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

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Supplementary Table 1. Revised-Myeloma Comorbidity Index (R-MCI) and other comorbidity scores

	R-MCI (Weighted)	I-MCI	CCI[a] (Weighted)	HCT-CI (Weighted)	KFI[a]
References	Engelhardt	Kleber	Charlson	Sorror	Kaplan; Extermann
Develop-ment	Pts with MM	Pts with MM	1 yr mortality in medical pts, validation in breast cancer pts	Development based on the CCI; specifically targeting transplant pts	Pts with diabetes
Factors	- Severe renal disease [1] - Moderate-severe lung disease [1] - Reduced KPS: 80-90% [2] ≤70% [3] - Age >60 - 69y [1] Age ≥70y [2] - Moderate-severe frailty [1] ± Unfavorable cytogenetics [1] **Definition of fit, intermediate and frail patients:** **Fit: R-MCI → 0-3** **Intermediate: R-MCI → 4-6** **Frail: R-MCI → 7-9**	- Severe renal disease [1] - Moderate-severe lung disease [1] - Reduced KPS ≤70% [1]	- Myocardial infarction [1] - Congestive heart failure [1] - Peripheral vascular disease [1] -Cerebrovascular disease [1] - Dementia [1] - Chronic pulmonary disease [1] - Connective tissue disease [1] - Peptic ulcer disease [1] - Mild liver disease [1] - Mild diabetes [1] - Hemiplegia [2] - Moderate-severe renal disease [2] - Diabetes with end organ damage [2] - Tumor without metastases (exclude if >5y from diagnosis) [2] - Leukemia [2] - Lymphoma [2] - Moderate-severe liver disease [2] - Metastatic solid tumor [6] - AIDS [6]	- Cardiac [1] - Arrhythmia [1] - Cerebrovascular [1] - Psychiatric disturbance [1] - Diabetes [1] - Infection [1] - Mild liver disease [1] - Obesity [1] - Inflammatory bowel disease [1] - Moderate-severe renal disease [2] - Moderate pulmonary disease [2] - Peptic ulcer [2] - Rheumatologic disease [2] - Heart valve disease [3] - Severe pulmonary disease [3] - Moderate-severe liver disease [3] - Prior solid tumor [3]	- Cardiac disease - Hypertension - Peripheral vascular - Respiratory - Hepatic - Renal - Gastrointestinal - Locomotor impairment - Cerebral/psych. - Alcoholism - Malignancy - Collagen disease, epistaxis, chronic active infections
Number of factors	5	3	19	17	12
Max. points	9	3	36 (+1 per decade from an age of 50)	29	3

Abbreviations:
MCI: Myeloma Comorbidity Index, CCI: Charlson Comorbidity Index, HCT-CI: Hematopoietic Cell Transplant Comorbidity Index, KFI: Kaplan Feinstein index, KPS: Karnofsky Performance Status, pts: patients, y: years

[a] both CCI and KFI were scored without lymphoma (CCI) / malignancy (KFI), in order to avoid falsely high comorbidity scores due to underlying MM in all patients

Supplementary Table 2. Patient characteristics in different therapy groups (n=801)

	SCT with NA n=300 (38%)		SCT w/o NA n=83 (10%)		Standard with NA n=173 (22%)		Standard w/o NA[c] n=170 (21%)		w/o CTx n=75 (9%)	
	n (%)	Median (range)	n (%)	Median (range)	n (%)	Median (range)	n (%)	Median (range)	n (%)	Median (range)
Patient-specific data										
Male : female	173 (58) : 127 (42)		48 (58) : 35 (42)		96 (56) : 78 (44)		92 (54) : 78 (46)		41 (55) : 34 (45)	
Age (years)		58 (27-74)		55 (32-70)		71 (40-93)		67 (27-89)		66 (21-90)
MM-specific data										
Type of myeloma										
IgG / IgA / IgM / IgD	186 (62)/49 (16)/1 (1)/0		44 (53)/23 (28)/1 (1)/0		90 (52)/36 (21)/1 (1)/0		88 (52)/30 (18)/3 (2)/2 (1)[e]		47 (63)/14 (19)/0/0	
Light-chain MM only	60 (20)		13 (16)		42 (24)		36 (21)		8 (11)	
Biclonal/Non-secretory	1 (1) / 3 (1)		2 (2) / 0 (0)		0 (0) / 4 (2)		3 (2) / 6 (4)[a]		0 (0) / 5 (7)[f]	
kappa / lambda	205 (68) / 90 (30)		54 (65) / 28 (34)		104 (60) / 65 (38)		98 (58) / 61 (36)		37 (49) / 32 (43)	
Biclonal LCs	2 (1)		1 (1)		0 (0)		2 (1)		0 (0)	
Durie & Salmon										
I / II / III	46 (15) / 51 (17) / 203 (68)		15 (18) / 12 (14) / 56 (68)		43 (25)/17 (10)/113 (65)		50 (29)/30 (18)/89 (52)[f]		50 (67)/7 (9)/18 (24)	
A / B	266 (89) / 33 (11)[f]		75 (90) / 8 (10)		130 (75) / 43 (25)		126 (74) / 44 (26)		66 (88) / 9 (12)	
ISS										
I / II / III	92 (31)/82 (27)/122 (41)[a]		29 (35) / 24 (29) / 26 (31)[g]		28 (16)/48 (28)/98 (56)		41 (24) / 35 (21) / 66 (39)[h]		35 (47)/17 (23)/16 (21)[i]	
Laboratory results										
β_2-MG (mg/dl)		4 (1-43)[o]		4 (1-45)[g]		6 (2-66)		5 (1-62)[k]		3 (2-38)[m]
Creatinine (mg/dl)		1 (0-10)		1 (0-8)		1 (1-18)		1 (0-13)		1 (1-11)
BM-infiltration (%)		40 (0-100)[j]		30 (0-90)[e]		30 (0-95)[d]		30 (0-95)[l]		15 (0-75)[n]
Cytogenetics										
Favorable	166 (55)		41 (50)		53 (31)		34 (20)		22 (29)	
Unfavorable[b]	109 (36)		19 (23)		52 (30)		22 (13)		10 (13)	
Unavailable	25 (8)		23 (28)		68 (39)		114 (67)		43 (57)	

Abbreviations: n: number, Ig: Immunoglobulin, HC: heavy-chain, MM: multiple myeloma, LC: light-chain, ISS: International Staging System, BM: bone marrow, NA: novel agents, SCT: stem cell transplantation, w/o CTx: without chemotherapy, MG: Microglobulin. [b]unfavorable defined as del(17p13), del(13q14), t(4;14), t(14;16), t(14;20), hypodiploidy, c-myc and chromosome 1 aberrations. [a]Not evaluated in n=3 because of missing data, [c]NA: e.g. thalidomide, lenalidomide, bortezomib, [d]Not evaluated in n=26 because of missing data, [e]Not evaluated in n=2 because of missing data, [f]Not evaluated in n=1 because of missing data, [g]Not evaluated in n=4 because of missing data, [h]Not evaluated in n=28 because of missing data, [i]Not evaluated in n=7 because of missing data, [j]Not evaluated in n=6 because of missing data, [k]Not evaluated in n=29 because of missing data, [l]Not evaluated in n=49 because of missing data, [m]Not evaluated in n=8 because of missing data, [n]Not evaluated in n=23 because of missing data, [o]Not evaluated in n=5 because of missing data.

Supplementary Table 3. Multivariate Cox proportional hazard model of the training analysis based on backward selection for overall survival (OS)

	Definition	n=552 (%)	HR (2.5-97.5%)	p-value
1. Renal disease ($eGFR_{MDRD}$)[a]	≥90 60-89 <60	184 (33) 193 (35) 175 (32)	1 (-) 1.29 (0.96-1.74) 1.85 (1.36-2.53)	0.0005
2. Lung disease	No/mild Moderate/severe	470 (85) 82 (15)	1 (-) 1.64 (1.23-2.17)	0.0007
3. KPS	100% 80-90% ≤70%	35 (6) 207 (38) 310 (56)	1 (-) 2.04 (0.98-4.26) 2.83 (1.36-5.88)	0.0045
4. Age (years)	<60 60-69 ≥70	226 (41) 185 (33) 141 (26)	1 (-) 1.39 (1.03-1.86) 1.87 (1.35-2.61)	0.0009
5. Frailty	No/mild Moderate Severe	323 (59) 140 (25) 89 (16)	1 (-) 1.51 (1.14-1.99) 1.98 (1.41-2.77)	<0.0001
6. Cytogenetics	Favorable Unfavorable Unavailable	214 (39) 140 (25) 198 (36)	1 (-) 1.62 (1.22-2.15) 1.52 (1.10-2.10)	0.0023

Abbreviations:
n: number, HR: hazard ratio, KPS: Karnofsky Performance Status, $eGFR_{MDRD}$: estimated glomerular filtration rate by MDRD (Modification of Diet in Renal Disease).
[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)

Supplementary Table 4A. Differences in organ function in subgroups of patients with favorable, unfavorable or unavailable cytogenetics

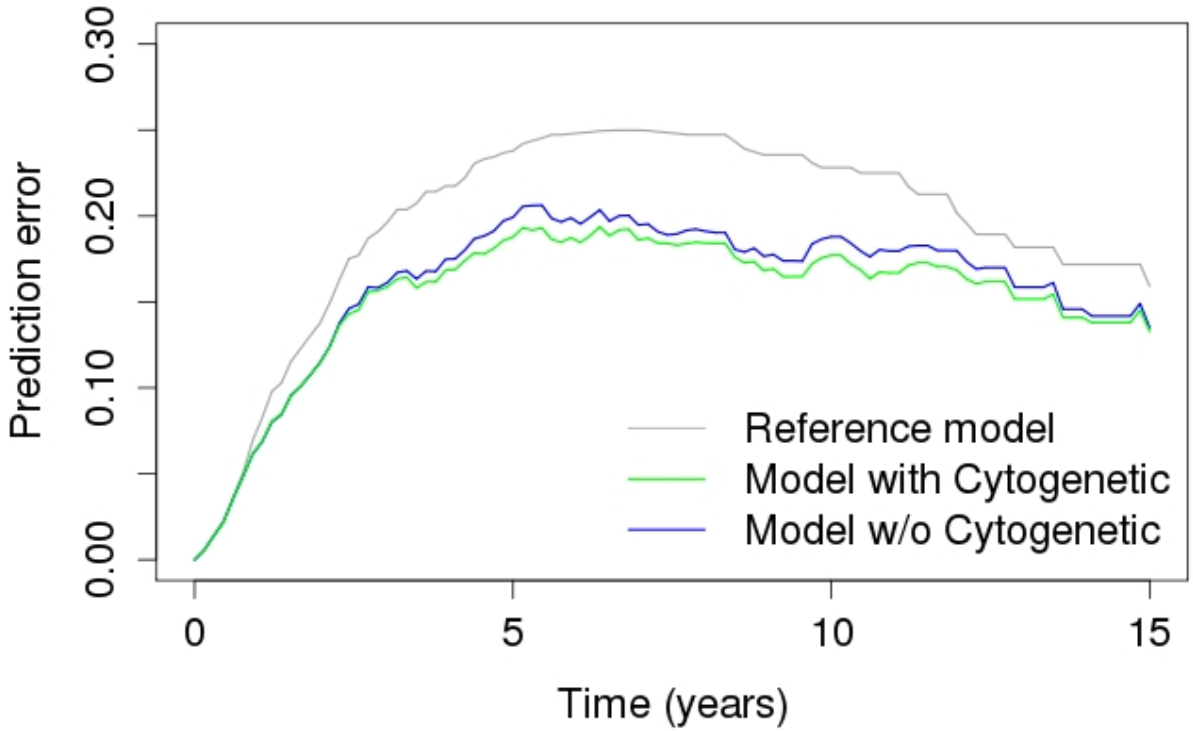
Organ impairment n (%) [range]		Favorable (n=317)	Unfavorable (n=212)	Unavailable (n=270)
KPS	***Median***	80	70	70
	≤70	151 (47.5)	111 (52.4)	181 (66.3)
$eGFR_{MDRD}$[a]	***Median [range]***	82 [5.5-185.2]	79 [2.2-181.5]	69 [4-174]
	eGFR >60	240 (75.8)	149 (70.3)	159 (58.2)
	eGFR 50-60	24 (7.5)	8 (3.8)	21 (7.7)
	eGFR 30-49	25 (7.9)	25 (11.8)	32 (11.7)
	eGFR 15-29	16 (5)	20 (9.4)	28 (10.3)
	eGFR <15	12 (3.8)	10 (4.7)	32 (11.7)
Lung	Moderate-severe	72 (22.6)	52 (24.5)	79 (28.9)
Cardiac	Mild-severe	128 (40.3)	105 (49.5)	131 (48)
Hepatic	Mild-severe	60 (18.9)	61 (28.8)	51 (18.7)
GI	Mild-severe	19 (6)	19 (9)	34 (12.5)
Infection	Mild-severe	61 (19.2)	52 (24.5)	63 (23.1)
Thrombosis	Mild-severe	27 (8.5)	16 (7.5)	38 (14.3)
Pain	Yes	116 (36.5)	99 (46.7)	103 (37.7)
	No	202 (63.5)	113 (53.3)	168 (62.3)
PNP	Mild-severe	27 (8.5)	10 (4.7)	22 (8.1)
2nd malignancies	Hematologic tumor	39 (12.3)	24 (11.3)	27 (9.9)
	solid tumor	8 (2.5)	8 (3.8)	11 (4)
	skin malignancy	10 (3.1)	10 (4.7)	6 (2.2)
	Before & synchronous after MM	38 (11.9)	32 (15.1)	34 (12.5)
		19 (6)	10 (4.7)	10 (3.7)
	Local	45 (14.2)	28 (13.2)	27 (9.9)
	disseminated	12 (3.8)	14 (6.6)	17 (6.2)
Disability	Moderate-severe	71 (22.3)	69 (32.5)	119 (43.6)
Frailty	Moderate-severe	106 (33.3)	89 (42.0)	136 (49.8)
Comorbidity scores	***Median [range]***			
	R-MCI	4 [0-8]	5 [1-9]	5 [0-8]
	I-MCI	1 [0-3]	1 [0-3]	1 [0-3]
	CCI	3 [0-9]	3 [0-13]	4 [0-12]
	HCT-CI	2 [0-11]	2 [0-14]	2 [0-17]
	KFI	1 [0-3]	2 [0-3]	2 [0-3]

Abbreviations:
KPS: Karnofsky Performance Status
$eGFR_{MDRD}$, estimated glomerular filtration rate by MDRD (Modification of Diet in Renal Disease; (ml/min/1.73m²))
GI: gastrointestinal, PNP: peripheral neuropathy
R-/I-MCI: Revised-/Initial-Myeloma Comorbidity Index, CCI: Charlson Comorbidity Index, HCT-CI: Hematopoietic cell transplantation-specific Comorbidity Index, KFI: Kaplan Feinstein index

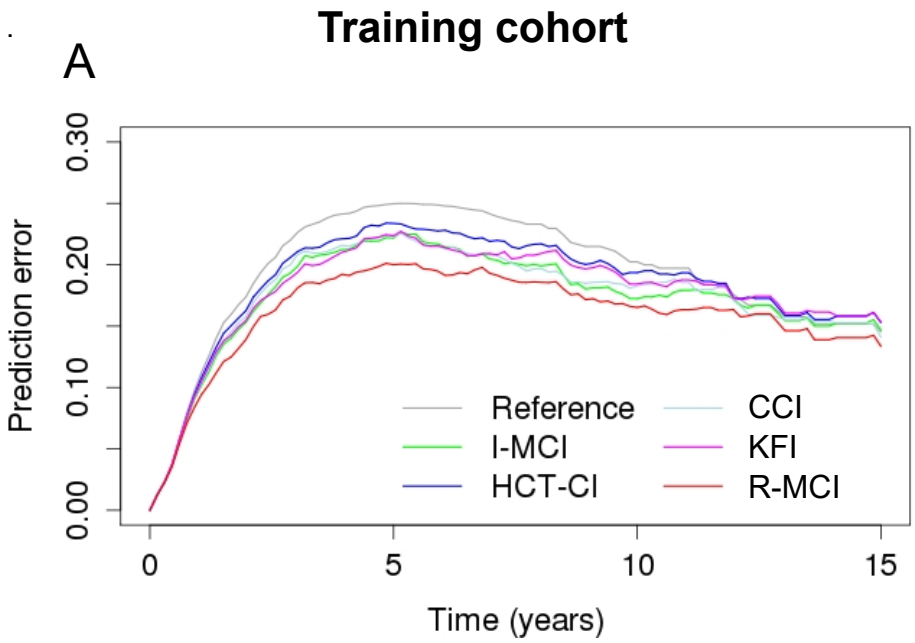
Supplementary Table 4B. Differences in patient-, MM-, laboratory and therapy-specific data in patients with favorable, unfavorable or unavailable cytogenetics.

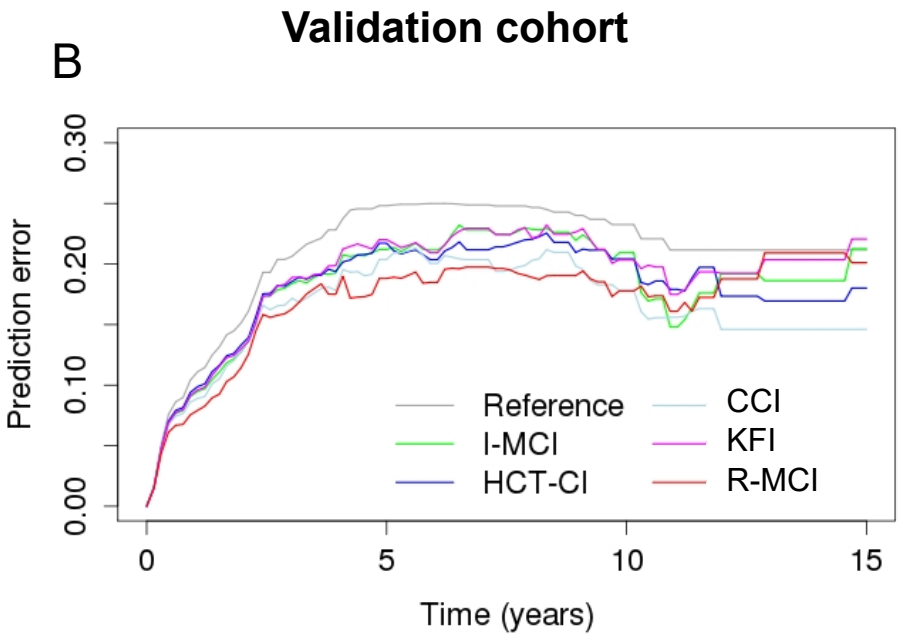
	Favorable (n=317)	Unfavorable (n=212)	Unavailable (n=270)
Patient-specific data			
Median age (years) [median, range]	61 [32-93]	61 [27-89]	67 [21-90]
Males : females; n (%)	192 (60.7) : 125 (39.3)	107 (50.5) : 105 (50)	149 (55.3) : 121 (44.7)
MM-specific data			
IgG / IgA / IgM / IgD; n (%)	186 (58.5) / 48 (15.1) / 3 (0.9) / 4 (1.3)	126 (59.4) / 43 (20.3) / 1 (0.5) / 0 (0)	142 (52.3) / 62 (22.7) / 2 (0.7) / 0 (0)
LC / Non-secretory; n (%)	63 (20.1) / 10 (3.1)	42 (19.8) / 0 (0)	54 (19.8) / 8 (2.9)
κ / λ / biclonal (LC); n (%)	193 (60.7) / 110 (34.6) / 3 (0.9)	154 (73)/ 58 (27.4) / 0 (0)	153 (56) / 108 (39.6) / 2 (0.7)
Disease stage			
Median Durie&Salmon	3 (1-3)	3 (1-3)	3 (1-3)
Durie&Salmon I / II / III; n (%)	82 (25.8) / 49 (15.4) / 185 (58.5)	38 (17.9) / 33 (15.6) / 141 (66.5)	82 (30.8) / 35 (12.8) / 153 (56.4)
Durie&Salmon A / B; n (%)	281 (88.7) / 36 (11.3)	178 (84) / 34 (16)	205 (75.1) / 66 (24.2)
Median ISS[a]	2 (1-3)	3 (1-3)	3 (1-3)
ISS I / II / III; n (%)	107 (33.6) / 105 (33) / 100 (31.2)	55 (25.9) / 46 (21.7) / 109 (51.4)	63 (23.1) / 55 (20.1) / 119 (43.6)
Laboratory parameters [median, range]			
Hb (g/dl)	11.8 [5.7-17.2]	10.9 [4.8-16.2]	11 [3.2-18.2]
Creatinine (mg/dl)	0.9 [0.4-10.2]	0.9 [0.4-17.9]	1 [0.4-14.2]
β_2-MG (mg/dl)	4 [1.22-62.2]	5.5 [1.25-65.5]	5.5 [1.1-44.8]
Albumin (g/dl)	3.9 [1.7-5.3]	3.8 [1.6-5.1]	3.7 [1.3-4.9]
LDH (U/L)	218 [74-3645]	214 [104-1673]	209 [70-3793]
PC BMI	30 [0-95]	40 [0-100]	30 [0-95]
Therapy-specific data			
Standard therapy n (%)	88 (27.7)	74 (34.9)	182 (66.7)
SCT n (%)	207 (65.4)	128 (60.4)	47 (17.6)
No CTx n (%)	22 (6.9)	10 (4.7)	43 (15.8)

Abbreviations:
n: number , Ig: Immunglobulin, LC: light-chain, κ: Kappa; λ: Lambda, ISS: International Staging System, Hb: hemoglobin, β_2-MG: ß$_2$-microglobulin, LDH: lactate dehydrogenase, PC: plasma cell, BMI: bone marrow infiltration, SCT: stem cell transplantation, no CTx: no chemotherapy; [a]Not evaluated in n=41 patients because of missing data.



Supplementary Fig.1. Prediction errors based on the Brier score compared the R-MCI, with and without cytogenetics, and showed smaller prediction errors with inclusion of cytogenetics, which provided significant and independent additional information.





C

Score	Integrated Brier score	
	0-15 y	0-10 y
Reference	0.194	0.205
R-MCI	0.159	0.162
I-MCI	0.172	0.178
KFI	0.175	0.180
CCI	0.172	0.178
HCT-CI	0.182	0.189

D

Score	Integrated Brier score	
	0-15 y	0-10 y
Reference	0.205	0.206
R-MCI	0.164	0.158
I-MCI	0.178	0.180
KFI	0.186	0.182
CCI	0.163	0.169
HCT-CI	0.175	0.180

Supplementary Fig.2. Prediction errors (A+B) and Brier scores (C+D) in training and validation cohorts comparing the R-MCI, I-MCI, KFI, CCI and HCT-CI