A concise revised Myeloma Comorbidity Index as a valid prognostic instrument in a large cohort of 801 multiple myeloma patients

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ABSTRACT

With growing numbers of elderly multiple myeloma patients, reliable tools to assess their vulnerability are required. The objective of the analysis herein was to develop and validate an easy to use myeloma risk score (revised Myeloma Comorbidity Index) that allows for risk prediction of overall survival and progression-free survival differences in a large patient cohort. We conducted a comprehensive comorbidity, frailty and disability evaluation in 801 consecutive myeloma patients, including comorbidity risks obtained at diagnosis. The cohort was examined within a training and validation set. Multivariate analysis determined renal, lung and Karnofsky Performance Status impairment, frailty and age as significant risks for overall survival. These were combined in a weighted revised Myeloma Comorbidity Index, allowing for the identification of fit (revised Myeloma Comorbidity Index ≤3 [n=247, 30.8%]), intermediate-fit (revised Myeloma Comorbidity Index 4-6 [n=446, 55.7%]) and frail patients (revised Myeloma Comorbidity Index >6 [n=108, 13.5%]): these subgroups, confirmed *via* validation analysis, showed median overall survival rates of 10.1, 4.4 and 1.2 years, respectively. The revised Myeloma Comorbidity Index was compared to other commonly used comorbidity indices (Charlson Comorbidity Index, Hematopoietic Cell Transplantation-Specific Comorbidity Index, Kaplan-Feinstein Index): if each were divided in risk groups based on 25% and 75% quartiles, highest hazard ratios, best prediction and Brier scores were achieved with the revised Myeloma Comorbidity Index. The advantages of the revised Myeloma Comorbidity Index include its accurate assessment of patients' physical conditions and simple clinical applicability. We propose the revised Myeloma Comorbidity Index to be tested with the "reference" International Myeloma Working Group frailty score in multicenter analyses and future clinical trials. The study was registered at the German Clinical Trials Register (DRKS-00003868).

Introduction

Over the past decade, overall survival (OS) has improved significantly in patients with multiple myeloma (MM). This is driven by better biological insights in the disease, implementation of more sensitive tests and technologies leading to earlier diagnosis, access to better combination therapies and increased access to supportive care measures.[1-3] However, MM typically affects elderly patients, who face the challenge that treatment endurance is poorer and prognosis more unfavorable.[4,5] Moreover, the simultaneous presence of additional diseases may complicate antimyeloma treatment.[1,3] In general, comorbidities have been shown to influence cancer patients' general health status, limit their physical condition and OS.[6-11] Therefore, with a growing number of elderly patients, reliable tools to assess patients' vulnerability as expressed in chronic conditions and limitations in daily activity are required to guide therapeutic decisions.[4,12-15]

Historically, treatment decisions in symptomatic MM patients have been largely age-based. Today, disease biology and fitness, including patients' Karnofsky Performance Status (KPS), are considered when assessing therapeutic options.[3,14] However, the KPS is often overestimated and does not reflect the entire functional status.[10] Therefore, advances in more precise ways of defining fitness are warranted. Moreover, since elderly MM patients are often excluded from clinical trials due to strict inclusion criteria,[16] these trial results are not necessarily transferable to elderly patients. In this context, the International Myeloma Working Group (IMWG), European Myeloma Network (EMN) and others (e.g., IFM, HOVON, DSMM, GMMG) recommended that age, physical condition and comorbidities are included in therapy decisions.[1,8,10,12,14] Since cytogenetic aberrations are additional prognostic factors in MM,[17-20] it may also be important to include cytogenetics in MM-specific risk scores. Risk scores for MM have indeed included disease-related risks (the International Staging System (ISS), lactate dehydrogenase (LDH), cytogenetics), combined comorbidities with cytogenetics or multiple comorbidity screening tests (IMWG frailty score).[12,17-19] Our prior test[8] and independent validation analyses[9,10] defined impaired renal function, lung function or KPS as relevant risks *via* thoroughly assessed univariate and multivariate analyses. These variables were combined in an additive Initial Myeloma Comorbidity Index (I-MCI),[8-10] which enabled the clear definition of risk groups with substantially different progression-free survival (PFS) and OS. Furthermore, it was found to add valuable information to the ISS.[10]

In order to refine and weight our I-MCI, we tested and validated a 'revised MCI' (R-MCI) based on a large cohort of 801 MM patients. Additionally, we compared the R-MCI to other internationally used Comorbidity Indices (CIs), namely Charlson CI (CCI), Hematopoietic Cell Transplantation-specific CI (HCT-CI) and Kaplan-Feinstein Index (KFI). Frailty scores are already used clinically for various cancers, but a comprehensive comorbidity, frailty and disability evaluation is time-consuming and less applicable outside centers with oncogeriatric teams,[21] which was the reason why we aimed to establish a concise, time-saving R-MCI.

Since the comparison of the Initial-/R-MCI (I-/R-MCI) with the IMWG frailty score was already meticulously performed by us,[22] it was not the focus of this analysis, rather, the aim was to define a concise, weighted, both tested and validated MM-specific risk score in a large cohort which could be subsequently used for the measurement of frailty in multicenter analyses and future clinical trials.

Methods

Patient population and study design

This prospective assessment was based on the analysis of 801 consecutive MM patients at the time of initial diagnosis and first presentation at our center between 1997 and 2012. The study was registered at the German Clinical Trials Register (DRKS-00003868). The primary objective was to optimize the I-MCI[8-10] within a weighted R-MCI in a large myeloma cohort. Secondary objectives included the impact of the R-MCI as compared to the I-MCI, CCI, HCT-CI and KFI (*Online Supplementary Table S1*), and their value for PFS and OS. The analysis was carried out according to the guidelines of the Declaration of Helsinki principles and good clinical practice. All patients gave their written informed consent for institutional-initiated research studies and analyses of clinical outcome studies conforming to the institutional review board guidelines.

Assessment

The I-MCI consists of an additive scoring system, namely renal, lung and/or KPS impairment.[8-10] In order to weight this in an even larger cohort, 13 comorbidities were assessed in 801 patients: these were graded and rated according to Common Terminology Criteria for Adverse Events (CTCAE) 4.03, which included: renal, lung and KPS impairment, cardiac, liver or gastrointestinal disease, disability, frailty, infection, thromboembolic events, peripheral neuropathy, pain and secondary malignancies (Table 1). In addition, age, cytogenetics *via* fluorescence *in situ* hybridization (FISH after CD138 selection), renal function (*via* estimated glomerular filtration rate [$eGFR_{MDRD}$]) and lung disease, including lung function tests, were determined as described.[8-11,22-25] We performed interphase FISH on CD138+ plasma cells, which were analyzed using DNA probes specific for the following chromosomal aberrations: t(11;14)(q13;q32), t(4;14)(p16;q32), t(14;16)(q32;q23) and t(14;20)(q32;q12 (Abbott Laboratories, IL, USA), XL 5q31/5p12, XCE 9, 11, 15, gain(1q21), del(1p32), del(13q14), del(17p13) and c-myc rearrangements (MetaSystems, Altlussheim, Germany). The score of Wuilleme *et al.*[26] was used to assess ploidy by using gains of at least two of the chromosomes. For each probe a minimum of 100 nuclei were scored. European Myeloma Network (EMN) cutoff values were applied for the detection of aberrations.[27] Unfavorable cytogenetics were defined as del(17p13), del(13q14), t(4;14), t(14;16), t(14;20), hypodiploidy, c-myc and chromosome 1 aberrations.[1,8,10,22,24,27-31] The KPS was defined as normal (100%), mildly (90%), moderately (80%) or more substantially impaired (≤70%). Frailty and disability were assessed in order to get a more precise determination of patients' physical condition. The Fried definition for frailty was used, which takes into account the added presence of weakness, poor endurance, low physical activity, slow gait speed and shrinking, with ≤2 factors defining frailty as moderate and with ≥3 factors determining frailty as severe.[32-34] The assessment was performed by a staff member trained in oncogeriatrics (A-SD, SMD, AZ, SJM), and was performed identically throughout the study period. Patient characteristics included age, myeloma type, stage, β_2-microglobulin (β2-MG), creatinine, bone marrow (BM) infiltration, cytogenetics and treatment (Table 2).

Statistical analysis

Data were analyzed using SAS 9.2 (SAS Institute Inc., NC, USA). OS was calculated from the date of initial diagnosis until the date of death from any cause, while PFS was calculated from the date of initial diagnosis until the date of progression, relapse or death from any cause. When no event of interest occurred, observations were censored at the time the patient was last seen alive/without documented event, or at the latest on June 1st, 2015. OS and PFS rates were estimated using the Kaplan-Meier method, and compared using the log-rank test.

In order to weight the MCI in a large cohort,[8-10] the data set was randomly split into 2/3 and 1/3, namely a training (n=552) and validation set (n=249). The training set was built by randomly drawing 552 samples. The training set was used to develop the R-MCI, and the validation set to validate our results. Multivariate Cox proportional hazards regression models with backward variable selection were applied to the training set to evaluate the prognostic significance of the comorbidity factors. Variable selection was based on complete case analysis. For all other variables, the 552 patients without any missing data with 294 events (deaths) were used. The results of the final model with prognostic factors contributing to the R-MCI were presented as estimated hazard ratios (HRs) with two-sided 95% confidence interval (CI), corresponding log hazard ratios and *P*-values (Table 3). Score weights were determined based on log hazard ratios, i.e., the regression coefficients of the prognostic factors, as these reflect the level of association with the outcome of OS on an additive scale. We assigned a score weight of 0 if the log hazard ratio was below 0.3, a score weight of 1 if the log hazard ratio was between 0.31 and 0.7, a score weight of 2 if the log hazard ratio was between 0.71 and 1.07, and a score weight of 3 if the log hazard ratio was 1.08 or higher, leading to a maximum of 9 points (Table 3). This rule very closely approximates the weights as described.[35] In order to additionally evaluate whether the co-variable cytogenetics can increase the predictive performance of this score (Table 3), a multivariate Cox model including a preliminary score as a co-variable was compared to a multivariable Cox model including both the preliminary score and cytogenetics: the models were based on 353 patients without any missing data in all co-variables, with or without the inclusion of cytogenetics (Table 3).[17–20] Prediction errors based on the Brier score[36] were used to compare the R-MCI, with and without cytogenetics, determining that the R-MCI could be improved with the inclusion of cytogenetics (*Online Supplementary Figure S1*). Of note, our final 9-point weighted R-MCI can be used as a risk tool both with or without cytogenetics (e.g., if cytogenetics were unavailable). Albeit there was no missing data for the prognostic factors

Table 1. Definition and grading of 13 comorbidities and physical functions in myeloma patients.

	Variables	Mild Moderate	Definition and grading	Severe	References
I-MCI	1. Renal function: eGFR / serum creatinine	CTCAE grade 1	CTCAE grade 2	CTCAE grade 3-4	Kleber[8–10]
	2. Lung function: dyspnea or FEV_1/FVC^a, FEV_1, TLC, respiratory insufficiency	dyspnea upon intense activity, mildly altered lung function	dyspnea upon moderate activity, moderately altered lung function or respiratory insufficiency	dyspnea at rest/few steps taken/the need for oxygen/non-invasive ventilation or FEV_1<50%	Kleber[8–10]
	3. Karnofsky Performance Status	90%	80%	≤70%	Kleber[8–10]
	4. Cardiac function: arrhythmias, myocardial infarction/CAD, heart failure	CTCAE grade 1	CTCAE grade 2	CTCAE grade 3-4	CTCAE, 4.0
	5. Hepatic function: chronic hepatitis, cirrhosis, fibrosis, hyperbilirubinemia	CTCAE grade 1	CTCAE grade 2	CTCAE grade 3-4	CTCAE, 4.0
	6. GI disease: nausea, vomiting, diarrhea, ulcer	CTCAE grade 1	CTCAE grade 2	CTCAE grade 3	CTCAE, 4.0
	7. Disability: help in personal care and household tasks	occasional	frequent	≥1x/day	Palumbo[12]
	8. Frailty: weakness, poor endurance, low physical activity, slow gait speed	1 factor	2 factors	≥3 factors	Rodriguez-Mañas,[32] Xue[33]
	9. Infection	local intervention	oral intervention	i.v. intervention	CTCAE, 4.0
	10. Thromboembolic event	venous thrombosis	thrombosis, medical intervention indicated	life-threatening, urgent intervention indicated	CTCAE, 4.0 Kristinsson[47]
	11. PNP	CTCAE grade 1	CTCAE grade 2	CTCAE grade 3-4	CTCAE, 4.0
	12. Pain	CTCAE grade 1	CTCAE grade 2	CTCAE grade 3-4	CTCAE, 4.0
	13. Secondary malignancy	1. chronological criteria: before, synchronous or after MM 2. local criteria: local *vs.* disseminated cancer 3. etiological criteria: hematological, solid or skin tumors			Hasskarl[28] Engelhardt[24] Kleber[8–10]

[a]FEV_1/FVC: Tiffeneau-Pinelli Index: ratio of the forced expiratory volume in 1 second and the forced vital capacity. CAD: Coronary Artery Disease; CTCAE: Common Terminology Criteria for Adverse Events; eGFR: estimated glomerular filtration rate; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; GI: gastrointestinal; PNP: peripheral neuropathy; TLC: total lung capacity; i.v.: intravenous; I-MCI: Initial Myeloma Comorbidity.

in our dataset, the provision of weighing unfavorable, favorable *vs.* "missing/unavailable cytogenetics" within this R-MCI, illustrates its usefulness for primary or secondary institutions and non-academic centers.

The R-MCI was also compared to the I-MCI, CCI, HCT-CI and KFI, evaluating the prognostic role on OS with Cox regression models (Table 4) in terms of HRs. The predictive ability of different scores was assessed using prediction error curves and Brier scores (*Online Supplementary Figure S2*):[36] the smaller this prediction error is, the better the curves' prediction rate turns out, with the 'reference' constituting a model without co-variables. Additionally, the R-MCI was assessed on OS in patients with different antimyeloma treatments and ages. Since the comparison of the MCI with the IMWG frailty score had already been performed,[22] it was not the focus of this analysis, which was rather to define a weighted, tested and validated MM-specific risk score in a large myeloma cohort.

Results

Patient characteristics

The analysis included 801 consecutive MM patients. The median follow up was 6.1 years. The median age was 63 years: 28% of patients were 66-75 years and 13% older than 75 years, which is very typical for tertiary centers.[7-11,22,24,37,38] Gender distribution and myeloma subtypes corresponded to the data as described.[7-11,24] Other characteristics were likewise representative of large MM centers, e.g., typical paraprotein frequencies and mostly advanced Durie-Salmon and ISS II/III disease stages. The median β_2-MG level was 4.5mg/dL, renal function showed a median creatinine level of 0.93mg/dL and BM plasma cell infiltration of 30%. Patients underwent treatment according to international guidelines, labels and practices as described.[1,10,11,22,24] Autologous stem cell transplantation

Table 2. Patient characteristics.

	Entire cohort (n=801)		Training set (n=552 / 68.9%)		Validation set (n=249 / 31.1%)	
	n (%)	Median (range)	n (%)	Median (range)	n (%)	Median (range)
Patient-specific data						
Male : female	450 (56.2) : 351 (43.8)		316 (57) : 236 (43)		134 (53.8) : 115 (46.2)	
Age (years)		63 (21-93)*		62 (21-93)		63 (32-89)
MM-specific data						
Type of myeloma						
IgG / IgA	455 (56.8) / 152 (19.0)		309 (56.0) / 105 (19.0)		146 (58.6) / 47 (18.9)	
IgM / IgD	6 (0.8) / 2 (0.2)		3 (0.5) / 2 (0.4)		3 (1.2) / 0 (0)	
Light-chain MM only	162 (20.2)		117 (21.0)		45 (18.1)	
Biclonal (HC)	6 (0.8)		4 (0.7)		2 (0.8)	
Non-secretory	18 (2.3)		12 (2.2)		6 (2.4)	
κ/λ	502 (62.7) / 276 (34.5)		355 (64.1) / 181 (32.9)		147 (59.0) / 95 (38.2)	
Biclonal (LC)	5 (0.6)		4 (0.7)		1 (0.4)	
Non-secretory	18 (2.3)		12 (2.2)		6 (2.4)	
Durie-Salmon						
I	204 (25.5)		139 (25.3)		65 (26.1)	
II	117 (14.6)		88 (15.8)		29 (11.7)	
III	480 (59.9)		325 (58.9)		155 (62.2)	
A / B	665 (83.1) / 136 (16.9)		456 (82.6) / 96 (17.4)		209 (83.9) / 40 (16.1)	
ISS	759 (94.8)[a]		517 (93.5)		242 (97.2)	
I	225 (28.2)		146 (26.5)		79 (31.7)	
II	206 (25.8)		139 (25.3)		67 (26.9)	
III	328 (41.0)		232 (42.0)		96 (38.6)	
Laboratory parameters						
β_2-microglobulin (mg/dL)	755 (94.3)[e]	4.5 (1.1-65.5)	516 (93.5)	4.72 (1.1-65.5)	240 (96.4)	4.20 (1.4-52.6)
Creatinine (mg/dL)		0.93 (0.4-17.9)		0.92 (0.4-17.9)		0.94 (0.5-10.5)
BM infiltration rate (%)	695 (86.8)[d]	30 (0-100)	487 (88.2)	30 (0-100)	208 (83.5)	30 (0-90)
Cytogenetics						
Favorable	316 (39.5)		214 (38.8)		102 (41.0)	
Unfavorable[b]	212 (26.5)		140 (25.4)		72 (28.9)	
Missing	273 (34.1)		198 (35.9)		75 (30.1)	
Therapy						
SCT with novel agents	300 (37.5)		194 (35.1)		106 (42.6)	
SCT w/o novel agents	83 (10.4)		62 (11.2)		21 (8.4)	
Standard with novel agents	173 (21.6)		118 (21.4)		55 (22.1)	
Standard w/o novel agents[c]	170 (21.2)		127 (23.1)		43 (17.3)	
w/o CTx[#]	75 (9.4)		51 (9.3)		24 (9.6)	

*13% of patients were >75 years, 7% were 76-79 years and 6.3% ≥80 years. [a]Not evaluated in n=42 patients because of missing data. [b]Unfavorable cytogenetics defined as del(17p13), del(13q14), t(4;14), t(14;16), t(14;20), hypodiploidy, c-myc and chromosome 1 aberrations. [c]Novel agents: e.g., thalidomide, lenalidomide, bortezomib. [d]Not evaluated in n=106 patients because of missing data. [e]Not evaluated in n=46 patients because of missing data. [#]Radiotherapy and steroids alone. n: number; Ig: immunoglobulin; HC: heavy-chain; MM: multiple myeloma; LC: light-chain; ISS: International Staging System; BM: bone marrow; SCT: stem cell transplantation; w/o CTx: without chemotherapy; κ / λ: kappa / lambda.

Table 3. Multivariate Cox proportional hazards model of the training set analysis (n=552) based on backward selection for overall survival (OS), and the value of inclusion of cytogenetics (n=353).

Multivariate Cox proportional hazards model of the training set analysis (n=552)	Definition	n=552 (%)	HR (2.5-97.5%)	*P*-value	log(HR)	Score weight
1. Renal disease ($eGFR_{MDRD}$)[a]	≥90	184 (33)	1 (-)		0	0
	60-89	193 (35)	1.25 (0.92-1.68)	<0.0001	0.22	0
	<60	175 (32)	1.96 (1.43-2.68)		0.67	1
2. Lung disease	No/mild	470 (85)	1 (-)	0.0005	0	0
	Moderate/severe	82 (15)	1.65 (1.24-2.18)		0.50	1
3. KPS	100%	35 (6)	1 (-)	0.0036	0	0
	80-90%	207 (38)	2.17 (1.04-4.52)		0.77	2
	≤70%	310 (56)	2.96 (1.43-6.12)		1.08	3
4. Age (years)	<60	226 (41)	1 (-)	<0.0001	0	0
	60-69	185 (33)	1.43 (1.06-1.92)		0.36	1
	≥70	141 (26)	2.08 (1.50-2.89)		0.73	2
5. Frailty	No/mild	323 (59)	1 (-)	<0.0001	0	0
	Moderate	140 (25)	1.54 (1.17-2.04)		0.43	1
	Severe	89 (16)	2.02 (1.45-2.82)		0.70	1
± Cytogenetics	Favorable					0
	Unfavorable					1
	Unavailable					0
Maximum points						9

Univariate and bivariate Cox model with and without inclusion of cytogenetics (n=353)		log(HR)	HR (2.5-97.5%)	*P*-value
Univariate Cox model with preliminary score	Preliminary score	0.10	1.11 (1.08-1.14)	<0.0001
Multivariable Cox model with inclusion of cytogenetics	Preliminary score	0.10	1.11 (1.08-1.13)	<0.0001
	Cytogenetics unfavorable	0.44	1.56 (1.13-2.15)	0.006

[a]eGFR calculated as MDRD 186 × (serum creatinine level [mg/dl]) $^{-1.154}$ × (age [y]) $^{-0.203}$ × (0.742 if female, 1.21 if black person), log hazard ratios: parameter estimates. We assigned a score weight of 0, if the log hazard ratio was below 0.3, a score weight of 1, if the log hazard ratio was between 0.31 and 0.7, a score weight of 2, if the log hazard ratio was between 0.71 and 1.07, and a score weight of 3, if the log hazard ratio was 1.08 or higher, leading to a maximum of 9 points. This rule very closely approximates the weights as previously described.[35] n: number; HR: hazard ratio; KPS: Karnofsky Performance Status; $eGFR_{MDRD}$: estimated glomerular filtration rate by MDRD (Modification of Diet in Renal Disease).

(ASCT) was recommended for medically fit, symptomatic patients up to the age of 70 years.[22,25] Induction usually consisted of bortezomib-based regimens, such as VCD (bortezomib, cyclophosphamide and dexamethasone) or CTD (cyclophosphamide, thalidomide and dexamethasone). Mobilization and conditioning were performed as described.[1,10,11,23,24] Patients ineligible for ASCT received melphalan, prednisone and bortezomib (MPV), melphalan, prednisone and thalidomide (MPT) or melphalan and prednisone (MP).[1] Novel agent-based therapies included immunomodulatory drugs and proteasome inhibitor treatment according to the approved indications and in line with treatment at other international centers (Table 2). In order to revise the MCI, the data set was randomly split into 2/3 and 1/3 of patients, using a training (n=552) and validation set (n=249). The training set was used to develop the R-MCI and the validation set to validate our results. Both groups were comparable with respect to relevant patient-specific and MM-specific data, laboratory parameters and therapy. The data of the entire patient cohort, and of both the training and validation sets are displayed in Table 2. Approximately one-half (43%) of the patients received standard treatment without stem cell transplantation (SCT), the other percentage of patients includes those who underwent SCT (Table 2). Patient characteristics according to treatment are displayed in the *Online Supplementary Table S2*. Treatment was not modified according to the comorbidity scores in line with prior studies.[7-10,12,35,39,40]

Frequency of specific comorbidities

Frequent comorbidities (>30%) of all grades were KPS impairment (94%), renal impairment (68%), frailty (62%), cardiac impairment (45%), disability (43%) and lung impairment (32%). More severely graded comorbidities were again KPS impairment, frailty, disability, renal impairment, lung impairment, cardiac impairment and infections. Other comorbid conditions, such as liver and gastrointestinal impairment and thrombosis occurred to a lesser extent and severity (Figure 1).

Multivariate analysis for OS, weighting and risk stratification *via* MCI

The multivariate Cox proportional hazards model based on backward selection revealed five highly significant risks as relevant for OS (Table 3). Score weights for comorbidities (Table 3) were determined based on regression coefficients of the prognostic factors, i.e., log hazard ratios. In a separate

Table 4. Univariate Cox proportional hazards model for overall survival (OS) - comparison of the R-MCI with other comorbidity scores: I-MCI, CCI, HCT-CI and KFI.

Score	low- *vs.* moderate- *vs.* high-risk[a] n (%)	HR (2.5-97.5%)	*P*-value
Training analysis (n=552)			
R-MCI	fit (n=176) intermediate-fit (n=302) frail (n=74)	 2.87 (2.14-3.85) 9.57 (6.52-14.03)	 <0.0001
I-MCI	fit (n=187) intermediate-fit (n=225) frail (n=140)	 2.47 (1.82-3.37) 4.45 (3.20-6.17)	 <0.0001
CCI	fit (n=198) intermediate-fit (n=181) frail (n=173)	 2.05 (1.51-2.79) 3.56 (2.65-4.80)	 <0.0001
HCT-CI	fit (n=155) intermediate-fit (n=220) frail (n=177)	 2.29 (1.67-3.15) 2.84 (2.05-3.92)	 <0.0001
KFI	fit (n=241) intermediate-fit (n=118) frail (n=193)	 2.16 (1.57-2.98) 3.53 (2.67-4.67)	 <0.0001
Validation analysis (n=249)			
R-MCI	fit (n=71) intermediate-fit (n=144) frail (n=34)	 5.26 (2.41-11.49) 28.35 (12.23-65.69)	 <0.0001
I-MCI	fit (n=84) intermediate-fit (n=104) frail (n=61)	 4.30 (2.11-8.73) 9.47 (4.61-19.44)	 <0.0001
CCI	fit (n=120) intermediate-fit (n=70) frail (n=59)	 2.37 (1.43-3.93) 6.40 (3.94-10.41)	 <0.0001
HCT-CI	fit (n=78) intermediate-fit (n=93) frail (n=78)	 1.80 (1.01-3.21) 5.06 (2.95-8.67)	 <0.0001
KFI	fit (n=125) intermediate-fit (n=48) frail (n=76)	 1.73 (0.98-3.04) 4.80 (3.00-7.67)	 <0.0001

[a]Scoring groups (fit, intermediate-fit, frail) based on the 25% and 75% quartiles of the scores evaluated from the training set. R-MCI: revised Myeloma Comorbidity Index; I-MCI: initial Myeloma Comorbidity Index; CCI: Charlson Comorbidity Index; HCT-CI: Hematopoietic cell transplantation-specific Comorbidity Index; KFI: Kaplan-Feinstein Index; HR: hazard ratio; n: number.

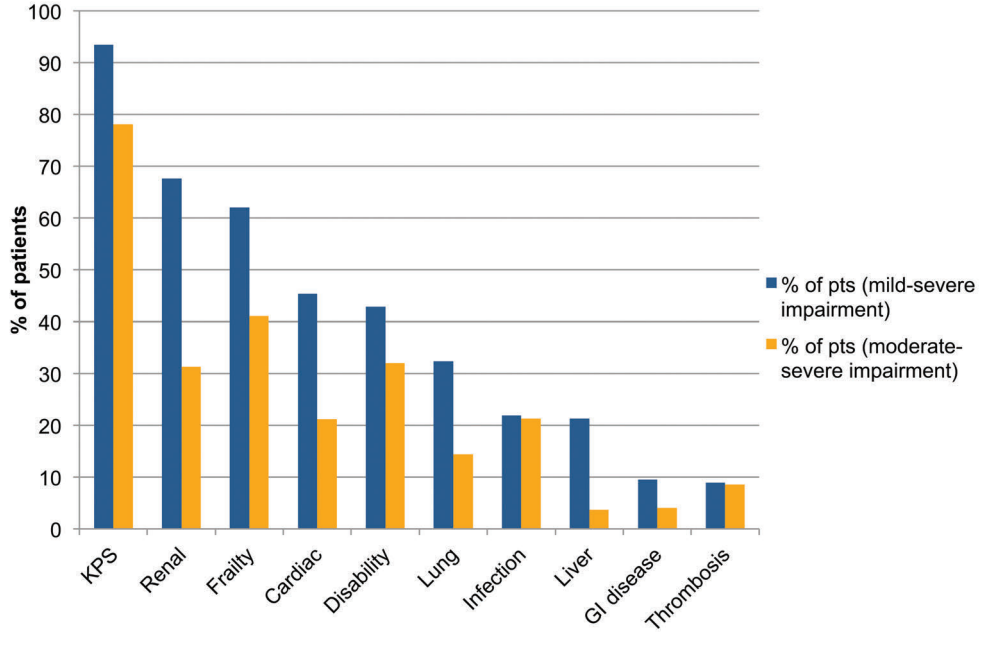

Figure 1. Frequency of entire (blue columns) and moderate-severe (yellow columns) organ impairment. Frequency of relevant comorbidities and impairment of general condition in all MM patients. Proportion of patients with any degree of impairment/grade of severity (blue bars) *vs.* proportion of patients with moderate to severe impairment/grade of severity (red bars). For cardiac function, hepatic function, GI disease, infection, thrombosis and renal function the CTCAE grading system was used, with CTCAE 1-4 (blue bars) *vs.* CTCAE ≥2 (red bars). KPS and lung function was graded as described.[8-10,22,23,46] Frailty was graded according to the definition of Rodriguez-Mañas L *et al.*[32] and Fried LP *et al.*[48] Disability was graded as described.[32,33] Table 1 shows the definition and grading of all assessed comorbidities. GI: gastrointestinal; KPS: Karnofsky Performance Status; pts: patients.

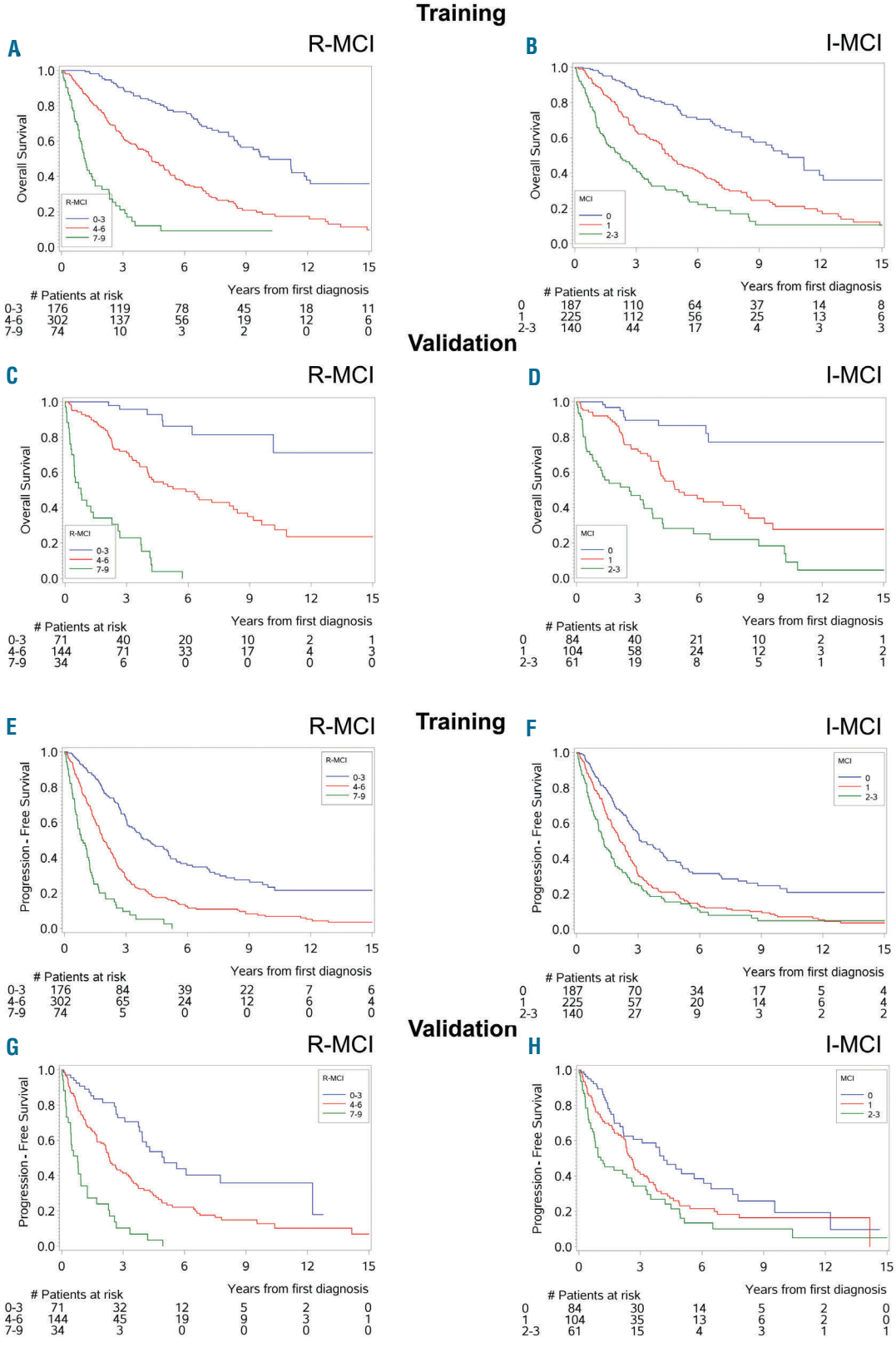

Figure 2. OS (A-D) and PFS (E-H) using the R-MCI (left) and I-MCI (right) in training and validation analyses. Overall survival (OS: A-D) and progression-free survival (PFS: E-H) curves using the revised MCI (R-MCI) and initial MCI (I-MCI) in the training and validation sets. Fit patients, with the use of the R-MCI, were defined with 0-3, intermediate with 4-6 and frail patients with 7-9 R-MCI points; with the use of the I-MCI with 0, 1 and 2-3 points, respectively. The survival curves of the R-MCI were stratified based on 25% and 75% quantiles leading to a stratification of fit patients with ≤3 R-MCI points, intermediate-fit patients with 4-6 R-MCI points and frail patients with >6 R-MCI points. The numbers of patients at risk in the respective groups are given below each Kaplan-Meier plot. PFS with the use of the R-MCI generated better group distinction both in the training set (E) and validation set (G) than with the use of the I-MCI (F and H). In line, OS was better distinguishable in 3 risk groups *via* the R-MCI in the training set (A) and validation set (C) *vs.* with the use of the I-MCI (B and D). R-MCI: revised Myeloma Comorbidity Index; I-MCI: initial Myeloma Comorbidity Index.

model, cytogenetics proved to supplement both additional and independent information to these risks (Table 3): prediction errors based on the Brier score[36] compared the R-MCI, with and without cytogenetics, and showed the smallest prediction errors with the R-MCI, with the inclusion of cytogenetics therein (*Online Supplementary Figure S1*). The weight for cytogenetics was based on the regression coefficient from the multivariable Cox model, including both the preliminary score and cytogenetics (*Online Supplementary Table S3*). A prognostic model was generated by combining and weighting the risks as displayed in the *Online Supplementary Table S3*, showing only marginal changes compared to the results of the final model used for determining score weights (Table 3). The R-MCI allowed for

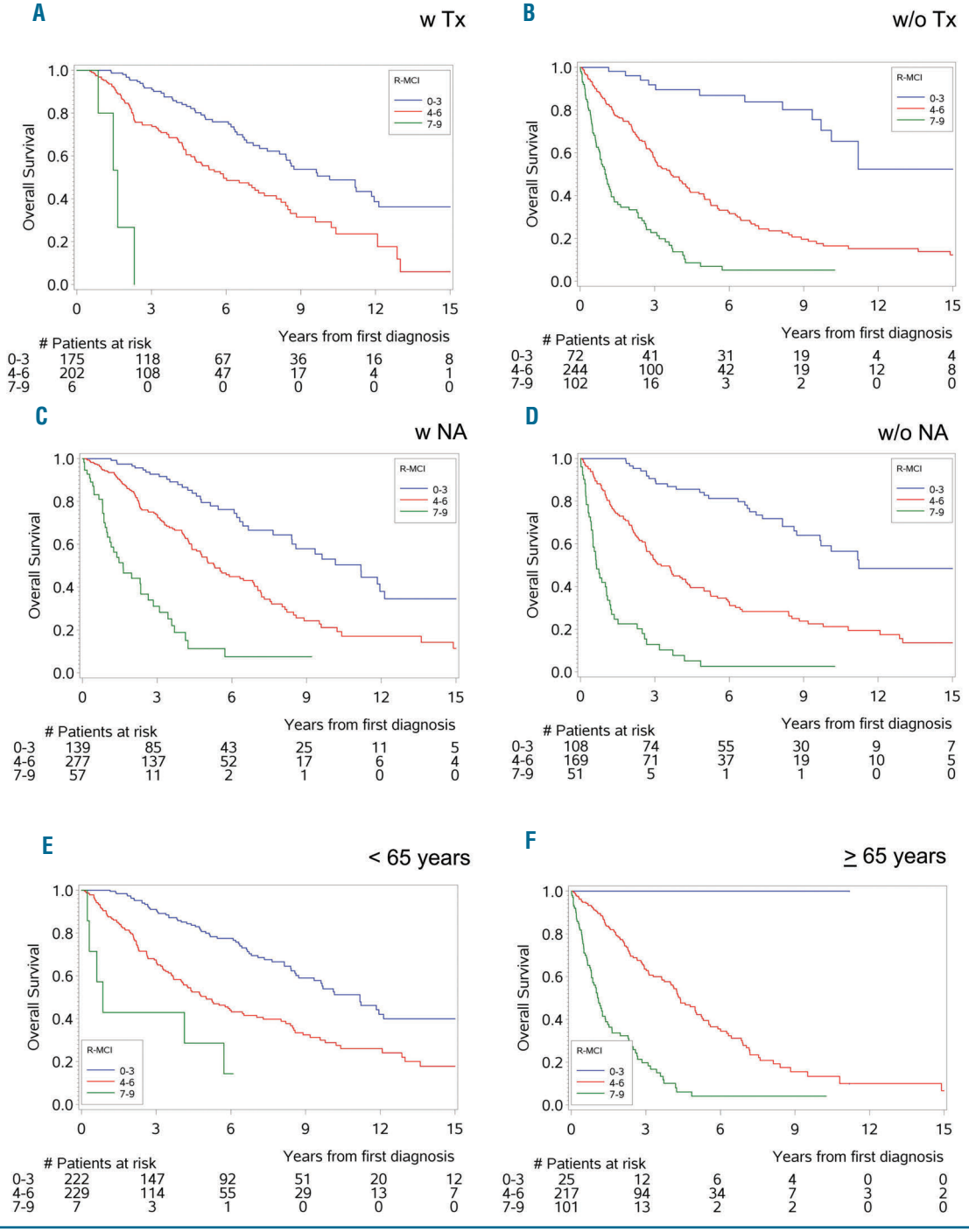

Figure 3. OS with the use of the R-MCI with different treatment intensity and age groups. OS with the use of the R-MCI in different treatment (A-D) and age cohorts (E,F), demonstrated excellent risk allocations of fit, intermediate and unfit patients with *vs.* without stem cell transplantation (A,B), with *vs.* without novel agent treatment (C,D) and <65 *vs.* >65 year old patients (E,F). Tx: transplantation; NA: novel agents; w: with; w/o: without.

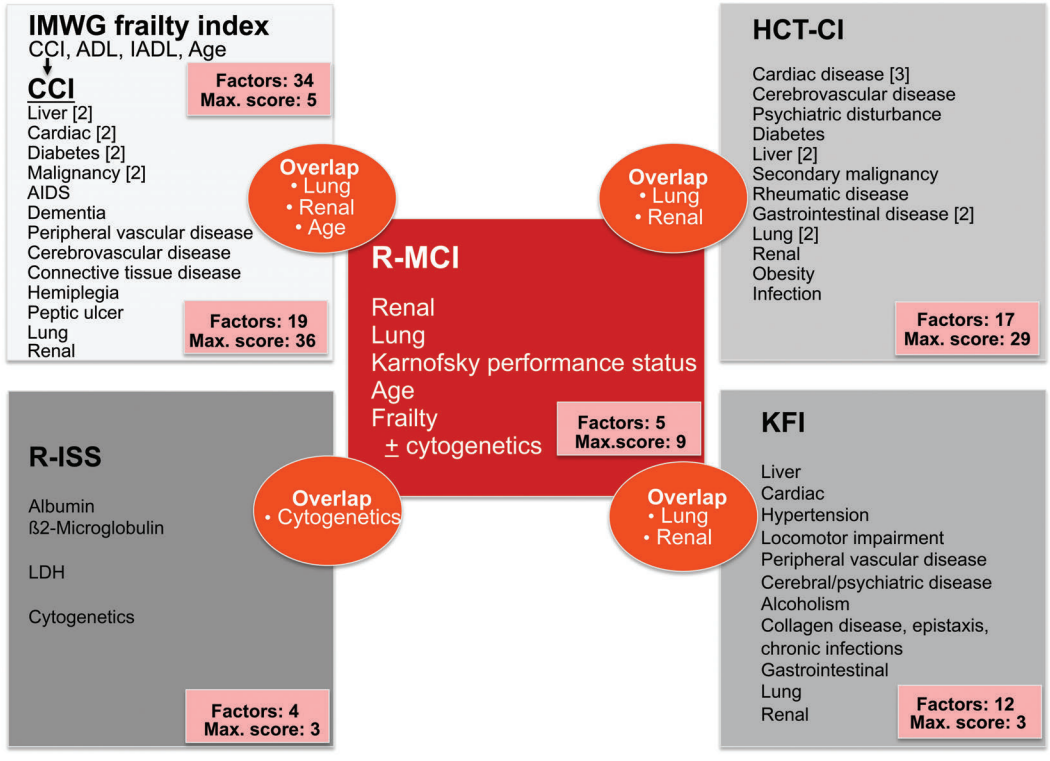

Figure 4. Scoring factors and maximum points of the R-MCI as compared to the IMWG frailty index, CCI, HCT-CI, KFI and R-ISS. Single factors of respective internationally used comorbidity scores, namely the IMWG frailty index, HCT-CI, KFI and R-ISS and R-MCI are displayed with their respective comorbidities therein. The number of risk factors and maximum score that can be achieved is also depicted. Moreover, respective overlapping risk factors with the R-MCI are shown. Impaired general condition is differently assessed with various scores, e.g., with the R-MCI *via* Karnofsky Performance Status (KPS) and frailty; with the IMWG frailty index *via* ADL and IADL and with the KFI *via* assessment of any locomotor impairment. IMWG: International Myeloma Working Group; CCI: Charlson Comorbidity Index; (I)ADL: (Instrumental) Activity of Daily Living; AIDS: Acquired Immune Deficiency Syndrome. HCT-CI: Hematopoietic cell transplantation-specific Comorbidity Index; R-MCI: revised Myeloma Comorbidity Index; KFI: Kaplan-Feinstein Index; ISS: International Staging System; R-ISS: revised ISS; LDH: lactate dehydrogenase.

the definition of largely different risk groups: in both training and validation analyses, it distinguished patients with clearly different OS and PFS (Figure 2A-H): patients with a R-MCI of ≤3 were defined as fit (247 patients [30.8%]), those with a R-MCI of 4-6 as intermediate-fit (446 patients [55.7%]) and those with a R-MCI >6 as frail (108 patients [13.5%]). The median OS in these defined groups was 10.1, 4.4 and 1.2 years, respectively, in the training set (Figure 2A), and in the validation set (Figure 2C) not reached (n.r.), 5.9 and 0.8 years, respectively. The median PFS in these groups was 4.1, 1.9 and 0.9 years, respectively, in the training set (Figure 2E), and 5.0, 2.3 and 0.8 years in the validation set, respectively (Figure 2G). From Figure 2, it can also be perceived that in the entire cohort, 13.5% were frail, if assessed *via* the R-MCI, whereas if assessed with the I-MCI, 25.1% of the cohort were determined frail. Intermediate-fit patients were fairly similar with 56% assessed intermediate-fit *via* the R-MCI *vs.* 41.1% *via* the I-MCI. Because the percentages of frail patients are distinctive, this highlights the relevance of performing a comprehensive comorbidity, frailty and disability evaluation also in 'intermediate-old' patients, and that different types of evaluations (e.g., scores: Table 4), result in diverse percentages of frail patients, namely of 13.5% with the R-MCI, 25.1% with the I-MCI, 29% with the CCI, 32% with the HCT-CI and 33.6% with the KFI, the latter four most likely overestimating frailty in MM, which illustrates the value of a prospectively validated MCI, also in intermediate-old MM patients.

MCI analysis in different treatment and age groups

To also determine whether the R-MCI remained a significant risk tool in different treatment and age groups, we assessed the risk group allocation of fit (R-MCI ≤3), intermediate-fit (R-MCI 4-6) and frail patients (R-MCI >6), with *vs.* without SCT (Figure 3A,B), with and without novel agents (NAs) (Figure 3C,D) and in younger (<65 years) *vs.* older patients (≥65 years; Figure 3E,F). In all subgroups, the value of the R-MCI was confirmed (P<0.0001). Of note, the R-MCI was a highly valuable risk tool for younger and older MM patients, demonstrating again that age alone is not sufficient to define fitness and therapy allocation (Figure 3E,F). Although subgroups of patients were limited, and these were non-randomized treatment comparisons, it was of interest that fit patients fared favorably, even without SCT (Figure 3B [n=72]), without NAs (Figure 3D [n=108]) or ≥65 years (Figure 3F [n=25]; all alive), whereas intermediate-fit and frail patients in these subgroups performed less favorably as compared to those with SCT (Figure 3A), with NAs (Figure 3C) or younger patients (Figure 3E). Figures 3E and 3F illustrate that patients <65 years were fit, intermediate-fit and frail in 48%, 50% and 2%, respectively, whereas in the >65 year old patient group, 7%, 63% and 29% were fit, intermediate-fit and frail, respectively. This showed that in the younger age group, there were also frail patients, albeit rarely, and that in the older cohort, fit patients were present, with 2% and 7%, respectively. Moreover, this demonstrates that frail patients increase with age, whereas intermediate-fit patients remained a very prominent group with

50% and 63% in both cohorts, respectively. Treatment was not modified according to the comorbidity scores, therefore, although very infrequently, frail patients (n=6; Figure 3A) as assessed *via* the R-MCI received transplants; even more impressively, 72 patients, notwithstanding being scored as fit *via* the R-MCI (Figure 3B), did not receive transplantation, suggesting more underutilization or undertreatment than overtreatment in a very rare subset. An even more detailed comparison of treatment subgroups of patients receiving more *vs.* less intensive treatment is depicted in the *Online Supplementary Table S2*, which shows comparable disease characteristics, but, as expected, more intensive treatment in younger patients.

Comparison of the R-MCI with other comorbidity scores

All patients were divided into three groups of fit, intermediate-fit and frail patients based on the 25% and 75% quartiles of the respective scores: the R-MCI, I-MCI, CCI, HCT-CI and KFI (Table 4). Differences and overlapping similarities are depicted in Figure 4. The univariate Cox proportional hazards model revealed that all scores allocated patients into 3 risk groups of fit, intermediate-fit and frail patients, with increasing HR. All scores reached statistical significance in terms of OS. Direct comparison of these comorbidity scores showed that the R-MCI generated the highest HRs in the training set, increasing to 2.87 and 9.57 for intermediate-fit and frail patients, respectively. Consistent with these results, the validation analysis confirmed the highest HRs of 5.26 for intermediate-fit and 28.35 for frail patients with the use of the R-MCI, which achieved much higher HRs than those generated through the use of the I-MCI, CCI, HCT-CI and KFI. The superiority of both the R- and I-MCI with the highest HRs was confirmed in the validation analysis (Table 4) and *via* prediction error curves and Brier scores: comparison of the reference, the R-MCI, I-MCI, KFI, CCI and HCT-CI demonstrated that the R-MCI generated the most favorable prediction curves (*Online Supplementary Figure S2*).

For the exact comparison, both the I- and R-MCI were also assessed side by side, both for OS and PFS (Figure 2A-H). Survival curves of the I-MCI groups with 0, 1 and ≥2 risk factors, generated clear group allocations of fit, intermediate-fit and frail patients in both training and validation analyses, for OS (Figure 2B and 2D) and PFS (Figure 2F and 2H), albeit subgroup allocation *via* R-MCI was improved (Figure 2A and 2C, 2E and 2G).

Differences in organ function and comorbidity with favorable *vs.* unfavorable cytogenetics

To determine whether unfavorable cytogenetics were also associated with organ dysfunction, increased comorbidity scores and unfavorable MM-associated characteristics, patients were separated into those with favorable, unfavorable and unavailable cytogenetics, the latter either due to patient preference, age, their location in external centers or other reasons.[11,19] Organ impairment differed in patients with unfavorable or missing *vs*. favorable cytogenetics: the former exhibiting higher frequencies of KPS impairment, renal impairment, cardiac impairment and hepatic impairment. Moreover, these patients had more comorbidities, such as pain, infections and limited physical conditions with disability and frailty. In line with this, the R-MCI and KFI increased in patients with unfavorable or unavailable cytogenetics (*Online Supplementary Table S4A*). The *Online Supplementary Table S4B* summarizes the respective MM patient characteristics: while the median age was equal in patients with favorable and unfavorable cytogenetics, it was, as expected, more advanced in those with unavailable cytogenetics, suggesting that cytogenetic analyses were less consistently performed in older patients. Gender and MM subtype distributions appeared comparable, whereas median β_2-MG levels were higher in patients with unfavorable and unavailable cytogenetics, and BM infiltration was increased in patients with unfavorable cytogenetics. In terms of therapy allocation, the differences between unfavorable and favorable cytogenetic groups were less obvious, whereas those with unavailable cytogenetics had received less intensive treatment.

Discussion

The results of the present study confirm the prognostic value of the R-MCI on a large independent patient cohort.[22] In order to weight our prior MCI,[8-10] 13 risk factors were thoroughly reassessed, including organ function and MM-specific risks (Table 1). The R-MCI was also compared to non-MM-specific comorbidity scores, namely CCI, HCT-CI and KFI. Since we have already compared the MCI and IMWG frailty score,[22] it was not the focus of this analysis, which was instead to define a weighted validated MM-specific risk score in a large myeloma cohort. Frequent comorbidities in MM proved to be frailty, disability, heart impairment, renal impairment, lung impairment and KPS impairment in agreement with prior studies.[3,12,38] Of interest, multivariate risks (renal impairment, lung impairment, KPS impairment, age, and frailty) matched with frequent comorbidities. Other previously suspected risk factors, such as liver or gastrointestinal dysfunction,[4,5,15] did not reach significance and proved not to be MM-specific risks. These less relevant comorbidities were generated from retrospective studies which were based on multicenter data entries and had assessed therapy-induced adverse events rather than baseline comorbidities. Therefore, they may bear the restriction of validity and information loss. Furthermore, the frequency of comorbidities in some retrospective studies was notably low,[5,12] which was possibly related to incomplete multicenter data entries and solely clinical trial patient inclusion.[12]

Aside from organ impairment, cytogenetic aberrations corroborate with impaired OS in MM patients. Our analysis confirmed that cytogenetics provide independent additional information,[17-20,41] and that patients with unfavorable cytogenetics had higher disease stages, adverse laboratory values and reduced organ and physical function. Although cytogenetics proved to be a relevant risk factor, our analysis also demonstrated that other factors, such as physical and organ conditions, are equally important. Moreover, the development of the R-MCI showed that the multivariate risks (renal function, lung function, KPS, age, and frailty) defined patients as fit, intermediate-fit and frail, which could be improved with the inclusion of cytogenetics, but was also readily usable if this information was unavailable (Table 3). Weighting of our R-MCI verified that this 9-point score was able to define 3 patient groups with clearly different median PFS and OS. Comparison of the R-MCI with others (CCI, HCT-CI, KFI) showed that they all divide patients into risk groups with substantially different OS, however, Brier scores determined the smallest prediction errors with the R-MCI. One reason for the comparability of the R-MCI with other risk scores is that they all include risk

factors that have some relevance in MM, namely renal function, lung function and in some physical condition (Figure 4). Compared to our non-weighted I-MCI,[8-10] the R-MCI led to an improvement in group distinction, which highlights the relevance to further improve a MM-specific risk score as performed here.

Although the HCT-CI and CCI have been tested and proven their usefulness,[12,35,42] studies in MM have suggested that both may not have as much impact in MM as the I-/R-MCI.[1,8-10,22,37] This led to some modification of prior comorbidity scores, albeit in diseases other than MM,[40,43-45] and verified that adapted scores (such as the International Prognostic Index (IPI) for diffuse large B-cell lymphoma, Mantle Cell Lymphoma International Prognostic Index (MIPI) for mantel cell lymphoma and Follicular Lymphoma International Prognostic Index (FLIPI) for follicular lymphoma) are valuable. Moreover, the CCI with 19 different factors, HCT-CI with 17 and KFI with 12 diverse factors are much more complex and time-consuming to assess, whereas the R-MCI involves 5 comorbid conditions only, uses information which is routinely collected and requires minimal interpretation (Figure 4 and *Online Supplementary Table S1*).

The strengths of our R-MCI lie in its inclusion of few comorbid conditions, that it is readily obtainable from the collection of the medical history and was obtained from the analysis of a large sample size. Furthermore, it is valuable both in younger and older patients. Other notable assets were that the R-MCI was tested and validated in the same cohort, randomly splitting the data into a training and validation set. Additional advantages of the R-MCI are that: 1) it allows for a more accurate assessment of physical conditions than best clinical judgment, age or KPS alone, 2) it precisely divides patients into fit, intermediate-fit and frail patients with definite PFS and OS risk groups, 3) current and relevant biological risks, namely cytogenetics can, but don't have to be included, and 4) it is very concise. Moreover, compared to other international comorbidity scores (the retrospectively assessed IMWG frailty score, CCI, HCT-CI and KFI),[8-10,22] the R-MCI was particularly effective in identifying patients at risk.[22,25]

A limitation of the present study was that the R-MCI was generated from a large, independent data set, but was acquired in a single center. Nevertheless, we have compared our patients to those of other tertiary centers,[22,46] demonstrating that our patients were representative, which is currently being assessed and affirmed in subsequent analyses and in prospective multicenter studies. Moreover, the cohort represented intermediate-old patients, which is typical for comprehensive cancer centers (CCCs).[7-11,19,22-24,46] Because of the accumulation of challenging cases in these CCCs, patients therein show typical comorbidities despite being "younger".[11] Since age is associated with increased comorbidity, our results will be even more pertinent for older patients.[8,10,11,22,25] Another criticism might be that different antimyeloma treatments were applied, nevertheless, in subgroups and prior analyses of our group,[8,10,22] we demonstrated that the R-MCI was equally relevant to distinguish highly significant risk groups (Figure 2 and Figure 3). Nevertheless, the heterogeneity of therapies may in part describe some differences in terms of PFS and OS, although it is noteworthy that our Kaplan-Meier curves of frail patients with transplants (Figure 3A), with novel agent treatment (Figure 3C) and in patients <65 years (Figure 3E) distinctly demonstrated that, despite intensive treatment and younger age, comorbidities and frailty induced a poor outcome.

In conclusion, although the retrospectively assessed IMWG frailty score is considered the "reference", we demonstrate the validity of this straightforward R-MCI as a valid prognostic instrument in a large cohort treated according to current standards. Based on existing recommendations, the R-MCI can be applied in routine clinical care, multicentre analyses and future clinical trials. It may further 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 biologic prognostic factors. Moreover, the R-MCI might be considered as an integral part in the development of individualized risk-adapted treatment strategies to further improve outcome in MM. This includes the correct use of resources, higher inclusion rates of older patients in clinical studies and the avoidance of an undersupply of older but fit patients. In the future, the R-MCI could help to support treatment decisions, aid in improving tolerability and avoiding toxicity. 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 which allows one to perform the MCI expeditiously (www.myelomacomorbidityindex.org).[34] With the retrospective "reference IMWG frailty score",[12] ours is an active website that allows one to calculate a concise MM-specific comorbidity index which can be tested side by side[22,25,46] by IMWG and EMN experts.

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