# Comorbidity indices for prognostic evaluation in multiple myeloma: a comprehensive evaluation of the Revised Myeloma Comorbidity Index and other comorbidity indices with pro- and retrospective applications

Multiple myeloma (MM) is a hematologic neoplasia that typically affects elderly patients. During the last decades, its prognosis has greatly improved. Nevertheless, older adults have multiple comorbidities, making therapy endurance a continuous challenge.[1] In order to personalize therapy, it has been suggested to objectively assess patients' overall fitness. Comorbidity/frailty scores (comorbidity indices [CI]) have shown prognostic precision to define "fit" *versus* "frail" patients.[2-4] They may also prove advantageous to adjust patient-specific regimens and reduce therapy-induced side effects.[5,6] There are several CI in clinical use, for example the International Myeloma Working Group (IMWG) frailty index or Revised Myeloma Comorbidity Index (R-MCI) apart from others (*Online Supplementary Table S1*).[7,8] For the R-MCI, patients can be divided in two or three risk groups ("fit" *vs*. "frail" or "fit", "intermediate-fit" *vs*. "frail") which reveal significantly different overall survival (OS), progression-free survival (PFS) and therapy endurance.[5,8,9] Since no CI is broadly established,[10] their selection may include the practicability for everyday use, and their applicability for retrospective and prospective data, assuring reproducibility and comparability if used from *post hoc* analyses.[1,11]

Here we evaluated, how the four CI R-MCI,[8] IMWG frailty index,[7] "Charlson Comorbidity Index" (CCI)[12] and Mayo risk score[13] perform, if determined from retrospective data (N=726 patients, test analysis) as compared to their prospective assessment (N=354 patients, validation analysis; Table 1; Figure 1). In addition, five internationally well-discussed CI, namely R-MCI,[8] IMWG frailty index,[7] CCI,[12] Mayo risk score[13] and Myeloma Research Alliance Risk Profile (MRP) score[14] were compared in terms of OS and PFS prediction in fit *versus* frail risk groups. This comparison was done in a pro-

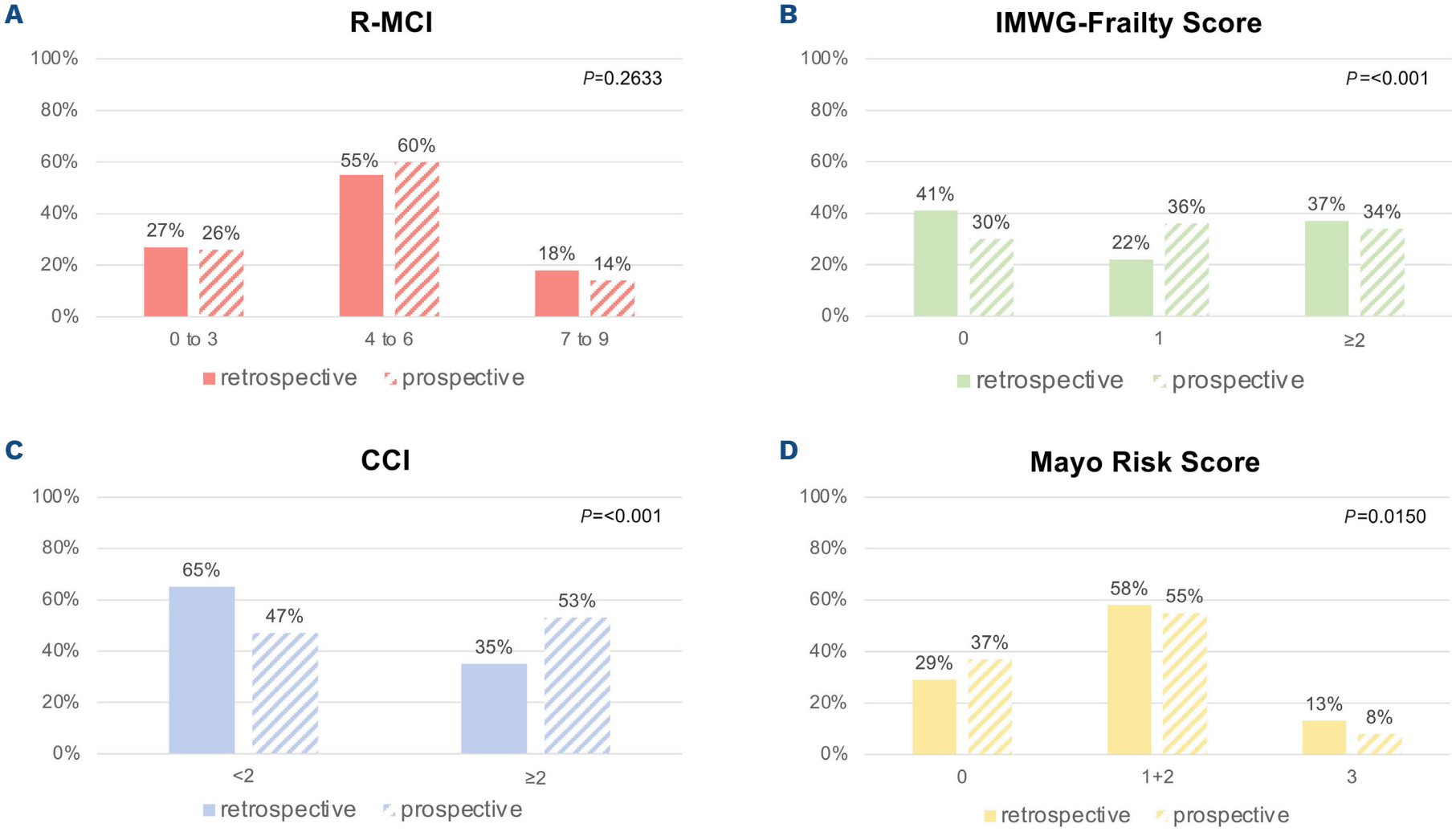



**Figure 1. Comparison of risk group designation via R-MCI, IMWG, CCI and Mayo risk score, using retrospective *versus* prospective data.** (A) Revised Myeloma Comorbidity Index (R-MCI), (B) International Myeloma Working Group (IMWG) frailty index, (C) Charlson Comorbidity Index (CCI) and (D) Mayo risk score compared between prospective and retrospective cohort.

spective cohort of 354 newly diagnosed (ND) MM patients treated at our university medical center (UKF) to determine each score's differentiation of fit *versus* frail patients and of notable differences (Figure 2; *Online Supplementary Table S2*). The patients were included only once in each analysis. As summarized in Table 1, 1,080 NDMM patients treated at the UKF were assessed for the comparison of a retrospective and prospective cohort, with focus on patient characteristics and CI risk group distribution. Differences in risk group distribution within both cohorts were analyzed via $\chi^2$ tests. The MRP score had to be excluded from the retrospective assessment due to missing laboratory data (CRP; Figure 1). For the prospective analysis, we performed a detailed geriatric assessment in 354 patients, assessing all five CI.[5] Patients were divided into three different risk groups "fit", "intermediate-fit" and "frail", except for the CCI, which incorporates two groups only (*Online Supplementary Table S1*). OS and PFS for the five CI and age groups were estimated by Kaplan-Meier method and compared via log-rank test in the prospective cohort (Figure 2; *Online Supplementary Figures S1* and *S2*).

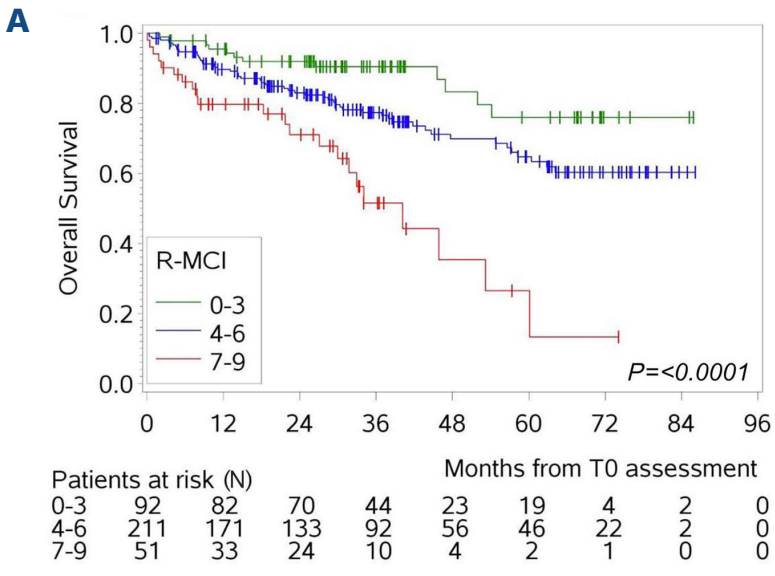
Both retrospective and prospective cohorts were well comparable in terms of patient- and myeloma-specific data (Table 1). The median age in both cohorts was typical for tertiary centers. Patients >70 years were fairly numerous (~1/3) in both cohorts. Concerning myeloma-specific characteristics, both cohorts were comparable, most with advanced International Staging System (ISS II+III) at time of the initial diagnosis (71% and 59%, respectively). Both retrospective and prospective cohorts showed similar organ impairments, like renal function impairment (estimated glomerular filtration rate [eGFR] <60 mg/mL/1.73m$^2$) in 30% and 36%, lung impairment in 25% and 12% and Karnofsky performance status (KPS) decline <70% in 59% and 46%, respectively (Table 1). Induction in both cohorts was predominantly bortezomib-alkylator-dexamethasone-based (VCD).[5,8,9]

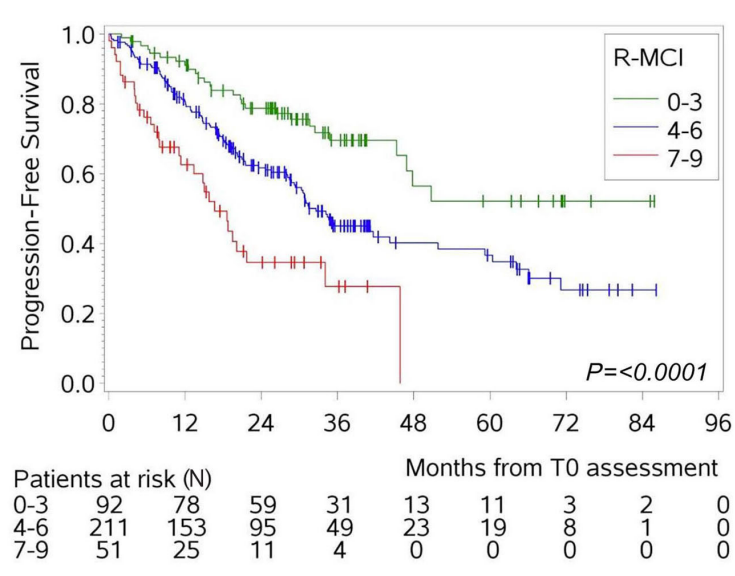
Of note, comparing the retrospective and prospective results of different CI via $\chi^2$ test, the R-MCI was the only CI that did not show significant differences in risk group distribution between retrospective and prospective cohorts, whereas for the IMWG frailty index ($P$<0.001), CCI ($P$<0.001) and Mayo risk score ($P$=0.0150), significant differences were apparent (Figure 1A; *Online Supplementary Table S2*). Respective results for the IMWG frailty index (Figure 1B) and CCI (Figure

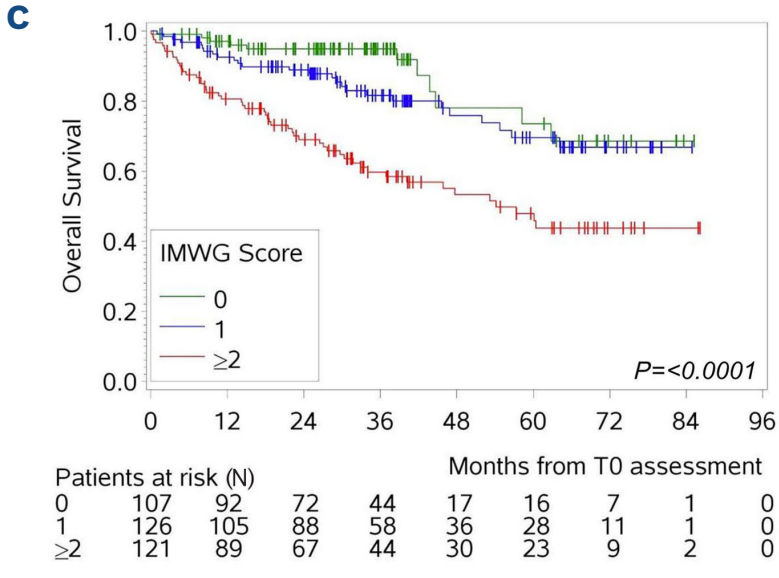
**Table 1.** Patient characteristics.

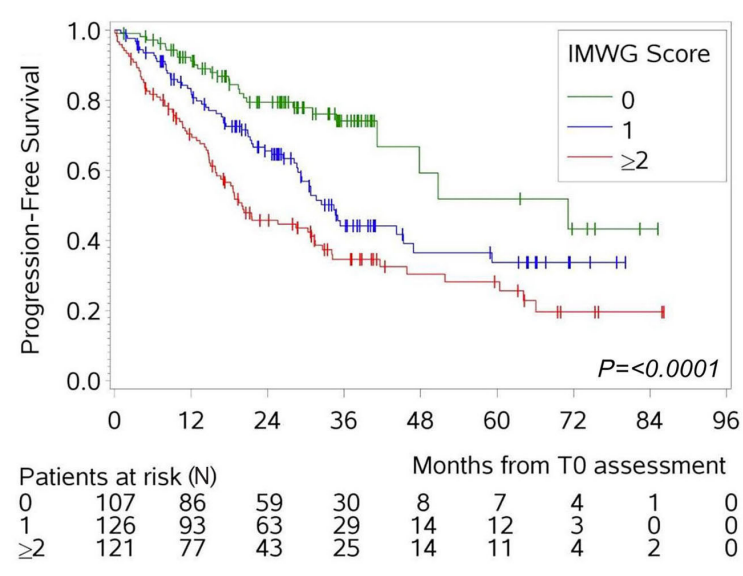
| | Entire patient cohort N=1,080 | | | |
|---|---|---|---|---|
| | Retrospective cohort N=726 (67%) | | Prospective cohort N=354 (33%) | |
| | N (%) | Median (range) | N (%) | Median (range) |
| **Time period** | 1997-2012 | | 2000-2018 | |
| Patient details | | | | |
| Male/female | 409 (56)/317 (44) | | 219 (62)/135 (38) | |
| Age in years | | 63 (22-92) | | 64 (22-92) |
| MM details | | | | |
| Type of MM | | | | |
| IgG/IgA/IgM/LC-only/biclonal/non-secretory | 412 (56)/140 (19)/5 (1)/142 (20)/5 (1)/20 (3) | | 196 (56)/66 (19)/11 (3)/72 (20)/5 (1)/4 (1) | |
| κ/λ/biclonal/non-secretory | 450 (62)/252 (35)/4 (1)/18 (2)[1] | | 222 (63)/129 (35)/2 (1)/1 (1) | |
| AL-amyloidosis | 55 (7) | | 20 (6) | |
| ISS: I/II/III | 211 (29)/193 (27)/322 (44) | | 144 (41)/96 (27)/114 (32) | |
| Cytogenetics: favorable/unfavorable/missing | 274 (38)/187 (26)/265 (36) | | 155 (44)/130 (37)/69 (19) | |
| Renal function: eGFR ≥60/<60 mg/mL/1.73m$^2$ | 506 (70)/220 (30) | | 228 (64)/126 (36) | |
| Lung function: non-impaired[2]/mild-severely impaired[3] | 542 (75)/184 (25) | | 312 (88)/42 (12) | - |
| Karnofsky performance status: | | | | |
| 100% | 46 (6) | | 15 (4) | |
| 80-90% | 250 (35) | | 178 (50) | |
| <70% | 430 (59) | | 161 (46) | |
| Anti-MM therapy | | | | |
| Supportive/localized therapy alone[4] | 72 (10) | | 42 (12) | |
| Standard NA-therapy w/o SCT | 321 (44) | | 82 (23) | |
| ASCT/allo-SCT | 244 (34)/89 (12) | | 204 (58)/26 (7) | |

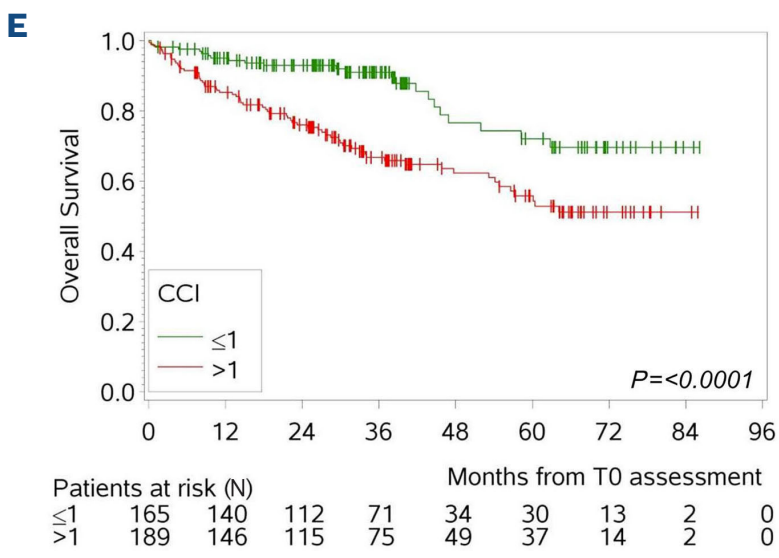
[1]Not evaluated in N=2 patients due to missing data; [2]FEV1 <80%; [3]FEV1 <60%; [4]watch & wait or radiation/local therapy or steroids alone. MM: multiple myeloma; Ig: immunoglobulin; eGFR: estimated glomerular filtration rate; ISS:International Staging System; NA: novel agent-based anti-MM-therapy; SCT: stem cell transplantation; allo-SCT: allogeneic stem cell transplantation; ASCT: autologous stem cell transplantation; w/o: without.

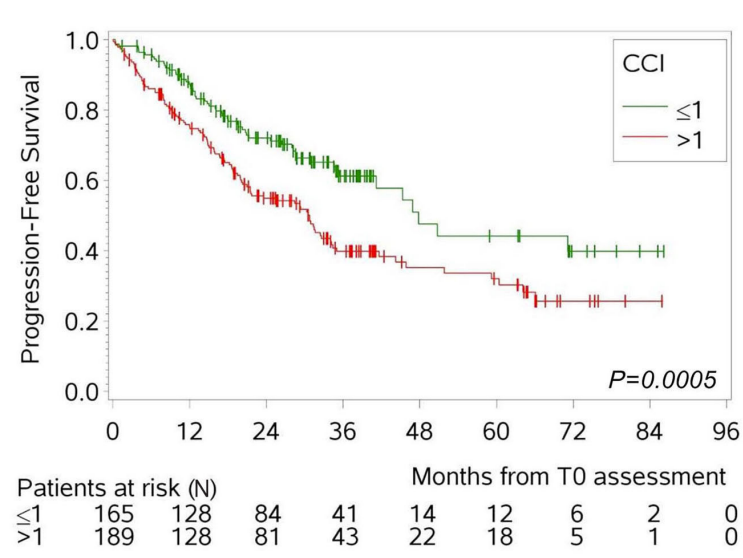


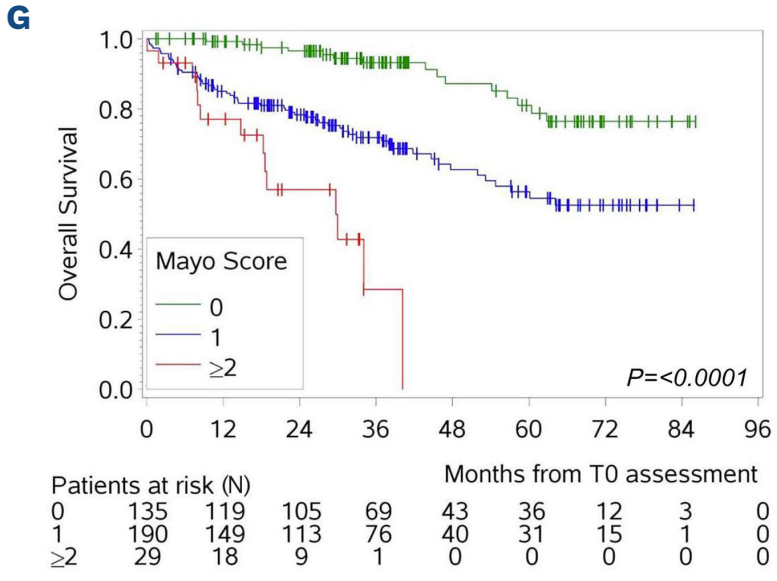



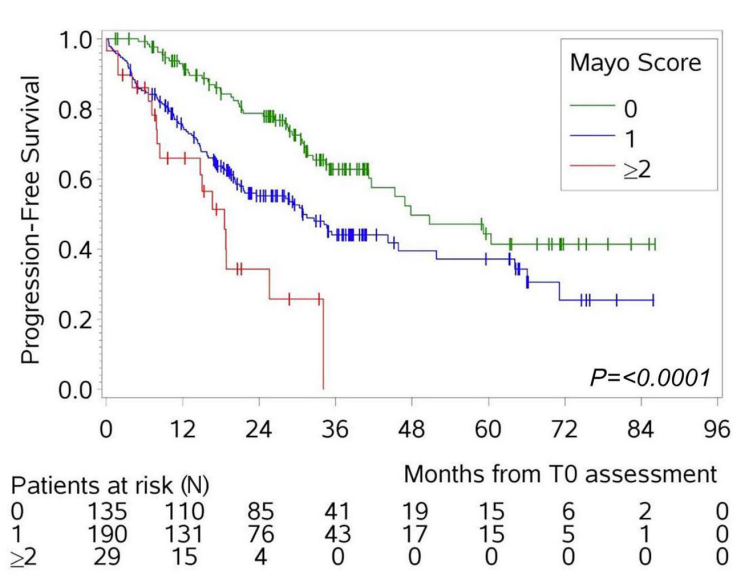




Continued on following page.

**Figure 2. Kaplan-Meier estimates for overall survival and progression-free survival (prospective cohort N=354) according to different comorbidity scores in prospective cohort.** (A) Overall survival (OS) and (B) progression-free survival (PFS) for Revised Myeloma Comorbidity Index (R-MCI). (C) OS and (D) PFS for International Myeloma Working Group (IMWG) frailty index. (E) OS and (F) PFS for Charlson Comorbidity Index (CCI). (G) OS and (H) PFS for Mayo risk score.

1C) showed that significantly more patients were defined as "fit" in the retrospective than prospective cohort with 41% *versus* 30% and 65% *versus* 47%, respectively. The CCI is no standard tool that is routinely assessed in clinical trials or real-world records (due to numerous comorbidities included therein), therefore has to be assessed as best as possible using retrospective data from medical documents. Thus, the number of "frail" patients is often underestimated in retrospective cohorts (*Online Supplementary Tables S1* and *S2*). In line, the IMWG frailty index overestimated "fit" patients from retrospective cohorts (Figure 1B). Not only is the CCI part of the IMWG frailty index, but two functional tests are included: "activity of daily living" (ADL) and "instrumental activity of daily living" (IADL). Since ADL and IADL results about self-care limitations cannot be assessed retrospectively, this information must be assumed as best as possible from medical records. If unavailable, misleading results are obtained retrospectively, which is why it is neither reliable nor feasible to assess the IMWG frailty index retrospectively. This was the reasons, why *post hoc* analyses on frailty were performed with a simplified IMWG frailty index, that contains only age, performance status and CCI.[6,9,10] In contrast, the results for the Mayo risk score (Figure 1D) revealed that 29% of the retrospective cohort were classified as "fit" *versus* 37% of the prospective cohort (*P*=0.0209), space missing (underestimating "fit" patients retrospectively. Moreover, for our retrospective assessment of the Mayo risk score, only 40% of patients could be included due to missing NT-proBNP data as this is not routinely assessed in MM patients (although being used now more frequently to evaluate cardiac function in some centers). Therefore, the Mayo risk score based on performance status, NT-proBNP and age may likewise be challenging to use for retrospective data (Figure 1).

Analyzing the prospective cohort with a median follow-up of 37 months and median OS and PFS of not reached and 35 months, respectively, important group differences in age groups for OS and PFS were evident (*Online Supplementary Figure S1*), but more substantially via CI (Figure 2A-H; *Online Supplementary Figure S2A, B*). Regarding the outcome of different age groups, the median OS was not reached for the younger two age cohorts *versus* 60 months in ≥70-year-old patients (*Online Supplementary Figure S1*). Although the Kaplan-Meier curves showed age group differences, especially the two older age groups did not distinctly separate. Thus, advanced age remains to have an impact on prognosis, but other risk factors beyond age play a significant role in determining outcome as well.

Therefore, the five CI R-MCI,[8] IMWG frailty index,[7] CCI[12], Mayo risk score[13] and MRP score[14] were compared regarding survival prediction (Figure 2A-H; *Online Supplementary Figure S2A, B*). Notable was, that all five CI could divide patients into risk groups with significantly different OS and PFS (*P*<0.05). The 3-year OS for "fit", "intermediate-fit" and "frail" patients via R-MCI was 91%, 77% and 52% (*P*<0.0001; Figure 2A), via IMWG frailty index 95%, 82% and 60% (*P*<0.0001; Figure 2C), via Mayo risk score 93%, 72% and 29% (*P*<0.0001; Figure 2G) and via MRP score 88%, 68% and 44% (*P*<0.0001; *Online Supplementary Figure S2A*), respectively. Consequently, the differences in 3-year OS between "fit" and "frail" patients for R-MCI score, IMWG frailty scrore, Mayo risk score and MRP score were 39%, 35%, 64% and 44%, respectively. Of note, the Kaplan-Meier survival curves for "fit" and "intermediate-fit" patients via IMWG frailty index were superimposable for OS (Figure 2C) and less distinct as compared to the other scores, suggesting that "fit" *versus* "frail" differentiation may suffice in the future.[9] Of interest was also, that albeit the CCI separated "fit" (CCI ≤1) from "frail" (CCI >1) patients, differences in 3-year OS for "fit" (91%) and "frail" (67%) patients were achieved with a 24% difference only (*P*<0.0001; Figure 2E).

The 3-year PFS for all the different risk groups ("fit", "intermediate-fit" and "frail" patients) was 70%, 45% und 28% via R-MCI (*P*<0.0001; Figure 2B), 74%, 44% und 35% via IMWG frailty index (*P*<0.0001; Figure 2D), 63%, 44% und 0% via Mayo risk score (*P*<0.0001; Figure 2H) and 59%, 39% and 19% via MRP score (*P*<0.0001; *Online Supplementary Figure S2B*). For the 3-year PFS, most obvious differences between "fit" and "frail" patients appeared for the R-MCI (42%), IMWG frailty index (39%), Mayo risk score (63%) and MRP score (40%). Again, the CCI showed lowest PFS difference with 21% between "fit" and "frail" patients: the 3-year PFS using the CCI was 61% for "fit" patients and 40% for "frail" patients (*P*=0.0005; Figure 2F).

In conclusion, this analysis (*registration no.: DRKS-00003868*) impressively revealed that the R-MCI was the only CI that did not show significant differences in risk group distribution for both retrospective and prospective data and was reliably assessable in both (Figure 1). Another convenience is that the R-MCI offers a user-friendly homepage (www.myeloma-comorbidityindex.org; *Online Supplementary Table S2*). Of interest, all five CI can divide patients into risk groups with significantly different OS and PFS, albeit group differences between "fit" and "frail" patients were distinctly different and less with age groups alone (Figure 2A-H; *Online Supplementary Figures S1* and *S2*). While in other hematological diseases, CI and fitness assessments are used for tailoring therapy, it is not yet routinely established in MM patients, albeit studies exist to elucidate their usefulness.[5,9,15] Studies showing that "overtreatment" in frail cohorts can impair outcomes have been performed (i.e., the MUK eight study

in which triple therapy was associated with worse OS than double therapy with near significance in frail patients[16]) or our test and validation analysis of the R-MCI, where both undertreatment in fit and overtreatment in frail patients were observed[8] - to name only two examples. The future perspective suggests to include CI in therapy decisions, as shown by Holler *et al*., who described that fitter patients benefit from intensive therapies, whereas frail patients may need initial and/or sustained dose reductions.[9] Despite this and ongoing studies in frail patients, there is still a shortage of standardized tools to assess frailty, hindering the full utilization of its potential to enhance outcome and minimize therapy-related toxicity. Moreover, there are limitations in our current knowledge of whether frailty-adjusted treatment should be generally applied, leads to better treatment outcomes and clinical trials testing 'treatment as usual' *versus* 'frailty-adjusted treatment choices' (i.e., performed in the UK-MRA Myeloma XIV trial) are rare.[2] As of today, 25% of MM physicians are reckoned to use frailty scores to aid in risk assessment and clinical decision making, whereas 75% rely on their clinical judgement alone (personal communication E. Terpos). Thus, our and other studies continue to substantiate benefits of CI-guided treatment decisions, which might change these percentages in the future. Further research through prospective clinical trials seems eminent to determine the optimal, personalized treatment options for each patient. Building on this approach, Mian *et al*. published a systematic review including 43 clinical trials considering frailty tools and showed an encouraging trend to incorporate frailty assessments in clinical evaluations and treatment decisions.[10] As demonstrated by the underlying analysis, the R-MCI provides a coherent score that provides the basis for further research into preeminent ways to personalize MM care according to patients' risk profiles today.

## Authors

Katja Schoeller,[1,2+] Gabriele Ihorst,[3] Heike Reinhardt,[1,2] Maximilian Holler,[1,2] Sophia Scheubeck,[1,2] Georg Herget,[2,4] Ralph Wäsch[1,2] and Monika Engelhardt[1,2+]

[1]Department of Medicine I Hematology and Oncology; [2]Comprehensive Cancer Center Freiburg (CCCF); [3]Clinical Trials Unit and [4]Department of Orthopedics and Trauma Surgery, Medical Center - University of Freiburg, Faculty of Medicine, Freiburg, Germany

[+]*KS and ME contributed equally.*

Correspondence:
M. ENGELHARDT - monika.engelhardt@uniklinik-freiburg.de

https://doi.org/10.3324/haematol.2023.283884

Received: August 23, 2023.
Accepted: November 21, 2023.
Early view: November 30, 2023.



**Disclosures**

No conflicts of interest to disclose.

**Contributions**

The results of this work are based on the results of the dissertation of KS. KS acquired and analyzed the data, and both ME and KS wrote the paper. GI performed the statistical analysis. All authors discussed the results and contributed to the final manuscript.

**Acknowledgments**

The authors thank distinguished IMWG, EMN, DSMM and GMMG experts and friends. We are specially obliged to Prof Dr J. Duyster (Freiburg, UKF), Dr Dr J. Jung (TU München), Dr J. Waldschmidt (UK Würzburg), Dr C. Miething (UKF), Dr M. Rassner (UKF, now postdoc in Japan). We are also very thankful to all AG Engelhardt & Wäsch group members for their utmost MM enthusiasm, feedback and revision input. We thank the Center for biobanking (FREEZE-Biobank) for their support. We acknowledge the interdisciplinary multiple myeloma (MM) tumor board group of our CCCF, Prof Dr G Herget, Dr H. Schäfer, PD Dr J. Neubauer, Prof Dr Dr R. Schmelzeisen, Prof Dr G. Walz, and Prof Dr W. Kühn for their outstanding support. We greatly acknowledge the anonymous reviewers for their input and recommendations. We are also indebted to IMWG, EMN and DSMM/GMMG experts for their insights on the data and manuscript, and thank all MM patients who participated in this study.

**Data-sharing statement**

The data that supports the findings of this study are available from the corresponding author upon reasonable request.

## References

1. Larocca A, Dold SM, Zweegman S, et al. Patient-centered practice in elderly myeloma patients: an overview and consensus from the European Myeloma Network (EMN). Leukemia. 2018;32(8):1697-1712.
2. Coulson AB, Royle K-L, Pawlyn C, et al. Frailty-adjusted therapy in transplant non-eligible patients with newly diagnosed multiple myeloma (FiTNEss (UK-MRA Myeloma XIV Trial)): a study protocol for a randomised phase III trial. BMJ Open. 2022;12(6):e056147.
3. Efficace F, Gaidano G, Petrucci MT, et al. Association of IMWG frailty score with health-related quality of life profile of patients with relapsed refractory multiple myeloma in Italy and the UK: a GIMEMA, multicentre, cross-sectional study. Lancet Healthy Longev. 2022;3(9):e628-e635.

4. Pawlyn C, Khan AM, Freeman CL. Fitness and frailty in myeloma. Hematol Am Soc Hematol Educ Program. 2022;2022(1):337-348.
5. Scheubeck S, Ihorst G, Schoeller K, et al. Comparison of the prognostic significance of 5 comorbidity scores and 12 functional tests in a prospective multiple myeloma patient cohort. Cancer. 2021;127(18):3422-3436.
6. Facon T, Dimopoulos MA, Meuleman N, et al. A simplified frailty scale predicts outcomes in transplant-ineligible patients with newly diagnosed multiple myeloma treated in the FIRST (MM-020) trial. Leukemia. 2020;34(1):224-233.
7. Palumbo A, Bringhen S, Mateos M-V, et al. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report. Blood. 2015;125(13):2068-2074.
8. Engelhardt M, Domm A-S, Dold SM, et al. A concise revised Myeloma Comorbidity Index as a valid prognostic instrument in a large cohort of 801 multiple myeloma patients. Haematologica. 2017;102(5):910-921.
9. Holler M, Ihorst G, Reinhardt H, et al. An objective assessment in newly diagnosed multiple myeloma to avoid treatment complications and strengthen therapy adherence. Haematologica. 2023;108(4):1115-1126.
10. Mian H, McCurdy A, Giri S, et al. The prevalence and outcomes of frail older adults in clinical trials in multiple myeloma: a systematic review. Blood Cancer J. 2023;13(1):1-13.
11. Mateos M-V, Dimopoulos MA, Cavo M, et al. Daratumumab plus bortezomib, melphalan, and prednisone versus bortezomib, melphalan, and prednisone in transplant-ineligible newly diagnosed multiple myeloma: frailty subgroup analysis of ALCYONE. Clin Lymphoma Myeloma Leuk. 2021;21(11):785-798.
12. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-383.
13. Milani P, Vincent Rajkumar S, Merlini G, et al. N-terminal fragment of the type-B natriuretic peptide (NT-proBNP) contributes to a simple new frailty score in patients with newly diagnosed multiple myeloma. Am J Hematol. 2016;91(11):1129-1134.
14. Cook G, Royle K-L, Pawlyn C, et al. A clinical prediction model for outcome and therapy delivery in transplant-ineligible patients with myeloma (UK Myeloma Research Alliance Risk Profile): a development and validation study. Lancet Haematol. 2019;6(3):e154.e166.
15. Eichhorst B, Hallek M, Goede V. Management of unfit elderly patients with chronic lymphocytic leukemia. Eur J Intern Med. 2018;58:7-13.
16. Auner HW, Brown SR, Walker K, et al. Ixazomib with cyclophosphamide and dexamethasone in relapsed or refractory myeloma: MUKeight phase II randomised controlled trial results. Blood Cancer J. 2022;12(4):52.