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LETTER

Multiple myeloma gammopathies

Improving the identification of frail elderly newly diagnosed multiple myeloma patients

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To the Editor:

There is a marked heterogeneity in clinical outcome among elderly non-transplant eligible newly diagnosed multiple myeloma (NTE-NDMM) patients, largely being explained by differences in frailty level [1]. Currently, the gold standard for frailty assessment in MM is the International Myeloma Working Group frailty index (IMWG-FI), based on age, comorbidities and (instrumental) Activities of Daily Living ((i)ADL). Using this definition, frailty is associated with an inferior progression free survival (PFS) and overall survival (OS), higher rates of treatment discontinuation and non-hematological toxicity [2]. The IMWG-FI was a crucial step in the introduction of the frailty paradigm in the treatment of MM patients in order to improve treatment outcome. However, there are several drawbacks of this gold standard in frailty assessment. First, with this index, age >80 automatically classifies a patient as frail, while it is known that there is considerable heterogeneity in frailty amongst octogenarians due to differences in performance and comorbidities and it is at least questionable whether all patients >80 are functionally frail [3–6]. Second, 3 of 5 parameters of the IMWG-FI (age 76–80, iADL≤5 and CCI ≥ 2) were not independently associated with OS (Table S1), offering the possibility for improvement [2]. Third, the discriminative power of the IMWG-FI is still insufficient to select patients for whom treatment benefit will be negligible. Therefore, we investigated whether the prognostic value of the IMWG-FI could be improved. The HOVON123-study (NTR4244) is a prospective, phase 2 multicenter trial, designed for patients ≥75 years with symptomatic NDMM treated with a dose-adjusted melphalan-prednisone-bortezomib (MPV) regimen. Only patients with severe organ dysfunction were excluded (Supplementary Methods). The primary objective was to assess the feasibility, defined as treatment discontinuation within nine MPV-cycles (TD9) [7]. For sample-size calculation of the primary endpoint, A'Hern single-stage phase II was used (Supplementary Methods). We evaluated the prognostic value of frailty according to the IMWG-FI [2]. To investigate which frailty factors were the best predictors for the primary objective (TD9), we used Akaike's Information Criterion (AIC) by backward selection procedure, including all frailty factors (age, CCI, ADL, iADL) as continuous variables in a logistic regression model. Additionally, each frailty factor was analyzed with its IMWG cut-off in the univariate and multivariable model for risk assessment on TD9. Finally, two revised-frailty indexes (RFIs) were proposed based on TD9. The predictive value of those RFIs for PFS, OS, and treatment discontinuation ≤3 cycles (TD3) was compared with the predictive value of the IMWG-FI using AIC model comparison. The study was approved by the Ethics Committee and informed consent was obtained from all participants. Analyses were based on complete cases of intermediate fit and frail patients

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(Supplementary Methods). Of the 238 patients included in the HOVON123-study, 37 were excluded from this analysis (Supplementary Methods). Of the remaining 201 patients, 71 (35%) were intermediate fit and 130 (65%) frail according to the IMWG-FI (Table S2). We confirmed the predictive value of the IMWG-FI, showing an inferior OS (Fig. 1a) and higher TD-rates (Table S3), but comparable PFS (Fig. S1a) in frail versus intermediate fit patients. Of the frail patients, 20 (15%) were frail based on age >80 alone, 55 (42%) based on only other frailty parameters and age <81 and the remaining 55 (42%) based on both age >80 plus other frailty parameters. We observed a statistically significant superior PFS and OS in patients who were frail based on age >80 alone and patients based on other frailty parameters and age <81, versus those >80 plus other frailty parameters (Fig. S2).

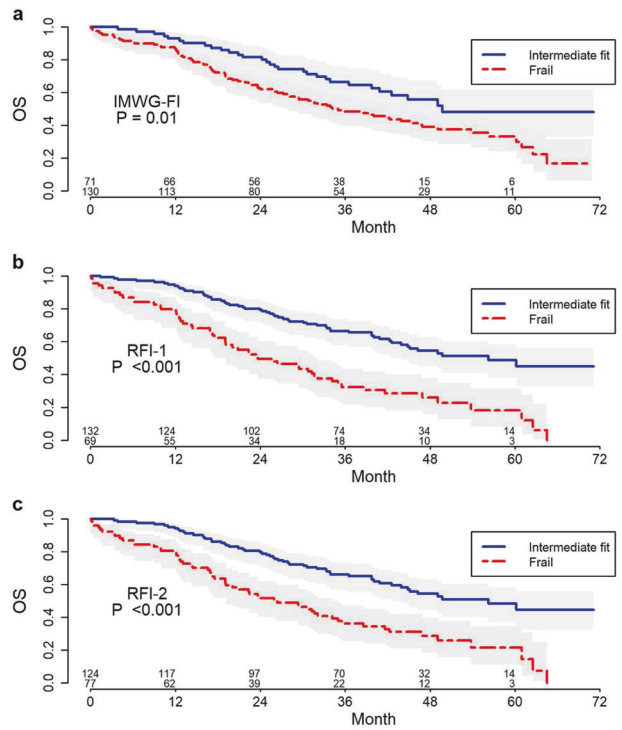

Fig. 1 Overall survival between intermediate fit and frail patients according to different frailty indexes. a original IMWG-FI; **b** revised frailty index 1 (RFI-1); **c** revised frailty index 2 (RFI-2). Including 95% confidence intervals (in grey) and *p* values for significant differences between frailty subgroups according to each frailty index (see also Table S3). Median follow-up of study population: 42.3 months (95% CI 33.8–49.1). IMWG-FI: original frailty index based on age, comorbidities (CCI) and dependency in activities of daily living (ADL) and instrumental ADL. Patients with a total frailty score of 1 are defined intermediate fit, and patients with a total score of ≥2 are defined frail. Both revised frailty indexes (RFIs) differ from the original IMWG-FI in defining intermediate fit patients (total frailty score 1 and 2) and frail patients (total frailty score ≥3). In addition, only for RFI-2, 1 additional point was assigned in case of CCI ≥ 3, giving more weight to comorbidities (Table 1c). IMWG International Myeloma working group; (R)FI (revised) frailty index; OS overall survival.

We investigated whether other IMWG-FI score cut-offs would better predict outcome. First, we compared the TD9 rates, PFS and OS between the separate IMWG-FI scores 1–5, instead of using the original dichotomized cut-off for intermediate fit (score 1) and frail (score ≥ 2). Based on the association between the individual scores with TD9 (Table 1a), PFS and OS (Fig. S3), we proposed an alternative cut-off of ≥3 for defining frailty (RFI-1) (Table 1b).

Table 1 Development of revised frailty indexes.

(a) TD9 stratified by total IMWG frailty score

Total frailty score	Yes (%)	No (%)	OR (95% CI)	Fisher exact test
1	33.8	66.2	1.00 (ref group)	–
2	34.4	65.6	1.03 (0.47-2.50)	1.00
3	57.9	42.1	2.67 (1.11-6.56)	0.024
4	60.0	40.0	2.90 (0.94-9.40)	0.042
5	81.8	18.2	8.58 (1.57-87.9)	0.006

(b) Score weights of IMWG-FI and revised FIs

Frailty parameter		Original IMWG-FI	RFI-1	RFI-2
Age	≤75	0	0	0
	76-80	1	1	1
	>80	2	2	2
CCI	≤1	0	0	0
	2	1	1	1
	≥3	1	1	**2**
ADL	≥5	0	0	0
	≤4	1	1	1
iADL	>5	0	0	0
	<5	1	1	1
Fit		Total score: 0	Total score: 0	Total score: 0
Intermediate fit		Total score: 1	**Total score: 1–2**	**Total score: 1–2**
Frail		Total score: ≥2	Total score: ≥3	Total score: ≥3

(c) Uni- and multivariate risk analysis of frailty cut-offs for TD9

Frailty cut-off	Univariate OR (95% CI)	*p* value	Multivariate OR (95% CI)	*p* value
Age > 80	2.34 (1.29–4.26)	0.005	1.70 (0.88–3.26)	0.11
CCI ≥ 2	2.45 (1.34–4.47)	0.004	2.14 (1.13–4.06)	0.019
ADL ≤ 4	1.78 (0.89–3.57)	0.10	1.05 (0.42–2.63)	0.91
iADL<5	1.85 (1.01–3.39)	0.046	1.62 (0.75–3.52)	0.22

Description of the development of the two revised frailty indexes (RFIs) from the original IMWG-frailty index. (a) Risk of treatment discontinuation ≤9 cycles stratified by total IMWG frailty scores (1 to 5); (b) Score weights of IMWG-FI and RFI-1 and RFI-2. The bold values represent the modifications from the original IMWG-FI: According to both RFIs patients with a total IMWG frailty score of 1 and 2 were defined intermediate fit and, only for RFI-2, patients with more (severe) comorbidities (CCI ≥ 3) received 1 additional point increasing the weight of comorbidities; (c) univariate and multivariable analyses of the impact of the original IMWG frailty factor cut-offs on treatment discontinuation ≤9 cycles.

ADL activities of daily living, *CCI* Charlson Comorbidity Index, *CI* confidence interval, *FI* frailty index, *IMWG* International Myeloma working group; *iADL* instrumental activities of daily living; *OR* odds ratio, *TD9* treatment discontinuation ≤9 cycles.

This classification was found to be superior in discriminating PFS (Fig. S1b versus Fig. S1a), OS (Fig. 1b versus Fig. 1a), TD9 and TD3 (Table S3) between intermediate fit and frail patients as compared to the original IMWG cut-off of ≥2.

Second, we investigated which IMWG-FI parameters (both according to original IMWG-FI cut-offs and as continuous variables) were superior in predicting outcome. Both analyses showed that the CCI best predicted TD9 (Table 1c and Table S4, respectively). Subsequently, we investigated whether another cut-off than CCI ≥ 2 would better predict TD9. A trend for a higher TD9 was found for a CCI of 2, which was statistically significant for CCI ≥ 3 (Table S5). Therefore, in addition to increasing the cut-off for frailty to ≥3 in the RFI-1, we increased the weight of CCI ≥ 3 in the second revised-frailty index (RFI-2) (Table 1b). Again, the RFI-2 was superior in discriminating between the outcome (PFS: Fig. S1c versus S1a; OS: Fig. 1c versus 1a; TD9 and TD3: Table S3) of intermediate fit versus frail patient as compared to the IMWG-FI. Based on AIC model comparison, the difference in OS and PFS between intermediate fit and frail patients was best detected by RFI-1, and in treatment discontinuation by RFI-2 (Table S6).

Using our novel risk classifications, 61/130 (47% using RFI-1) and 53/130 (41% using RFI-2) patients were reclassified from frail to intermediate fit. In both RFIs, all 20 patients (15% of total) previously defined frail based on age >80 alone were reclassified intermediate fit. Of the 41 (RFI-1) and 33 (RFI-2) other reclassified patients, the majority were aged 76–80 with either impairments in iADL ($n = 15$) or CCI ≥ 2 ($n = 21$), including $n = 8$ with CCI ≥ 3. Almost all patients were able to carry out ADL (Fig. S4). The newly reclassified intermediate fit patients, either using RFI-1 or RFI-2, had a comparable PFS and OS with the intermediate fit patients according to the IMWG-FI, supporting a correct reclassification (Fig. S5).

The baseline disease characteristics ((R-)ISS, LDH, cytogenetic risk) of intermediate fit and frail patients were independent of the FI that was used. In contrast, patient-related characteristics differed between FIs. When using the RFIs, the remaining frail patients had more comorbidities and (i)ADL impairments (Table S2). The IMWG-FI made a plea for frailty assessment of elderly MM patients which is important as with a growing aging population the number of older patients with MM increase, of whom many, even octogenarians, are in general good health. Notwithstanding, with the current gold standard IMWG-FI, all patients >80 are considered to be frail. We here propose a revision of the IMWG-FI based on the outcome of community-based elderly intermediate fit and frail patients treated with a modified MPV-scheme. Patients who were defined frail based on age alone, were found to have a comparable outcome, compared to intermediate fit patients, supporting that age >80 alone is insufficient for prognostication. Our data add to the increasing evidence that chronological age is not a substitute for biological age [3, 8, 9]. Moreover, in accordance to previous literature, comorbidities best predicted treatment discontinuation [10].

By increasing the cut-off for frailty and weight of comorbidities, both RFIs classified ~45% less patients as frail, by which the power to discriminate between the outcome of intermediate fit and frail NTE-NDMM patients was improved. The variation in outcome between frail patients across FIs appeared to be due to differences in patient-related than disease-related factors. The fact that we could determine a more pronounced impact of comorbidities on clinical outcome in our study versus the original IMWG-trial is probably due to a higher incidence of patients with comorbidities and number of comorbidities in individual patients (CCI ≥ 2 in 35%, of which 43% even had a CCI ≥ 3) in our study, while in the IMWG-trial only 17% patients had a CCI ≥ 2 [2]. Accordingly, in a Danish population-based study with a high prevalence of comorbidities, the cut-off CCI ≥ 3 was found to best predict survival, supporting the use of a higher cut-off [11]. This is important in view of a higher level of comorbidities in real-life, promoting the suitability of our RFIs in general practice [12, 13].

There are several limitations that have to be addressed in future studies. First, we only included patients >75 years. This does probably not allow to extrapolate our RFIs to patients ≤75 years without further investigation. Although, it has been observed that the effect of comorbidities on outcome was independent of age, which would support the use of our RFIs independent of age [11]. Second, we were not able to validate our RFIs in separate patient and/or treatment cohorts. However, our findings are supported by a recent analysis of D'agostino et al., who also compared the outcome of patients who were defined frail based on age alone versus other frail patients. Early mortality was lower in the first group indeed. In contrast, OS was comparable between the 2 groups, but this can be well explained by the fact that the other frail subgroup also harbored patients who were <81 with additional frailty parameters, of whom we also showed a comparable outcome with frail patients based on >80 alone [6]. Moreover, the impact of CCI on outcome has already been observed in numerous non-myeloma populations [14, 15]. Our RFIs will help in changing models from prognostic to predictive when validated in differently treated patient populations. In conclusion, we found a pronounced heterogeneity in the outcome of patients who were defined frail based on the original IMWG-FI. Frail patients based on age >80 alone or age <81 with limited geriatric impairments/comorbidities had a superior outcome as compared to patients >80 plus additional geriatric impairments/comorbidities. Based on these observations we revised the cut-off for frailty, allowing the

identification of a smaller but more vulnerable frail population with inferior outcome. We encourage other study groups to validate our revised prognostic models in differently treated patient populations, creating a global platform for refinement of frailty assessment in MM aiming at improvement of frailty-based treatment strategies in the near future.

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Compliance with ethical standards

Conflict of interest NvdD has received research support from Janssen, Amgen, Celgene, Novartis, and BMS; and serves in advisory boards for Janssen, Amgen, Celgene, BMS, Takeda, Roche, Novartis, Bayer, and Servier. ISN serves in advisory boards for and received speakers fee from Celgene and Takeda. PS has received research support from and serves in advisory boards for Janssen, Takeda, Skyline Dx, Karyopharm and Amgen. MDL has received travel support from Janssen, Takeda and Roche, and serves in advisory boards for Takeda. SZ has received research funding from and has served in advisory boards for Celgene, Janssen and Takeda, Sanofi and Oncopeptids. Other authors have no conflicts of interest to report.

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