)vs \( \leq \) age median – 6.97.

\(^c\)vs \( \leq \) age median – 6.24.
RESULTS

Patient Characteristics

Patient characteristics were representative for tertiary centers (Table 3). The median age was 62 years, with 59% of the patients aged 51 to 70 years and 24% older than 70 years. Advanced stage III according to the International Staging System and the Durie-Salmon system was present in 37% and 71% of the patients, respectively. Laboratory and bone marrow results were typical for referral centers: 22% of patients were treated with novel agent–based chemotherapy, 70% underwent stem cell transplantation (SCT), and 9% were treated with local measures (radiation) or supportive treatments alone. The median PFS and OS were 29 and 58 months, respectively. Because some data were missing for the follow-up analysis, the calculation of changes was performed only for those patients for whom both assessments had been measured. The mean of the individually calculated changes corresponded to the change of the means (the Wilcoxon signed-rank test requires the calculation of individual changes).
The IMWG frailty score classified 29% of our patients as fit, 35% as intermediate-fit, and 37% as frail (Table 4 and Fig. 2A). In the cohort analyzed for the development of the IMWG frailty score, 18 the proportions of fit, intermediate-fit, and frail patients had been higher (39%), similar (31%), and lower (30%), respectively (Fig. 2B). In its initial description, 18 the IMWG frailty index had been scored exclusively in study patients retrospectively, but it was assessed prospectively in this cohort (Fig. 2A).

With the CCI, HCT-CI, and KF, approximately half of our patients were classified as fit versus frail (Fig. 2A). Remarkably, frail and intermediate-fit patients with MM appeared numerous (Fig. 2A).

To assess the impairment of functional abilities, 12 functional tests were also performed. Risk group definitions for uncompromised (fit) patients versus compromised (frail) patients were achieved according to comorbidity scores and as summarized in Table 1. In line with the comorbidity scores, the risk group distribution via these 12 functional tests revealed considerable impairment in patients with MM (Fig. 2C). According to the cutoffs defined in Table 1, compromised IADL, MMSE, GDS were present in 13% to 22%; more frequent for pain, ADL, TUGT, SF-12 MCS, physician-rated fitness, and patient-rated fitness in 35% to 44%; and most prevalent for KPS, SF-12 PCS, and malnutrition in 47% to 67% (Fig. 2C).

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TABLE 3. Patient Characteristics (n = 266)

| Characteristic | No. (%) | Median (Range) |
|---------------|---------|----------------|
| Age, y        | 62 (27-92) |
| Age groups    |         |                |
| 27-50 y       | 43 (16)  |
| 51-70 y       | 158 (59) |
| >70 y         | 65 (24)  |
| Sex           |         |                |
| Female:male   | 100 (38):166 (62) |
| Myeloma subtype |       |                |
| IgG/IgA/IgM   | 143 (54)/56 (21)/4 (2) |
| Biclonal/light chain/ascretory | 3 (1)/56 (21)/4 (2) |
| κ/λ/ascretory | 165 (62)/100 (38)/1 (0.4) |
| ISS stage     |         |                |
| I/I/III       | 94 (35)/74 (28)/98 (37) |
| Durie-Salmon stage |   |                |
| I/I/III       | 50 (19)/26 (10)/190 (71) |
| A:B           | 205 (77)/61 (23) |
| Bone marrow infiltration |       |                |
| Cytology/histopathology | 40 (0-90)/40 (0-100) |
| Cytogenetics  |         |                |
| Standard risk/high risk*missing | 184 (69)/36 (14)/46 (17) |
| Laboratory parameters |       |                |
| eGFR, mL/min/1.73 m² | 67 (7-163) |
| Creatinine, mg/dL | 1.0 (0.5-8.4) |
| β₂-microglobulin, mg/dL | 3.8 (0.8-38.4) |
| Albumin, g/dL | 4.0 (1.5-47.2) |
| Lactate dehydrogenase, U/L | 207 (79-862) |
| Therapy       |         |                |
| NA-CTx, ∅SCT  | 58 (22)  |
| Auto/allo-SCT | 161 (61)/23 (9) |
| ∅ NA-CTx, ∅SCT | 24 (9)  |
| Patients within clinical trials | 66 (23) |
| Best response |         |                |
| CR/vgPR/PR    | 53 (20)/87 (33)/65 (24) |
| SD/PD         | 55 (21)/6 (2) |
| Survival analysis |       |                |
| PFS/OS, mo    | 29 (0-65)/58 (0-65) |

Comorbidity scores and functional tests

| Characteristic | No. (%) | Median (Range) |
|---------------|---------|----------------|
| R-MCI         | 4 (0-9)  |
| IMWG frailty score | 1 (0-4)  |
| CCI           | 2 (0-7)  |
| HCT-CI        | 2 (0-9)  |
| KF            | 1 (0-3)  |
| Patient-rated fitness | 3 (1-6)  |
| Physician-rated fitness | 3 (1-6)  |
| TUGT          | 10 (4-32) |
| MMSE          | 28 (15-30) |
| ADL           | 5 (1-6)  |
| IADL          | 8 (1-8)  |
| Pain (NRS)    | 2 (0-10) |
| GDS           | 2 (0-13) |
| KPS           | 80 (30-100) |

Abbreviations: ∅ NA-CTx, no novel agent-based chemotherapy performed; ∅ SCT, no stem cell transplantation performed; ADL, Activity of Daily Living; auto/auto-SCT, autologous/allologenic stem cell transplantation; CCI, Charlson Comorbidity Index; CR, complete remission; eGFR, estimated glomerular filtration rate; GDS, Geriatric Depression Scale; HCT-CI, Hematopoietic Cell Transplantation-Specific Comorbidity Index; IADL, Instrumental Activity of Daily Living; Ig, immunoglobulin; IMWG, International Myeloma Working Group; ISS, International Staging System; KF, Kaplan-Feinstein Index; KPS, Karnofsky Performance Status; MMSE, Mini-Mental State Examination; NA-CTx, novel agent-based chemotherapy; NRS, numeric rating scale; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial remission; R-MCI, Revised Myeloma Comorbidity Index; SCT, stem cell transplantation; SD, stable disease; SF-12 PCS, 12-Item Short Form Health Survey Physical Composite Scale; SF-12 MCS, 12-Item Short Form Health Survey Mental Composite Scale; TUGT, Timed Up and Go Test; vgPR, very good partial remission.

*Defined as t(4;14), t(14;16), t(14;20), or del(17p).
Therefore, a large proportion of patients with MM presented with existing comorbidities and an impaired physical and functional constitution that was easily perceivable via comorbidity scores and functional tests.

### Comparison of Comorbidity Scores and Functional Tests via Univariate and Multivariate Analyses and Proposal of an Abbreviated Assessment

With risk group definitions of fit, (intermediate-fit), and frail patients according to Table 1, comorbidity scores and functional tests could be compared. The prognostic significance of different comorbidity scores and functional tests was assessed via univariate Cox regression analyses (Table 4).

| No. | Scores and Functional Tests | Risk Group | No. | % | HR (95% CI) | P |
|-----|-----------------------------|------------|-----|---|-------------|---|
| 1.  | Comorbidity scores (n = 5)  |            |     |   |             |   |
| 1   | R-MCI                       | Fit        | 79  | 30| 2.2 (1.0-4.9) | .0014 |
|     |                             | Intermediate-fit | 154 | 58| 5.2 (2.1-13.0) | .0003 |
|     |                             | Frail      | 33  | 12|             |   |
| 2   | IMWG frailty score          | Fit        | 76  | 29*| 1.0 (0.4-2.6) | .0079 |
|     |                             | Intermediate-fit | 92  | 35*|             |   |
|     |                             | Frail      | 98  | 37|             |   |
| 3   | CCI                         | Fit        | 120 | 45|             | .0177 |
|     |                             | Frail      | 146 | 55| 2.3 (1.2-4.2) | .0326 |
| 4   | HCT-CI                      | Fit        | 129 | 48|             |   |
|     |                             | Frail      | 137 | 52| 1.2 (0.7-2.1) | .4304 |
| 5   | KF                          | Fit        | 146 | 55|             | .0002 |
|     |                             | Frail      | 120 | 45|             |   |
| 6   | Functional tests (n = 12)   |            |     |   |             |   |
| 1   | Patient-rated fitness       | Fit        | 150 | 56| 2.2 (1.3-3.8) | .0045 |
|     |                             | Frail      | 116 | 44|             |   |
| 2   | Physician-rated fitness     | Fit        | 153 | 58| 2.0 (1.2-3.5) | .0100 |
|     |                             | Frail      | 113 | 42|             |   |
| 3   | TUGT                        | Fit        | 168 | 63| 1.9 (1.1-3.2) | .0187 |
|     |                             | Frail      | 98  | 37|             |   |
| 4   | MMSE                        | Fit        | 231 | 87| 3.1 (1.7-5.6) | .0002 |
|     |                             | Frail      | 35  | 13|             |   |
| 5   | ADL                         | Fit        | 168 | 63| 1.9 (1.1-3.3) | .0177 |
|     |                             | Frail      | 98  | 37|             |   |
| 6   | IADL                        | Fit        | 232 | 87|             | .0312 |
|     |                             | Frail      | 34  | 13| 2.5 (1.3-4.6) | .0048 |
| 7   | Pain (NRS)                  | Fit        | 174 | 65| 1.7 (1.0-3.0) | .0639 |
|     |                             | Frail      | 92  | 35| 1.8 (1.1-3.1) | .0002 |
| 8   | GDS                         | Fit        | 207 | 78| 3.2 (1.7-5.9) | .0002 |
|     |                             | Frail      | 59  | 22| 1.7 (1.0-3.0) | .0002 |
| 9   | KPS                         | Fit        | 142 | 53|             | .0112 |
|     |                             | Frail      | 124 | 47| 2.3 (1.2-4.4) | .0073 |
| 10  | SF-12 PCS                   | Fit        | 105 | 40|             | .5049 |
|     |                             | Frail      | 158 | 60|             |   |
| 11  | SF-12 MCS                   | Fit        | 184 | 62| 1.2 (0.7-2.1) | .4073 |
|     |                             | Frail      | 99  | 38|             |   |
| 12  | Malnutrition Checklist by Suter | Fit      | 89  | 33|             | .0177 |
|     |                             | Frail      | 177 | 67|             |   |

Bold indicate statistical significance with values <0.05. Abbreviations: ADL, Activity of Daily Living; CCI, Charlson Comorbidity Index; CI, confidence interval; GDS, Geriatric Depression Scale; HCT-CI, Hematopoietic Cell Transplantation–Specific Comorbidity Index; HR, hazard ratio; IADL, Instrumental Activity of Daily Living; IMWG, International Myeloma Working Group; KF, Kaplan-Feinstein Index; KPS, Karnofsky Performance Status; MMSE, Mini-Mental State Examination; NRS, numeric rating scale; R-MCI, Revised Myeloma Comorbidity Index; SF-12 MCS, 12-Item Short Form Health Survey Mental Composite Scale; SF-12 PCS, 12-Item Short Form Health Survey Physical Composite Scale; TUGT, Timed Up and Go Test.

Asterisk state that the IMWG-frailty score percentages of group made up 101% due to rounding, because sum of 29%+35%+37% = 101%.
well-separated risk groups for OS and PFS (Fig. 3A-H). The 3-year OS rates were 90%, 74%, and 43% via the R-MCI for fit, intermediate-fit, and frail patients, respectively ($P = .0006$; Fig. 3A); 80% and 66% via the ADL for fit and frail patients, respectively ($P = .0159$; Fig. 3D); 78% and 48% via the MMSE for fit and frail patients, respectively ($P = .0001$; Fig. 3E), and 86% and 66% via the SF-12 PCS for fit and frail patients, respectively ($P = .0091$; Fig. 3G).

The 3-year PFS rates were 50%, 34%, and 15% via the R-MCI for fit, intermediate-fit, and frail patients, respectively (Fig. 3B); 41% and 29% via the ADL for fit and frail patients, respectively (Fig. 3D); and 37% and 27% via the MMSE for fit and frail patients, respectively (Fig. 3F). In contrast, the SF-12 PCS showed no statistical significance for PFS (Fig. 3H).

The Kaplan-Meier curves of the 4 additionally tested comorbidity scores (IMWG, CCI, KF, and HCT-CI) are
shown in Supporting Figure IA-H; those of the remaining functional tests (KPS, physician-rated fitness, patient-rated fitness, IADL, pain score, GDS, TUGT, malnutrition, and SF-12 MCS) are shown in Supporting Figure 2A-R.

Brier scores were calculated to compare the prediction errors of the abbreviated FA (R-MCI + ADL + MMSE + SF-12 PCS) with the R-MCI alone (Fig. 4). Both the abbreviated FA and the R-MCI alone showed lower prediction errors in comparison with the reference model (without any variable). The abbreviated FA revealed the lowest prediction error. The addition of 3 functional tests (ADL, MMSE, and SF-12 PCS) to the R-MCI, therefore, allowed a better risk assessment of patients with MM than the R-MCI alone.

Moreover, the R-MCI proved to be the strongest predictor of OS via univariate analysis, with the addition of 3 functional tests (ADL, MMSE, and SF-12 PCS) further improving this survival prediction.

**Follow-Up Analysis (T0 vs T1 Assessment)**

Because the vulnerability of patients may change during the course of treatment, we conducted a follow-up analysis at least 6 months (mean follow-up, 11 months; range, 6-38 months) after the baseline assessment (Fig. 1C and Table 2). We compared the results of the comorbidity scores and functional tests between T0 and T1. The follow-up cohort included 165 patients with both T0 and T1 assessments. Patient characteristics are displayed in Supporting Table 1. Nevertheless, it has to be kept in mind that only 62% of the initially assessed patients could be included. Therefore, a certain bias cannot be excluded: the follow-up analysis assessed less fragile, younger, and more responsive patients.

Mean values of all 5 comorbidity scores and 12 functional tests at T0 and T1 as well as the resulting mean individual changes between T0 and T1 are shown with corresponding \( P \) values in Table 2. Notably, 4 of the 5 comorbidity scores (R-MCI, IMWG frailty score, CCI, and KF) improved significantly during the course of treatment. Consequently, patients benefited from the applied MM therapy, and their constitution did improve through therapy. Remarkably, score changes were most pronounced for the R-MCI (Table 2).

All functional tests showed improvements between T0 and T1 likewise. This was significant for the KPS, physician- and patient-rated fitness, ADL, MMSE, TUGT, and SF-12 PCS (Table 2).

The changes between T0 and T1 were also assessed in younger (≤70 years; \( n = 120 \ [73\%] \)) and older patients (>70 years; \( n = 45 \ [27\%] \)) and in those with a therapy response (≥PR; \( n = 138 \ [84\%] \)) or less (<PR; \( n = 27 \ [16\%] \)), as shown in Supporting Tables 3 and 4. Among patients ≤70 years old, 4 of the 5 assessed comorbidity scores (R-MCI, IMWG frailty score, CCI, and KF) improved significantly during therapy. In contrast, among patients >70 years old, only the R-MCI improved significantly. Among functional tests, 8 tests significantly improved in patients ≤70 years old (patient- and physician-rated fitness, TUGT, MMSE, ADL, IADL, KPS, and SF-12 PCS), whereas only 2 (ADL and KPS) did in patients >70 years old (Supporting Table 3).

Likewise, in responding patients (reaching at least partial remission), 3 comorbidity scores (R-MCI, IMWG frailty score, and CCI) improved significantly at follow-up. Moreover, all functional tests in patients with ≥PR improved at follow-up. This was significant for 7 tests (patient- and physician-rated fitness, TUGT, ADL, IADL, KPS, and SF-12 PCS). In contrast, in lesser responding patients (<PR), no comorbidity score showed significant improvements. Half of the functional tests improved; this reached significance for the MMSE, KPS, and SF-12 PCS (Supporting Table 4).

Thus, FA scores and tests more numerously and significantly changed in younger patients (vs older patients) and those with ≥PR (vs those with <PR). This suggests better functional reconstitution in younger and responsive patients versus older and less responsive patients.

**R-MCI Distribution and MM Therapy in Patients ≤70 Years old Versus Patients >70 Years Old**

To evaluate the distribution of fit, intermediate-fit, and frail patients in different age groups, a subgroup analysis was performed for patients ≤70 years old (≈76% of the entire cohort) and patients >70 years old (≈24%; Fig. 5A). Although 38% were classified as fit, 58% were classified as intermediate-fit, and 4% were classified as

**TABLE 5. Multivariate Cox Regression Model With Backward Selection (R-MCI Forced in, \( P = .1 \))**

| Functional Tests | Risk Group Test | HR (95% CI) | \( P \) |
|------------------|----------------|-------------|--------|
| 1. R-MCI         | Intermediate-fit vs fit | 2.0 (0.9-4.6) | .0432  |
|                  | Frail vs fit     | 3.5 (1.3-9.2) | .0658  |
| 2. ADL           | Frail vs fit     | 1.7 (1.0-2.9) | .0131  |
| 3. MMSE          | Frail vs fit     | 2.3 (1.2-4.4) | .0128  |
| 4. SF-12 PCS     | Frail vs fit     | 2.3 (1.2-4.4) | .0128  |

Bold indicate statistical significance with values <0.05.

Abbreviations: ADL, Activity of Daily Living; CI, confidence interval; HR, hazard ratio; MMSE, Mini-Mental State Examination; R-MCI, Revised Myeloma Comorbidity Index; SF-12 PCS, 12-Item Short Form Health Survey Physical Composite Scale.
frail among patients ≤70 years old via the R-MCI, these proportions were 3%, 60%, and 37% in patients >70 years old, respectively (Fig. 5B).

Subsequently, the treatment of younger (Fig. 5C) and older patients (Fig. 5D) was evaluated in defined age groups. Only 8% of patients ≤70 years old but 63% of patients >70 years old were treated with novel agent–based chemotherapy without SCT. In contrast, 72% of the patients ≤70 years old and only 26% of the patients >70 years old were treated with ASCT. Allogeneic SCT was exclusively performed in younger patients (Fig. 5C,D). The R-MCI subgroup distribution of fit, intermediate-fit, and frail patients according to different treatment groups is shown in Figure 5E,F for patients ≤70 years old and patients >70 years old. Those with discrepant results were analyzed separately (potential overtreatment

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**Figure 3.** Kaplan-Meier plots of the 4 different tests of the abbreviated assessment. (A) OS and (B) PFS according to the R-MCI. (C) OS and (D) PFS according to the ADL. (E) OS and (F) PFS according to the MMSE. (G) OS and (H) PFS according to the SF-12 PCS. ADL indicates Activity of Daily Living; MMSE, Mini-Mental State Examination; OS, overall survival; PFS, progression-free survival; R-MCI, Revised Myeloma Comorbidity Index; SF-12 PCS, 12-Item Short Form Health Survey Physical Composite Scale.
or undertreatment; see the groups boxed in purple in Fig. 5E,F).

Expectedly and in line with the R-MCI distribution, intensive treatment such as SCT was performed significantly more often in younger patients (≤70 years) than older patients (>70 years).

**Subgroups of Patients With Potential Overtreatment or Undertreatment**

An exemplary assessment of potentially overtreated and undertreated patients was performed for the few patients with MM shown in purple boxes in Figure 5E,F: potentially overtreated was defined as those patients who received ASCT despite frail R-MCI scores (frail ASCT patients with purple borders in Fig. 5E,F).

Supporting Table 2A summarizes the outcome of 8 patients ≤70 years old (6%) who received ASCT and were classified as frail (R-MCI, 7-9; Fig. 5E and Supporting Table 2A). These patients benefited from ASCT, especially because of their aggressive MM, but received reduced melphalan conditioning and were carefully monitored. Therefore, PFS was substantial (5+ to 155 months), and serious therapy-related complications could be avoided.

The clinical course of 1 frail patient >70 years old (2%) who received ASCT is shown in Figure 5F (again highlighted in purple). This patient also benefited from ASCT (PFS, 32 months), which was well tolerated with dose-reduced melphalan conditioning (Supporting Table 2B).

Furthermore, the medical history of a patient who may have been undertreated was examined (2%; highlighted in purple as fit in Fig. 5F): Supporting Table 2C shows the medical history of this 71-year-old patient who, although classified as fit via the R-MCI, did not receive ASCT but might have benefited from it (PFS, 9 months). ASCT was not performed because of patient concerns.

Therefore, an FA may contribute to identifying high-risk patients who should receive reduced melphalan conditioning, additional supportive treatments, and careful monitoring to be safely treated, with intensive approaches thereby not entirely avoided.

**DISCUSSION**

There is evidence that certain comorbidities are prognostically relevant for the survival of patients with MM. However, other geriatric domains, such as cognition, psychological status, and geriatric syndromes, have not been sufficiently investigated. Because of the limited resources of medical professionals, especially in times of the coronavirus disease 2019 pandemic, it seems useful to design an abbreviated, time-efficient FA. For this reason, we conducted a test battery with 7327 tests
altogether; this consisted of 17 different comorbidity scores and functional tests for 266 prospectively assessed patients with MM at the baseline and follow-up. Because we had previously compared the UK Myeloma Research Alliance Risk Profile score, which was published in 2019 (after the start of this analysis), it was not a focus of this analysis.37,38

On the basis of defined cutoffs, our MM cohort was grouped into uncompromised (fit) patients and compromised (frail) patients via comorbidity scores and functional tests (Table 1). Intermediate-fit and frail patients were numerous among patients with MM, although their median age at our referral center was just 62 years in contrast to older cohorts at others.18,39,40 Notably, the R-MCI and IMWG frailty scores generated comparable results, and so did the CCI, KF, and HCT-CI. In line with this, the risk group distribution via 12 functional tests revealed considerable impairment: compromised IADL, MMSE, GDS were present in 13% to 22%; were more frequent for pain, ADL, TUGT, SF-12 MCS, physician- and patient-rated fitness in 35% to 44%; and were most prevalent for KPS, ADL, and functional tests. We found that assessment results for most of the conducted comorbidity scores and functional tests seem to suggest that an assessment of cognitive function via the MMSE is relevant. The TUGT, with our cutoff of <11 seconds versus ≥11 seconds and as an objective measure of physical function, did not add to our model; in contrast, Liu et al in 201941 found gait speed to be prognostic (mean age, 79.7 years). Nevertheless, gait speed and the TUGT are different measures, the former not being used in our FA battery.41 In our uniform MM cohort, we did confirm, nevertheless, that a deteriorated TUGT has an effect on survival in MM (HR, 1.9), although other risk factors such as the R-MCI are stronger predictors (HR, 5.2). Moreover, our results determined that the R-MCI provides a robust survival prediction among the performed comorbidity scores.

On the basis of univariate and multivariate Cox regression analyses, we were able to determine 3 functional tests to complement the R-MCI: namely, the ADL, MMSE, and SF-12 PCS, which, in addition to the R-MCI, had a predictive effect on survival. Our newly developed abbreviated FA can be used to evaluate the prognosis and risk status precisely. However, FA-guided therapy decision-making is still to be tested in future clinical trials. Our results confirm other studies demonstrating that the comorbidities, self-sufficiency, cognitive abilities, and quality of life of hematologic-oncological patients affect their prognosis.1,2,8,10,42-44

Although older people are often excluded from clinical studies and intensive treatment regimens, several studies have proven the feasibility and effectiveness of intensive treatment regimens, such as ASCT, triplets, and quadruplets, in elderly patients as well.7 Our data have verified that intensive treatment regimens are considerably less common in older patients; this seems up for discussion because 48% of patients >70 years old who did not receive ASCT were classified as fit or intermediate-fit via the R-MCI (Fig. 5F and Supporting Table 2C). Our abbreviated FA could, therefore, help to adapt the treatment intensity individually to a patient’s condition more objectively and further improve the survival of patients with MM in the future.8,13,15

Antoine-Pelpeljuguosi and Braunstein in 201945 recommended that an FA should be repeated throughout the entire treatment to modify treatment if necessary. We also conducted a follow-up analysis in 165 of our patients (62%) after ≥6 months of treatment with all 17 scores and tests. We found that assessment results for most of the conducted comorbidity scores and functional tests...
significantly improved over time. This indicates that the general physical condition and accompanying comorbidities may improve upon response. Indeed, we observed that patients’ fitness, self-sufficiency, cognition, and quality of life improved because of treatment among patients with responses to MM therapy (≥PR) in comparison with those with lesser responsiveness (<PR). Moreover, in older patients with MM (>70 years), FA changes were less prominent in comparison with younger patients (≤70 years); this suggests that full FA reconstitution may decrease with age and require longer time periods than our mean follow-up of 11 months. Thus, an FA may not only help to differentiate between fit and frail patients but also contribute to a more objective assessment of health changes during the course of therapy.

The strengths of this analysis included the large number of tests performed (n = 7327), the broad range of comorbidity scores and functional tests, and the dynamic assessment after ≥6 months of treatment in a prospective MM patient cohort. This enabled us to evaluate the functional constitution of our patients precisely both at the baseline and at follow-up to address longitudinal changes. A potential limitation of this work might be the heterogeneity of our patient cohort. Their ages ranged from 27 to 92 years, and patients were treated with different, standard National Comprehensive Cancer Network/IMWG/European Myeloma Network–approved MM therapies. Because it was our intention to perform our analyses on real-world patients and to examine patients with different, albeit typical MM therapies, our patient cohort represented a usual cohort for tertiary centers.16,18,46 Moreover, the statistical approach of using a backward variable elimination approach may be criticized, and a vast variety of alternative procedures exist. Therefore, we checked the stability of the final model by applying forward and stepwise selection. The stepwise procedure led to the identical model presented. The forward selection procedure additionally included the IADL, but with \( P = .24 \). Thus, we consider our results to be sufficiently stable. Also, it can be criticized that some follow-up patients were missing for whom the FA repetition was not available. These patients did not just drop out at random but may have died or may be suspected to have been frail. With respect to a potential selection bias, it should be taken into consideration whether the analysis of changes is actually relevant for the complete population or only for those who survive until the next assessment time point. Lastly, our intention to develop an abbreviated FA, which included the R-MCI, MMSE, ADL, and SF-12 PCS, may also prove time-consuming in comparison with the R-MCI alone. The suggested FA added robustness to the breadth of domains of older adult health measured but may be at risk of the same barriers to implementation in busy oncology practices. The implementation of an FA in myeloma tumor boards may support physicians in necessary treatment decisions because this adds an objective assessment of a patient’s individual constitution and possible treatment endurance. Future studies are needed to evaluate the benefits of a functionally adapted treatment approach versus treatment as usual.

In conclusion, we have demonstrated that intensive treatment is still less common in older patients versus younger patients. Our newly developed FA is suitable to assess the prognosis and functional health status of patients with MM even more precisely than the R-MCI alone. In the future, the FA could help to individualize therapy decisions and thus further and sustainably improve the effectiveness and tolerance of MM therapy. Further studies are needed to evaluate the benefits of this functional-adapted treatment approach in patients with MM.

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**AUTHOR CONTRIBUTIONS**
Sophia Scheubeck: Performance of analysis, analysis of results, preparation of tables and figures, and writing of the manuscript. Gabriele Ihorst: Performance of analysis, analysis of results, preparation of tables and figures, research design, and writing of the manuscript. Katja Schoeller: Performance of analysis. Maximilian Holler: Performance of analysis. Mandy-Deborah Möller: Performance of analysis. Heike Reinhardt: Performance of analysis. Ralph Wäsch: Performance of analysis and research design. Monika Engelhardt: Performance of analysis, analysis of results, preparation of tables and figures, research design, and writing of the manuscript. All authors approved and carefully corrected the manuscript.

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