Validation of the Revised Myeloma Comorbidity Index and other comorbidity scores in a multicenter German study group multiple myeloma trial

In the past decade, the survival of patients with multiple myeloma (MM) has improved significantly. This encouraging progress has been driven by deeper biological insights, implementation of more sensitive diagnostic tests leading to earlier diagnosis, access to more effective therapies and better supportive care.[1] MM typically affects elderly patients, who are less likely to endure treatment and who have a less favorable long-term prognosis.[2] Moreover, accompanying diseases may complicate anti-myeloma treatment.[1] In general, comorbidities have been shown to influence cancer patients' general health status, limit their physical condition, and worsen their progression-free and overall survival.[3,4] Therefore, with the growing number of elderly (and frail) MM patients, reliable tools to assess patients' vulnerability, as expressed by chronic conditions and limitations in daily activities, are wanted to guide us through today's multiple possible therapeutic options.[5,6]

Historically, treatment decisions for symptomatic MM patients were age-based. Ideally nowadays disease biology and fitness, including patients' Karnofsky Performance Status (KPS) or Eastern Cooperative Oncology Group Performance Status (ECOG-PS), are considered when assessing therapeutic options.[5] However, KPS and ECOG-PS are often overestimated and may not reflect patients' entire functional status.[4,6] We and others have learnt from re-scoring cancer patients that initially estimated KPS and ECOG-PS scores, measured by physicians and health staff, are often claimed to be much better than those determined by objective definition and the patients' actual fitness status. In a prior analysis, we re-scored the KPS in approximately 500 MM patients who had appeared, according to the physicians' initial estimate, almost uncompromised with a median score of 90%, but on re-scoring had scores 30% lower than initially presumed.[4,6] More objective parameters to assess patients' PS and fitness are therefore warranted. Moreover, since elderly MM patients are often excluded from clinical trials due to strict inclusion criteria,[7] trial results typically reflect <10% of 'real-world patients' and are less well transferable to elderly patients.[8,9]

In this context, the International Myeloma Working Group (IMWG), European Myeloma Network (EMN) and

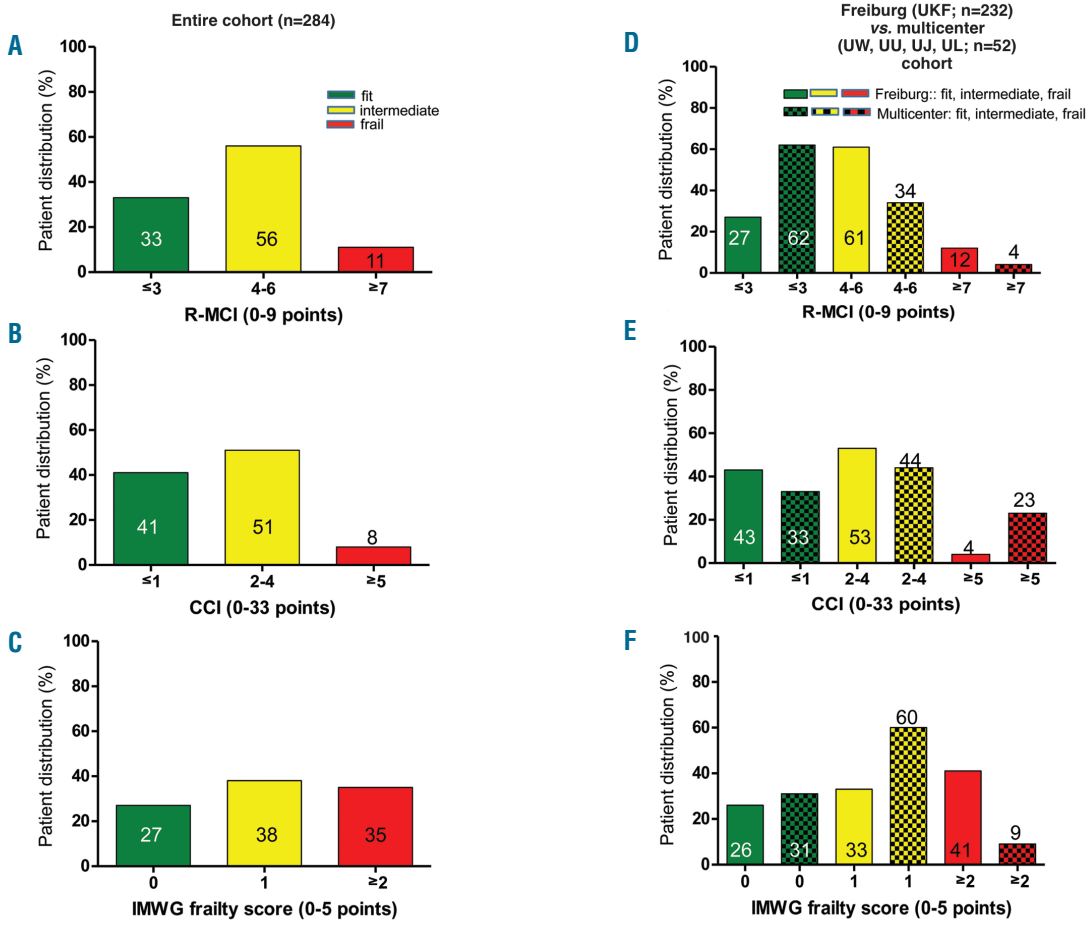

Figure 1. Distribution of fitness status according to the different comorbidity scores in the different cohorts. (A) According to the Revised Myeloma Comorbidity Score (R-MCI), 33% of the entire cohort (n=284) were fit, 56% were intermediate-fit and 11% were frail. (B) According to the Charlson Comorbidity Index (CCI), 41% of the entire cohort (n=284) were fit, 51% were intermediate-fit and 8% were frail. (C) According to the International Myeloma Working Group (IMWG) frailty score, 27% of the entire cohort (n=284) were fit, 38% were intermediate-fit and 35% were frail. (D) According to the R-MCI, 27% of the Freiburg cohort were fit, 61% were intermediate-fit and 12% were frail. The corresponding percentages for the multicenter cohort were 62%, 34% and 4%. (E) According to the CCI, 43% of the Freiburg cohort were fit, 53% were intermediate-fit and 4% were frail. The corresponding percentages for the multicenter cohort were 33%, 44% and 23%. (F) The IMWG frailty score determined that 26% of the Freiburg cohort were fit, 33% were intermediate-fit and 41% were frail. The corresponding percentages for the multicenter cohort were 31%, 60% and 9%.

Table 1. Baseline characteristics of the entire cohort of patients and of the Freiburg *versus* multicenter cohorts.

Variables	All (n=284) Mean (range)	%	Freiburg cohort (UKF; n=232) Mean (range)	%	Multicenter cohort (UW, UU, UJ, UL; n=52) Mean (range)	%
Patients' characteristics						
Age at initial diagnosis, years	62 (27-85)		62 (27-85)		60 (32-84)	
Gender, male /female		59 / 41		62 / 38		42 / 58
KPS, %	80 (30-100)		80 (30-100)		90 (60-100)	
Disease characteristics						
Durie & Salmon						
I / II / III		18 / 12 / 70		17 / 10 / 73		23 / 19 / 58
A / B		80 / 20		78 / 22		92 / 8
ISS, I / II / III		37 /29 / 34		34 / 28 / 38		50 / 33 / 17
PC histology, %	43 (0-100)		43 (0-100)		47 (5-100)	
PC cytology, %	42 (0-100)		40 (0-90)		46 (5-100)	
Cytogenetics (FISH)						
favorable		39		44		37
unfavorable[a]		41		41		46
missing		20		20		17
Estimated GFR, mL/min/1.73 m^2	67 (7-163)		65 (7-163)		73 (8-130)	
Comorbidity scores and frailty						
R-MCI (scale 0-9)	4 (0-9)		4 (0-9)		3 (0-7)	
IMWG-frailty score (scale 0-5)	1 (0-3)		1 (0-3)		1 (0-3)	
CCI (scale 0-33)	2 (0-8)		2 (0-7)		3 (0-8)	
Frailty[b]						
no/mild		51 / 21		46 / 21		73 / 19
moderate		12		14		2
severe		16		19		6
Fitness assessments						
ADL (scale 0-6)	5 (2-6)		5 (2-6)		6 (4-6)	
IADL (scale 0-8)	7 (1-8)		7 (1-8)		8 (3-8)	
Physician-rated fitness[c] (scale 1-6)	3 (1-6)		3 (1-6)		2 (1-5)	
TUGT[d] (s)	12 (4-80)		12 (4-32)		10 (6-80)	

[a]unfavorable cytogenetics (FISH) defined as t(4;14) or t(14;16) or del17p13 or chr.1 aberrations. [b]Frailty (adapted according to Fried) defined as Karnofsky Performance Status ≤70%; physician-rated fitness as: 5 or 6; : timed up and go test >10 sec; instrumental activities of daily living ≤4; no = no parameters compromised; mild = 1 parameter compromised; moderate = 2 parameters compromised; severe >2 parameters compromised (*http://www.myelomacomorbidityindex.org/en_calc.html*). [c]Physician-rated fitness (1-6): 1 represents best fitness and 6 represents worst fitness status. [d]Timed up and go test in seconds (s): <10 s = fit, 10-20 s: moderate-fit, >20 s unfit/frail. UKF: University of Freiburg; UW: University of Würzburg; UU: University of Ulm; UJ: University of Jena; UL: University of Leipzig; ISS: International Staging System; FISH: fluorescence *in situ* hybridization; KPS: Karnofsky Performance Status; PC: plasma cell; GFR: glomerular filtration rate; R-MCI: Revised Myeloma Comorbidity Index; IMWG: International Myeloma Working Group; CCI: Charlson Comorbidity Index; IADL: instrumental activities of daily living; ADL: activities of daily living; TUGT: timed up and go test.

others (Deutsche Studiengruppe Multiples Myelom [DSMM], German-Speaking Myeloma Multicenter Group [GMMG], Intergroupe Francophone du Myélome [IFM], Hemato-Oncology Foundation for Adults in the Netherlands [HOVON], Scandinavian and UK study groups) recommended that physical condition and comorbidities should be included in therapy decisions.[5,10,11] Risk scores for MM have included disease-related risks (scores of the International Staging System and its Revision [ISS/R-ISS], lactate dehydrogenase concentration, cytogenetics and, recently, comorbidity screening tests (Revised Myeloma Comorbidity Index [R-MCI], IMWG-frailty score and others).[5,11–13] Prior test[14] and repeated independent validation analyses[4,15] established the IMWG-frailty score and R-MCI in MM,[6,11-13] and enable the objective designation of fit, intermediate-fit and frail groups of patients with substantially different progression-free and overall survival rates. The intention of this multicenter analysis was the prospective validation of the R-MCI and comorbidity scores in five EMN/DSMM study sites (Universities of Freiburg [UKF], Würzburg [UW], Ulm [UU], Jena [UJ], and Leipzig [UL]). The external centers we chose for this multicenter analysis had to be: (i) equally large as ours (i.e., UKF); (ii) treat similar numbers of MM patients; and (iii) use identical DSMM study protocols. Of the centers we visited, the UW, UU, UJ and UL met these criteria. The aims of the study were to assess possible differences in: (i) patient and disease characteristics; (ii) comorbidity scores (R-MCI, IMWG-frailty score, Charlson Comorbidity Index [CCI]); and (iii) simple, functional fitness tests (Tables 1 and 2). The evaluation of whether comorbidity scores and a brief selection of fitness tests allow more precise detection of group variations in different centers, rather than that determined via patients' characteristics such as age and stage alone, was performed because previously postulated as highly relevant.[11,16]

This prospective, multicenter assessment was per-

Table 2. Revised Myeloma Comorbidity Index classification and parameters for the entire cohort of patients, and the Freiburg and multicenter cohorts.

Parameters, mean ± SD	Entire cohort (n=284)	Freiburg cohort (n=232)	Multicenter cohort (n=52)
R-MCI 0-3 (fit)	**n=94 (33%)**	**n=62 (27%)**	**n=32 (62%)**
Age (years)	57 ± 9.3	57 ± 8.8	56 ± 10.2
Karnofsky Performance Status (%)	88 ± 8.6	86 ± 8.4	92 ± 7.4
Renal function: eGFR (mL/min/1.73 m^2)	79 ± 23.3	76 ± 24.0	84 ± 21.4
Bone marrow plasma cells (%)	44 ± 26.6	41 ± 26.0	48 ± 27.6
IMWG-frailty score (scale 0-5)	1 ± 0.7	1 ± 0.7	1 ± 0.6
CCI (scale 0-37)	2 ± 1.6	1 ± 1.1	2 ± 2.1
Frailty (scale 0-3)	0 ± 0.5	0 ± 0.5	0 ± 0.3
ADL (scale 0-6)	5 ± 0.9	5 ± 0.9	6 ± 0.0
IADL (scale 0-8)	8 ± 0.5	8 ± 0.6	8 ± 0.0
Fitness (scale 1-6)	3 ± 0.8	3 ± 0.8	2 ± 0.6
TUGT (s)	9 ± 2.6	10 ± 3.0	8 ± 1.0
R-MCI 4-6 (intermediate fit)	**n=159 (56%)**	**n=141 (61%)**	**n=18 (34%)**
Age (years)	63 ± 10.4	62 ± 10.5	67 ± 8.4
Karnofsky Performance Status (%)	73 ± 13.2	73 ± 13.5	81 ± 7.3
Renal function: eGFR (mL/min/1.73 m^2)	64 ± 27.5	65 ± 27.2	56 ± 29.5
Bone marrow plasma cells (%)	43 ± 29.2	43 ± 29.0	44 ± 31.9
IMWG-frailty score (scale 0-5)	1 ± 1.1	1 ± 1.0	1 ± 0.8
CCI (scale 0-37)	2 ± 1.4	2 ± 1.2	4 ± 2.0
Frailty (scale 0-3)	1 ± 1.1	1 ± 1.1	1 ± 0.9
ADL (scale 0-6)	5 ± 1.1	5 ± 1.1	6 ± 0.5
IADL (scale 0-8)	7 ± 1.7	7 ± 1.7	8 ± 1.2
Fitness (scale 1-6)	3 ± 1.1	4 ± 1.1	3 ± 0.8
TUGT (s)	12 ± 5.7	12 ± 6.0	10 ± 2.7
R-MCI 7-9 (frail)	**n=31 (11%)**	**n=29 (12%)**	**n=2 (4%)**
Age (years)	73 ± 6.1	73 ± 5.9	67 ± 9.9
Karnofsky Performance Status (%)	60 ± 10.2	59 ± 10.3	65 ± 7.1
Renal function: eGFR (mL/min/1.73 m^2)	42 ± 25.9	42 ± 26.7	53 ± 4.3
Bone marrow plasma cells (%)	46 ± 20.9	45 ± 19.9	50 ± 42.4
IMWG-frailty score (scale 0-5)	2 ± 1.0	2 ± 1.0	2 ± 0.7
CCI (scale 0-37)	3 ± 1.4	3 ± 1.4	2 ± 1.4
Frailty (scale 0-3)	2 ± 0.8	2 ± 0.8	3 ± 0.7
ADL (scale 0-6)	5 ± 1.3	4 ± 1.3	6 ± 0.0
IADL (scale 0-8)	6 ± 2.1	6 ± 2.1	4 ± 0.7
Fitness (scale 1-6)	5 ± 0.9	4 ± 0.9	5 ± 0.7
TUGT (s)	21 ± 13.7	19 ± 8.3	46 ± 48.1

R-MCI: Revised Myeloma Comorbidity Index; n: number; KPS: Karnofsky Performance Status; eGFR: estimated glomerular filtration rate; PC: plasma cells; CCI: Charlson Comorbidity Index; IMWG: International Myeloma Working Group; ADL: Activities of Daily Life; IADL: Instrumental Activities of Daily Life; TUGT: timed up and go test; SD: standard deviation; s: seconds.

formed in 284 consecutive MM patients at the time of initial diagnosis or first presentation at five DSMM/EMN centers between July 2015 and March 2016. The cohort was assessed as a whole and in a subgroup analysis, in which the UKF cohort (n=232) was compared to the multicenter cohort (UW, UU, UJ, UL; n=52). Age, gender, disease characteristics, R-MCI, IMWG-frailty score, CCI and functional geriatric tests were assessed. Frailty, determined via: (i) KPS <70%; (ii) physician-rated fitness grade 5 or 6 (=dismal); (iii) timed-up-and-go-test (TUGT) >10 seconds; and/or (iv) instrumental activities of daily living (IADL) ≤4, as described elsewhere,[12,13,17] was scored as no/mild with 0/1, moderate with 2, or severe with >2 of parameters (i) – (iv) (Table 1). Due to logistics, allowing a time-restricted assessment in the external EMN/DSMM centers (UW, UU, UJ, UL: 1 week each), the multicenter cohort reflected primarily outpatients and the UKF cohort both in- and outpatients. The assessment was consistently performed by the same person (SMD).[6,12,13] Detailed methods and the definition of risk scores are described in *Online Supplementary Tables S1* and *S2*.

The patients' characteristics of the entire cohort (n=284) and both the UKF (n=232) and multicenter (n=52) cohorts were typical for tertiary centers and fairly similar. Advanced MM stages, according to the Durie & Salmon staging system and the ISS, and renal function (assessed by the estimated glomerular filtration rate) were somewhat more favorable in the multicenter cohort

than in the UKF one. Age, KPS, bone marrow plasma cells and cytogenetics were comparable in the two groups (Table 1).

In all 284 MM patients, the R-MCI, IMWG-frailty score, CCI and other functional tests (Table 1) were expeditiously assessable. The R-MCI confirmed that patients in the multicenter cohort were fitter than those in the UKF cohort with a mean score of 3 *versus* 4, respectively. In contrast, according to the IMWG-frailty score, there was no difference, with a mean of 1 in both cohorts. It is noteworthy that the IMWG-frailty score and CCI were increased in this prospective analysis compared to the prior IMWG description,[11] confirming our previous, prospective validation analysis of the R-MCI and IMWG-frailty score.[12] Frailty and functional tests confirmed that patients were fitter in the multicenter cohort than in the UKF cohort with regards to severe frailty (6% *vs.* 19%), and mean activities of daily living (ADL) score (6 *vs.* 5), IADL score (8 *vs.* 7), physician-rated fitness (2 *vs.* 3) and TUGT results (10 s *vs.* 12 s; respectively) (Table 1).

We also assessed and compared the patients' characteristics and functional differences in the three R-MCI subgroups of fit (R-MCI 0-3), intermediate-fit (R-MCI 4-6) and frail (R-MCI 7-9) patients of the entire, UKF and multicenter cohorts (Table 2). We considered patients' characteristics (age, KPS), MM risk factors (renal function, bone marrow plasma cells), frailty scores and functional fitness tests separately for intermediate-fit and frail patients as compared to fit patients. This confirmed that single R-MCI components and the R-MCI itself were of relevance to defining risks in both the UKF and multicenter cohorts.[6,12]

Comparison of the fit, intermediate-fit and frail R-MCI subgroups in the multicenter *vs.* UKF cohorts confirmed that there more fitter (62% *vs.* 27%) and fewer frail patients (4% *vs.* 12%) in the former than the latter cohort. The differences between the two cohorts were more impressive for risk scores (frailty, CCI, IMWG) and functional tests (ADL/IADL, physician-rated fitness, TUGT) than for age, KPS, renal function or bone marrow plasma cell results (Table 2).

We also compared the frequencies of fit, intermediate-fit and frail patients identified directly via the R-MCI, CCI and IMWG-frailty score (Figure 1A-F): according to the R-MCI, 33% of the entire cohort were considered fit, 56% intermediate-fit and 11% frail (Figure 1A). Similarly, according to the CCI, 41% were fit, 51% intermediate-fit and 8% frail (Figure 1B), whereas according to the IMWG-frailty score, 27% were fit, 38% intermediate-fit and 35% frail (Figure 1C). The allocation into fit, intermediate-fit and frail patients was consequently comparable via the R-MCI and CCI, whereas the IMWG-frailty score identified fewer intermediate-fit and more frail patients (Figure 1A-C).[3,11,13]

When comparing the R-MCI, CCI and IMWG-frailty score allocations in the UKF *versus* multicenter cohorts (Figure 1D-F), the R-MCI identified more fitter patients (27% *vs.* 62%, respectively) and fewer intermediate-fit and frail patients in the multicenter cohort (Figure 1D).

According to the CCI assessment, the differences between the UKF and multicenter cohorts were least marked for fit and intermediate-fit patients with 43% *versus* 33% and 52% *versus* 44%, respectively, but substantial for frail patients with the allocation being 4% *versus* 23%, respectively. Via the CCI, more multicenter than UKF patients were unsustainably defined as frail (Figure 1E), which did not reflect the results of the patients' characteristics (Table 1A and B) or the R-MCI-defined group differences (Figure 1D).

When comparing subgroups of fit, intermediate and frail patients via the IMWG-frailty score (Figure 1F), we observed a similar proportion of fit patients in the UKF *versus* multicenter cohorts (26% *vs.* 31%), fewer intermediate-fit patients (33% *vs.* 60%) and more frail patients (41% *vs.* 9%, respectively), with the largest proportion of UKF patients being misguidedly assigned to the frail subgroup. Since the allocations via the IMWG-frailty score in the UKF versus multicenter cohorts were very different from those via the R-MCI and CCI, a difference which had already been perceivable in the comparison of the entire cohort of MM patients (Figure 1A-C), we postulate that the IMWG-frailty score overestimates frail patients when prospectively assessed (as here). This was most apparent when the proportions of frail patients defined by the different scores were compared, since this proportion was four times greater with the IMWG-frailty score than with the R-MCI in the UKF group (41% *vs.* 12%, respectively) (Figure 1C and E) and, again in the UKF group, ten times greater with the IMWG-frailty score than with the CCI (41% *vs.* 4%, respectively) (Figure 1D and E).

Since IMWG-frailty scores in the UKF and in the multicenter cohorts did not differ (mean: 1) and the CCI was higher in the latter (2 *vs.* 3, respectively) (Table 1), the R-MCI was of interest and verified cohort differences (4 *vs.* 3, respectively). Moreover, the R-MCI was in line with all functional/frailty tests (Table 1). Thus, the R-MCI and functional fitness tests confirmed greater fitness in the multicenter cohort than in the UKF cohort, and the comparative analysis of results from five DSMM/EMN myeloma centers showed that a risk score and functional assessment may indeed help to better define patients' differences. Fitter patients in the multicenter compared to the UKF cohort were best clarified via R-MCI and only this score was consistently in line with frailty, ADL/IADL, physician-rated fitness and TUGT results.

The strength of this study was the prospective assessment in the five EMN/DSMM centers. Furthermore, frailty and functional assessments were done by the same skilled person in all centers, which excluded differences in handling the patients' assessment and data acquisition. The R-MCI was compared with the IMWG-frailty score, CCI and fitness tests, the former including a few comorbid conditions that are readily obtainable from the collection of the medical history and were obtained from the multivariate risk analysis of a large prospective sample.[6,12,13,18,19] Additional advantages of the R-MCI are that it: (i) allows more accurate assessment of physical conditions than via clinical judgment, age or KPS/ECOG alone; (ii) precisely divides patients into fit, intermediate-fit and frail patients with different progression-free and overall survival risks;[12,13,18,19] (iii) allows the inclusion of biological risks, namely cytogenetics; and (iv) consistently divides risk groups of R-MCI 0-3 (=fit), 4-6 (=intermediate-fit) and R-MCI 7-9 (=frail) patients, irrespective of age and treatment (i.e. <65/≥65; <70/≥70; or <75/≥75 years, and with/without novel agents or with/without transplantation; as reported elsewhere[12,13,18,19]).

A limitation of the present study was the application of different anti-myeloma therapies (typically bortezomib, cyclophosphamide, dexamethasone or bortezomib, lenalidomide, dexamethasone). It is, however, worth noting that in prior analyses, we demonstrated that the R-MCI distinguished highly significant risk groups despite different anti-myeloma treatments,[12,13] a finding confirmed by others.[5,11,20] Another criticism that could be raised concerns the limited number of patients in the multicenter cohort, which was a consequence of our

time-restricted assessment in each of the external EMN/DSMM centers (Würzburg, Ulm, Jena and Leipzig). Our results do, therefore, warrant even larger confirmatory analyses.

In conclusion, based on existing recommendations, the R-MCI can be applied in routine clinical care, multicenter analyses and future clinical trials. It may also be used in research to compare risk profiles of MM cohorts, to adjust for imbalanced risk profiles and to provide a basis to establish new clinical or biological prognostic factors.[6] We use the R-MCI for both clinical trial and non-trial patients and in our MM-tumor assessment, in which the R-MCI is immediately scored by those who see and treat the patient. In the future, the R-MCI may help to support treatment decisions, improve treatment tolerability and avoid toxicity.[21] Since any prospective comorbidity, frailty and disability evaluation in MM can be time-consuming, we have implemented the R-MCI within a web-based technology application (*www.myelomacomorbidityindex.org*).[6]

Moreover, with the present study we have verified that comorbidity score analyses can be similarly and swiftly performed at other centers, that these scores add to the description of a population of patients, compared to that provided by the patients' characteristics alone (Table 1), and that the scores may show substantial differences between centers (Table 2). The comparative analysis of different comorbidity scores (R-MCI, CCI, IMWG-frailty score) in the entire cohort is best illustrated in Figure 1A-C, in which the application of different scores resulted in substantial differences in proportions of fit *versus* frail MM patients. This was of interest because one might have postulated, contrarily, that the entire prospective MM cohort with 284 patients would have consisted of very similar proportions of fit, intermediate-fit and frail patients with each score. This difference between proportions, namely between fit *versus* frail patients, was most striking when the Freiburg and multicenter cohorts were compared (Figure 1D-F). We therefore demonstrate that the R-MCI is a useful tool to assess the fitness status of MM patients and can be implemented into MM care at different centers. It was prospectively compared to two other comorbidity scores often used in MM; i.e., the IMWG frailty score, which has the CCI implemented therein. With five multivariate risk factors (*vs.* age, ADL, IADL and CCI [this last with 18 factors that need to be assessed]), the R-MCI is convenient to use.

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Contributions: MM and SMD acquired the data. SMD analyzed the data. SMD and ME wrote the manuscript. SMD, RW and ME designed the project. CL, LOM, WP and SK provided access to patients' data and assessment. GI controlled the statistics. MM, JJ, CG, CL, LOM, WP, SK, GI, RW and ME revised the manuscript. RW and ME supported the project.

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