REVIEW

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Geriatric assessments and frailty scores in multiple myeloma patients: a needed tool for individualized treatment?

Mandy-Deborah Möller, Laura Gengenbach, Giulia Graziani, Christine Greil, Ralph Wäsch, and Monika Engelhardt**

Purpose of review
Multiple myeloma is a disease of elderly adults. Improvement in survival has occurred because of biological insights and novel agents. Therapeutic options involve choices today, thus have become more complex. Demographics have led to an increased number of elderly patients and age may be associated with a poorer outcome but is not the only prognostic predictor today.

Recent findings
To evaluate patients' health status rather than their chronological age alone, frailty scores and functional geriatric assessments are used to identify prognostic groups, avoid adverse events, compare clinical trials and tailor treatment. As most clinical trials exclude frail elderly patients, those enrolled therein are often younger and healthier than the typical multiple myeloma patient. This represents a challenge for frail cohorts because of their increased risk of adverse events, overtreatment and undertreatment and/or therapy discontinuation, which may lead to poorer survival and quality of life (QoL). Reassessing patients' status via geriatric assessments is also relevant during treatment to adjust interventions appropriately.

Summary
Integrating geriatric assessments may lead to individual treatment decisions, dose adjustments, better clinical outcome and QoL. Prospective clinical trials that enroll elderly multiple myeloma patients with comorbidities, incorporate frailty scores/geriatric assessments and help with prognostication, adverse event avoidance and QoL maintenance, remain warranted.

Keywords
fitness, frailty scores/functional geriatric assessment, multiple myeloma

INTRODUCTION

Multiple myeloma is the second most common hematological malignant neoplasm driven by clonal proliferation of plasma cells in the bone marrow and increased production of monoclonal immunoglobulins [1▪]. The incidence of multiple myeloma is growing with aging of the general population, with an annual increase of older newly diagnosed multiple myeloma patients of 90% being expected by 2034 [2].

With a median age of 70 years at the time of diagnosis, multiple myeloma is indeed a disease of elderly adults, with 30–40% of patients being older than 75 years and only less than 2% being very young (<40 years) [3]. The elderly group remains at higher risk for poorer outcome and early mortality, underlining the need for tools to optimize anti-myeloma treatment especially in these patients [2].

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KEY POINTS

- Advanced age, frailty and comorbidities are challenging risk factors that should be observed by physicians when treating elderly myeloma (or other cancer) patients.
- In order to evaluate patients' health status more objectively, rather than via the chronological age alone, functional geriatric assessments are helpful.
- Frailty scores help to identify risk groups to define prognostic groups, avoid adverse events, adjust treatment, plan interventions and maintain patients' quality of life.
- There is an urgent need in myeloma (and cancer) research for more clinical trial support, using geriatric assessment prospectively in elderly patients to improve disease management in this important and growing patient group.

EVALUATION OF FRAILTY TO IDENTIFY THE BEST TREATMENT OPTION

Age-related pathologies become more important when focusing on comprehensive treatment for older cancer patients. The biological process of aging, including immunosenescence in cancer and multiple myeloma patients, leads to sarcopenia [4], reduces strength, power and walking speed and causes less energy expenditure, chronic malnutrition and decreased physical activity. These factors cause a negative feed-back loop, which intensifies these processes and thereby clinical worsening ending in frailty. Moreover, multiple myeloma-specific comorbidities, like fatigue or osteolytic lesions, may boost this downward spiral (Fig. 1a). In summary, frailty is mainly driven by age-related biological changes [5].

To evaluate aging and frailty more objectively, it has been proposed that simple but suitable biomarkers, which predict physiological capacity, should be identified and used in clinical practice. These should ideally be better predictors of patients' lifespan than their chronological age alone. In addition, biomarkers of aging and frailty should monitor physiological processes and not disease itself. Current biomarkers of inflammation, cellular senescence, endocrine, genomic and immune profiles are examined and displayed in Fig. 1b [6,7▪]. Additionally, imaging like dual-energy X-ray absorptiometry (DXA), computer tomography, MRI and bioelectrical impedance analysis are used to assess sarcopenia (Fig. 1a and b) [7▪].

Overall survival (OS) in multiple myeloma patients has improved substantially in recent years because of ample biological insights, use of novel agents and innovative immunotherapies, autologous stem cell transplantation (ASCT) and better supportive care (Fig. 2) [8,9]. Nonetheless, aging remains a poor prognostic factor in cancer in general, including in multiple myeloma patients [1▪,8,10]. As therapy decisions have become more complex and involve multiple choices today, individual management of patients – ranging from fit to frail – should balance efficacy, toxicity and practicability (Fig. 2) [1▪]. Due to comorbidities and frailty, treating older patients can be challenging for physicians as these patients bear an increased risk of complications or adverse events leading to therapy discontinuation and treatment-related mortality (TRM) [8,11]. Patients who are identified as frail are, therefore, at risk of toxicity/severe adverse events and shorter progression-free survival (PFS) and OS [2]. Moreover, not only patient-related factors like advanced age or impaired Karnofsky Performance Status (KPS) but also myeloma-related factors, like advanced International Staging System (ISS) stage, high-risk cytogenetics, extramedullary involvement, no achieved partial response (PR) and short remission durations are associated with worse PFS/OS [12▪▪]. Both, over-treatment of frail patients and under-treatment of fit elderly patients are clinical challenges, which may induce poorer survival and reduce patients' quality of life (QoL) [1▪,13,14▪▪]. Therefore, balancing efficacy and toxicity of therapy is highly relevant to obtain deep and long-lasting remission and preserve patients' QoL (Fig. 2) [2]. The choice of the numerous available treatment options for older patients affected by frailty and comorbidities should consequently be individualized [1▪]. Indeed, adjusting for comorbidities induced significant differences in patients' survival [10,11,14▪▪]. For example, clinical trials have shown feasibility and benefit of ASCT in older multiple myeloma patients, even with full-dose Melphalan (200 mg/m^2) [15], highlighting that biologically fitter elderly patients can profit from intensive treatment as well as from interventions strengthening their performance and physical capabilities [10,14▪▪,16].

GERIATRIC AND FRAILTY SCORES

Frailty is defined as increased vulnerability to stressors because of a multisystem reduction in reserve capacity, which can be associated with poor response to treatment, increased toxicity and worse survival [1▪]. About one-third of myeloma patients are frail at the time of diagnosis. There are several frailty scores that can be used to stratify patients' fitness, albeit a standardized frailty score remains to be defined [5]. The initial International Myeloma Working Group (IMWG)-frailty index [17] was simplified by Facon [18] using only age, Eastern Cooperative Oncology Group (EGOC) performance status

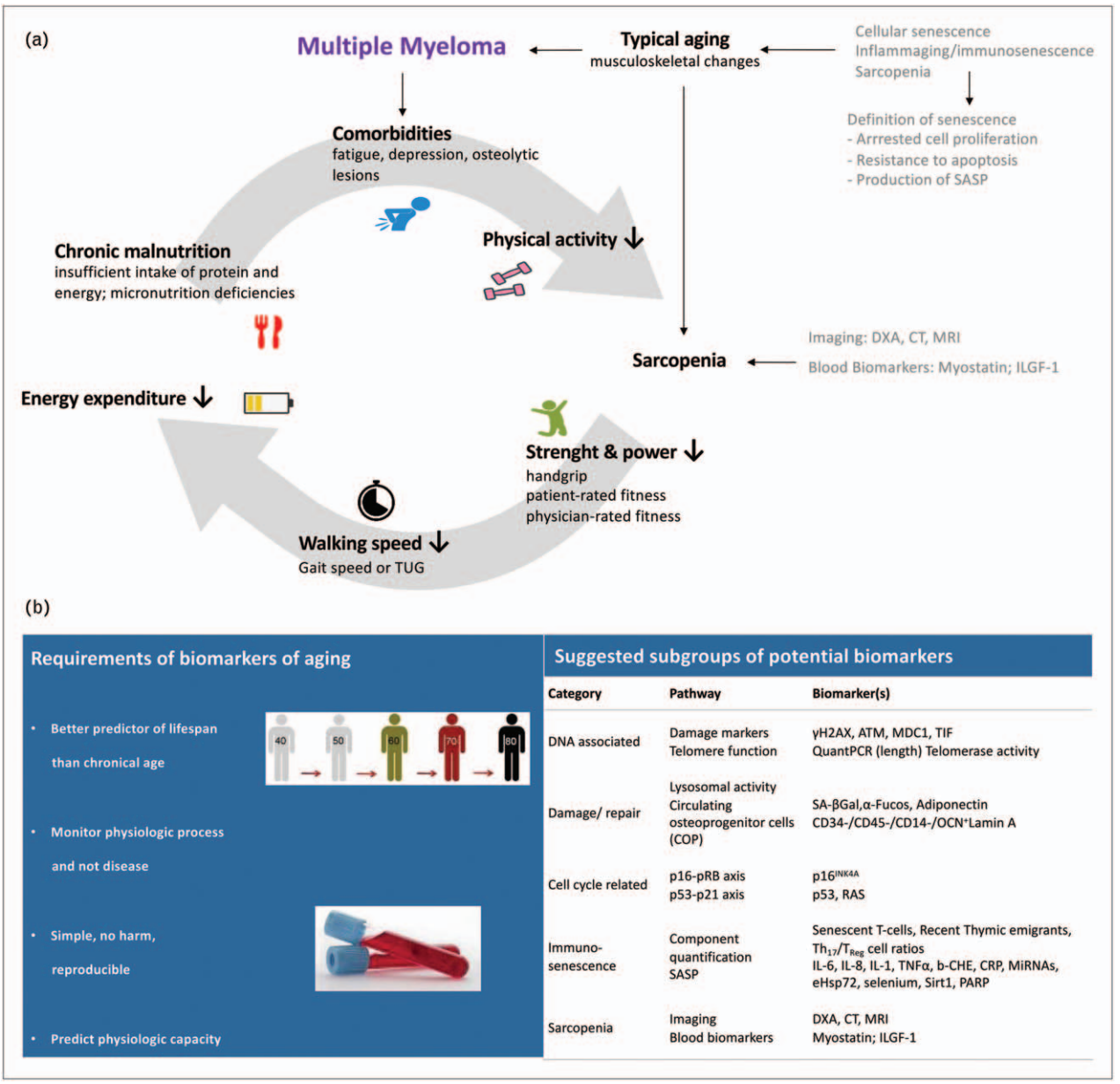

FIGURE 1. Biological aging and multiple myeloma. (a) Biological process of aging and senescence in multiple myeloma patients. CT, computer tomography; DXA, imaging like dual-energy X-ray absorptiometry; SASP, senescence-associated secretory phenotype; TUG, time up and go test. (b) Frailty measures and biomarkers of aging in multiple myeloma patients. Adapted with permission from Soto Perez de Celis, *Lancet Oncol*, 2018; Cook, *Leukemia*, 2020. Adapted with permission from Dr A. Rosko's pivotal work/slides and American Federation for Aging Research (AFAR).

and Charlson comorbidity index (CCI) [19], both assessed in retrospectively scored multiple myeloma patients. Several others, such as the revised myeloma comorbidity index (R-MCI) [20,21,22▪▪], the Mayo risk score [17] and the UK myeloma research alliance risk profile [7▪,23] have additionally been proposed as valuable clinical tools.

The simple assessment of patient fitness is performed via KPS or ECOG and CCI. However, these tools, as illustrated in Fig. 3a, have been criticized to be prone to subjective judgement, as too simple, often with the KPS being notoriously overestimated by a median of 30% and/or impossible to be evaluated retrospectively for the CCI [7▪,22▪▪,24].

Instead, geriatric assessments have proven to be more reliable tools to measure patients' physical and psychological status [17,20,21,22▪▪,25–28]. As geriatric assessments are time-consuming and may be difficult to integrate in daily clinical practice, shorter and more objective assessments of frailty have been proposed. These involve the Time Up and Go (TUG) test, handgrip strength, the short

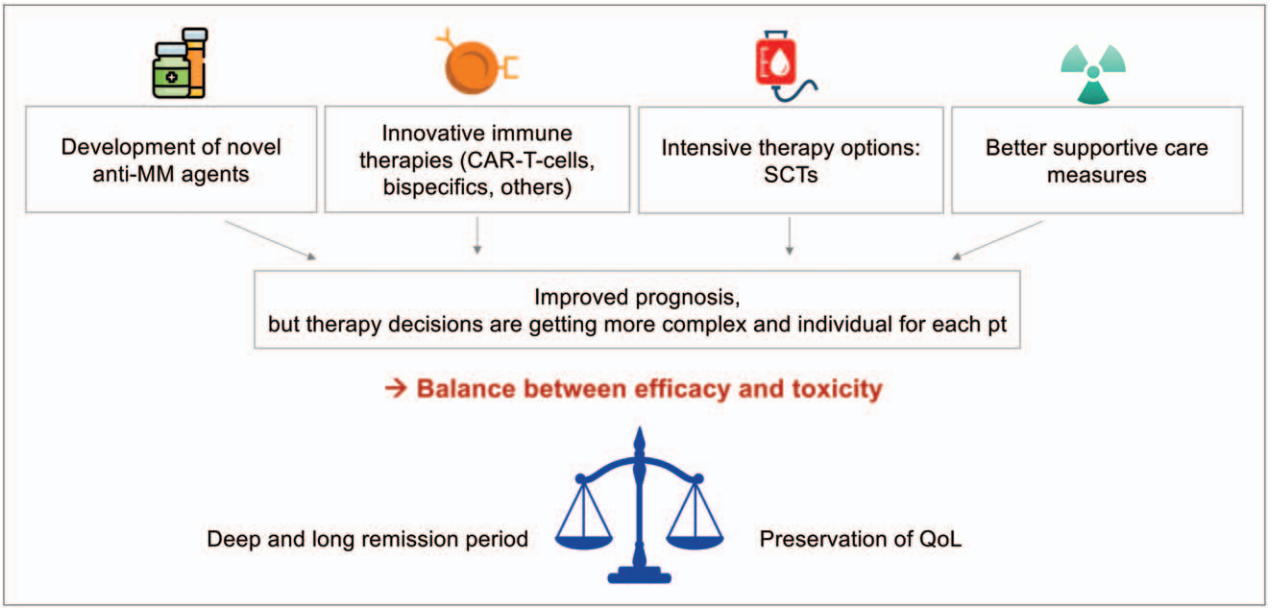

FIGURE 2. Advances in antimyeloma therapies. MM, multiple myeloma; pt, patient; QoL, quality of life; SCT, stem cell transplantation.

Physical Performance Battery or self-reported items, like the Katz scale of basic activities of daily living (ADL), Lawton and Brody's instrumental ADL (IADL), Brief Fatigue Inventory (BFI) or Medical Outcomes Study Short Form 36/12 (SF-36/12; Fig. 3a). Albeit these provide more objective and self-reported metrics of patients' fitness, they are not myeloma-specific and have been used less frequently [14▪▪,24].

RISK-ASSESSMENT VIA REVISED MYELOMA COMORBIDITY INDEX

Objective assessment of patients' fitness – at best over time – has been postulated as desirable [7▪,17, 21,22▪▪,25–29]. Indeed, myeloma-specific geriatric assessments have been examined to objectively divide patients into fit, intermediate-fit and frail. Ideally, these assessments should be based on repeatedly tested and validated, multivariately determined and weighted risk factors [7▪,20,21,22▪▪, 25–29]. This has led to the development of the R-MCI and IMWG-frailty index. The R-MCI has been evaluated in a large cohort of more than 1500 multiple myeloma patients and incorporates five risk factors, determined via multivariate Cox proportional hazard ratio model out of 12 meticulously assessed comorbidities (Fig. 3b). The five most relevant R-MCI risk factors were an impaired renal function [measured via estimated glomerular filtration rate (eGFR)], lung function, KPS, advanced age and frailty (according to Fried) [30], with cytogenetics, if available, being possible to include therein. The number of patients in the initial test analysis, with given risk groups, hazard ratio, *P* values and weights are depicted in Fig. 3b. A maximum of nine R-MCI points can be obtained, which generate risk groups of fit (0–3 points), intermediate-fit (4–6 points) and frail patients (7–9 points) with distinctly separating Kaplan–Meier curves for both PFS and OS [20,21], different TRM and risk of complications/adverse events. The side-by-side comparison of prospectively assessed multiple myeloma patients via R-MCI and IMWG-frailty index demonstrated that fit vs. frail patients were better distinguished with the R-MCI [20,21]. Of interest, Jackson *et al.* [10], Palumbo *et al.* [17] and Schinke *et al.* [12▪▪] demonstrated that similar to molecular markers being relevant predictors of outcome, clinical risk factors were equally important in elderly multiple myeloma patients, such as frailty, falls or nonresponsiveness, especially when repeatedly assessed over time [10,12▪▪]. Assessing frailty, with defined risk scores, should therefore, involve objectively weighted single risk factors, in order to most precisely describe a patient status, as the R-MCI or IMWG-frailty index do. Indeed, the R-MCI combines multivariate risk factors and has been prospectively used in clinical routine and clinical trials, both before therapy and at follow-up to assess patients' improvement over time [14▪▪,20,31].

Notably, almost all risk scores, as summarized in Fig. 3c, have determined age as a relevant risk factor, albeit age cut-offs were different with more than 70 years in the R-MCI vs. more than 80 years in the IMWG-frailty index [17,20,21]. All these scores have

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(a)

Oversimplified?

Examples of metrics

Age, PS, CCI	Objective measures	Self report
Age	TUG	ADL / IADL
ECOG / KPS	Handgrip	BFI
CCI	Short Physical Performance Battery	Medical Outcomes Study SF-36/12

KPS in MM notoriously overestimated by median +30%
→ i.e. if KPS by physician is 90% → according to KPS definition: was actually 60%

(b)

12 comorbidities analyzed		n	HR (2.5-97.5%)	log(HR) (2.5-97.5%)	p-value	Weight
1. eGFR	≥90	184	1 (-)			0
	60 to <90	193	1.25 (0.92-1.68)	**0.22**	<0.001	0
	<60	175	1.96 (1.43-2.68)	**0.67**		1
2. Lung disease	No/mild	470	1 (-)	0	<0.001	0
	Mod./severe	82	1.65 (1.24-2.18)	**0.50**		1
3. KPS	100%	35	1 (-)	0	<0.001	0
	80-90%	207	2.17 (1.04-4.52)	**0.77**		2
	≤70%	310	2.96(1.43-6.12)	**1.08**		3
4. Age	≤60	226	1 (-)	0	<0.001	0
	>60 to ≤70	185	1.43 (1.06-1.92)	**0.36**		1
	>70	141	2.08 (1.50-2.89)	**0.73**		2
5. Frailty (weakness, poor endurance, low physical activity, slow gait speed)	No/mild	323	1 (-)	0	0.002	0
	Moderate	140	1.54 (1.17-2.04)	**0.43**		1
	Severe	89	2.02 (1.45-2.82)	**0.70**		1
6. Cytogenetics	Favourable					0
	Unfavourable					1
	Missing					0
Max. points						End score: 9 (0-9)

Web-based, publicly available scoring: http://www.myelomacomorbidityindex.org

(c)

Risk score name and *typical variables therein included*	R-MCI	IMWG frailty score	Simplified IMWG score	Mayo risk score	Binder risk score	UK MRP	GAH
Risks included	eGFR, Lung disease, KPS/PS, Frailty, Age +/-CG	ADL, IADL, CCI, Age	PS, CCI, Age	PS≥2, NT-proBNP ≥300pg/ml, Age≥70y	Stage CG >20% PCs Thrombocytopenia Age	PS, ISS, CRP, Age	# of drugs, Frailty, ADL, Nutrition, Mental status, Comorbidities
Analyses:							
Retrospective	+	+	+	+	+	+	-
Prospective	+	+ Larocca ASH 2018	-	-	-	-	+
Validation	+	in Engelhardt M 2016*	-	-	-	-	-
# of pts assessed	>1500	869	1618	351	428	2372	363
Clinical trial + non-clinical trial pts	both	clinical trial	clinical trial	non-clinical trial	non-clinical trial	clinical trial	non-clinical trial
Homepage	http://www.myelomacomorbidityindex.org	http://www.myelomafrailtyscorecalculator.net	-	-	-	-	-

in yellow: often used risk scores, implemented in MM clinics, tumor boards and/or clinical trials to:
- objectively assess MM pts' risk for treatment toxicity (AEs), pauses and impaired PFS/OS,
- adjust therapy doses and avoid treatment-related toxicity,
- implement supportives and plan incentives to improve frailty, disability, falls and QoL-impairment,
- Better compare trial pts/cohorts with each other and within different clinical trials.

FIGURE 3. Myeloma-specific risk scores. (a) Examples of geriatric assessment tools for myeloma patients. ADL, activity of daily living; BFI, Brief Fatigue Inventory; CCI, Charlson Comorbidity Index; ECOG, Eastern Cooperative Oncology Group; IADL, Instrumental Activities of Daily Living; KPS, Karnofsky Performance Status; MM, multiple myeloma; SF-2612, Short Form 36/12; TUG, Time Up and Go test. (b) Multivariable cox proportional hazard model and weights of 12 comorbidities of the revised Myeloma Comorbidity Index (R-MCI). eGFR, estimated glomerular filtration rate; HR, hazard ratio; KPS, Karnofsky

(continue)

(d)

Fitness

Patient-rated fitness
Fitness evaluated by the pt based on grades from 1 (very good) to 6 (insufficient)
Overall grade: 1-6

Physician-rated fitness
Fitness evaluated by physician based on grades from 1 (very good) to 6 (insufficient)
Overall grade: 1-6

TUG
Time it takes to rise from a chair, walk 3 meters, turn around, walk back and sit down
Total value: time in seconds

Cognitive function

Mini-Mental State Examination
30 questions to measure cognitive impairment (e.g. memory, reaction, orientation in time & place)
Total score: 0-30

Self-sufficiency

ADL
Questionnaire of 6 self-care tasks to estimate pt´s self-sufficiency
Total score : 0-6

IADL
Questionnaire of 8 instrumental self-care tasks to estimate pt´s self-sufficiency
Total score : 0-8

Pain

Pain scale (NRS)
Pain assessment on a scale from 0 (no pain) to 10 (unbearable pain) at the current time
Total score : 0-10

Depression

Geriatric depression scale
30-item self-report assessment used to identify depression
Total score : 0-15

Quality of life

KPS
Quantification of pt's general well-being from 100% (perfect) to 0% (death)
Total value: 0-100%

SF-12: Physical composite scale
Questionnaire with 12 questions to measure physical quality of life
Total value: 0-100

SF-12: Mental composite scale
Questionnaire with 12 questions to measure mental quality of life
Total value: 0-100

Nutrition

Malnutrition
10-item questionnaire with regard to pt´s appetite, current medication and drug consumption
Total score : 0-21

(e)

Frailty index risk factors			
R-MCI	**0-3**	**4-6**	**7-9**
Definition	**"go-go"**	**"intermediate-go"**	**"slow-go"**
Treatment doses	**Level 0**	**Level -1**	**Level -2**
Dexamethasone	40mg day (d)1, 8, 15, 22 of 28d cycle	20mg d1, 8, 15, 22 of 28d cycle	8-10mg d1, 8, 15, 22 of 28d cycle
Melphalan	0.25mg/kg d1-4 of 4-6 wk cycle	0.18mg/kg d1-4 of 4-6 wk cycle	0.13mg/kg d1-4 of 4-6 wk cycle
Bortezomib	1.3mg/m^2 twice weekly: d1, 4, 8, 11 or d1, 8, 15 every 3 weeks	1.3mg/m^2 once weekly d1, 8, 15, 22 every 5 weeks	1.0mg/m^2 once weekly d1, 8, 15, 22 every 5 weeks
Thalidomide	100 (-200) mg/d	50 (-100) mg/d	50 mg qod (-50mg/d)
Lenalidomide	25mg d1-21 of a 28d cycle	15mg d1-21 of a 28d cycle	10mg d1-21 of a 28d cycle
Ixazomib	4mg d1, 8, 15, every 4 weeks	3mg d1, 8, 15, every 4 weeks	2.3mg d1, 8, 15, every 4 weeks
Daratumumab	16mg/kg bw iv or 1800mg sc cy1+2 weekly, out-pt treatment/in combo	16mg/kg bw iv or 1800mg sc cy1+2, weekly	8mg cy d1→ increase 16mg d8 or weekly 1800mg sc, possibly: start in-pt-therapy
Various others such as antibodies, checkpoint inhibitors, study options, doublets, triplets, quadruplets etc.			

Performance Status; *n*, number. (c) Examples of myeloma-specific risk scores. ADL, activity of daily living; AE, adverse event; CCI, Charlson Comorbidity Index; CG, cytogenetic; CRP, c-reactive protein; eGFR, estimated glomerular filtration rate; GAH, Geriatric Assessment in Hematology; IADL, Instrumental Activities of Daily Living; IMWG, International Myeloma Working Group; ISS, International Staging System; KPS, Karnofsky Performance Status; MRP, Myeloma Research Alliance Risk Profile; OS, overall survival; PFS, progression-free survival; PS, Performance Status; QoL, quality of life; UK, United Kingdom. (d) Examples of multidimensional functional tests. ADL, activity of daily living; IADL, Instrumental Activities of Daily Living; KPS, Karnofsky Performance Status; NRS, Numerical Rating Scale; SF-12, Short Form 12; TUG, Time Up and Go test. (e) Frailty index risk factors and dose adjustments with the aid of R-MCI. bw, bodyweight; cy, cycle; d, day; i.v., intravenous; R-MCI, Revised Myeloma Comorbidity Score; s.c., subcutaneous; wk, week.

shown their relevance in multiple myeloma patients, reveal risk group allocation into fit vs. frail patients, with different PFS and OS, and with substantially differing therapy toxicity, adverse events and TRM [17,20,21,23,24,32▪▪,33–35]. Apart from age, some include impaired organ function (renal, lung, performance status), comorbidity scores (CCI), laboratory parameters (NT-pro-BNT, platelets, ß2-MG, albumin, CRP), ISS stage and the possibility to include adverse cytogenetics therein, thus are

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fairly different (Fig. 3c). Suggestions for their improvement or even fusion moving forward are discussed in the hematology–oncology/multiple myeloma community (G. Cook, A. Larocca, V. Goede, U. Wedding, H. Auner, K. Yong, S. Kumar, A. Brioli, S. Zweegman, and others; personal communication). Commentaries have suggested that using any of these scores in clinics and clinical trials should be better than none at all [22▪▪]. Moreover, as depicted in Fig. 3d, geriatric assessments may not only involve frailty scores but also multidimensional functional tests, including fitness measures, tests for cognitive function, self-sufficiency, pain, depression, QoL and nutrition. Not all of these factors have proven to be equally relevant in multiple myeloma, which was demonstrated in a large prospective multiple myeloma cohort, where functional tests were compared with frailty scores at the time of patients' initial myeloma diagnosis and at follow-up [14▪▪].

As previous clinical trials have shown that frailty increases the risk of treatment-related adverse events and TRM, the US National Comprehensive Cancer Network, International Society of Geriatric Oncology and European Organization for Research and Treatment of Cancer recommended frailty assessment for older cancer patients to detect unrecognized health setbacks [5]. Risk scores, such as the R-MCI, include more objective fitness assessments that allow better patient prognostication than age alone, to allocate therapy intensity correctly and to avoid treatment toxicities, interruptions and early mortality. Risk scores are already used in tumor boards, follow-up assessments to determine improvement vs. deterioration, to compare trial cohorts but as yet less routinely in daily practice [7▪,17,22▪▪,28,31]. Recommended therapy doses for fit, intermediate-fit and frail multiple myeloma patients have been published in current guidelines and chemotherapy manuals (Fig. 3e) [20,36].

SELECTED CLINICAL TRIALS IMPLEMENTING FRAILTY ASSESSMENT IN MULTIPLE MYELOMA PATIENTS

As frailty is a known risk factor in older cancer patients, there are now more studies that evaluate the effectiveness of geriatric assessments to define risk groups, feasibility for dose-adjustments, effect on adverse events/TRM and whether a defined treatment schedule is equally superior in fit and frail cohorts (Table 1): most involve dose adjustments in intermediate-fit and frail patients, supportive interventions or the retrospectively performed analysis,

Table 1. Selected clinical trials with used frailty measures in multiple myeloma

Author	Number of patients/study	Frailty measure	Results	Pros	Cons
Larocca (GIMEMA) NCT02215980	199/II	IMWG frailty score	Rd ($n = 101$) vs. Rd-R10 ($n = 98$) in intermediate-fit	Randomized	Intermediate, not frail pts, R10 later rather than initially = upfront reduced
Suvannasankha NCT04223661	44/Indiana/II	IMWG frailty score	Dara-Rd in fit: Len 10 mg → 15 mg Dara-Rd frail: Len 5 → 10 mg	Prospective data: intermediate/frail profit from dose-reductions	Nonrandomized, Small study → needs confirmation
Cook (UKMRA) NCT03720041	740/III	UK myeloma score and IMWG frailty score	IxRd w/o dose reduction, −1 and −2 dose reduction	Randomized, large study	Industry sponsor, no (i.e. exercise) intervention
Zweegman (HOVON) NCR6297	130/II	IMWG frailty score	IDd dose-adjustments feasible	Might translate in better outcome	Effect on early mortality not shown
Möller, …Engelhardt	30/REAL-Fitness/II	R-MCI and others	Ongoing	Randomized, prospective data	Small → needs confirmation
Mateos	706/Alcyone/III	Simplified IMWG frailty score	Dara-VMP vs. VMP	Frail and fit seem to profit	Frailty score was retrospectively assessed
Schjesvold	307/Icaria/III	Simplified IMWG frailty score	Isa+Pd ($n = 154$) vs. Pd ($n = 153$)	Frail and fit seem to profit	Frailty score was retrospectively assessed
Auner	402/Boston/III	Simplified IMWG frailty score	Selinexor (X)Vd ($n = 195$) vs. Vd ($n = 207$)	Frail and fit seem to profit	Frailty score was retrospectively assessed

cons, disadvantages/issues to be considered; Dara, Daratumumab; IDd, Ixazomib, Daratumumab, Dexamethasone; IMWG, International Myeloma Working Group; Isa, Isatuximab; Pd, Pomalidomide, Dexamethasone; Pros, advantages of the study; pts, patients; Rd, Lenalidomide, Dexamethasone; R-MCI, Revised Myeloma Comorbidity Index; Vd, Bortezomib, Dexamethasone; VMP, Bortezomib, Melphalan, Prednisone.

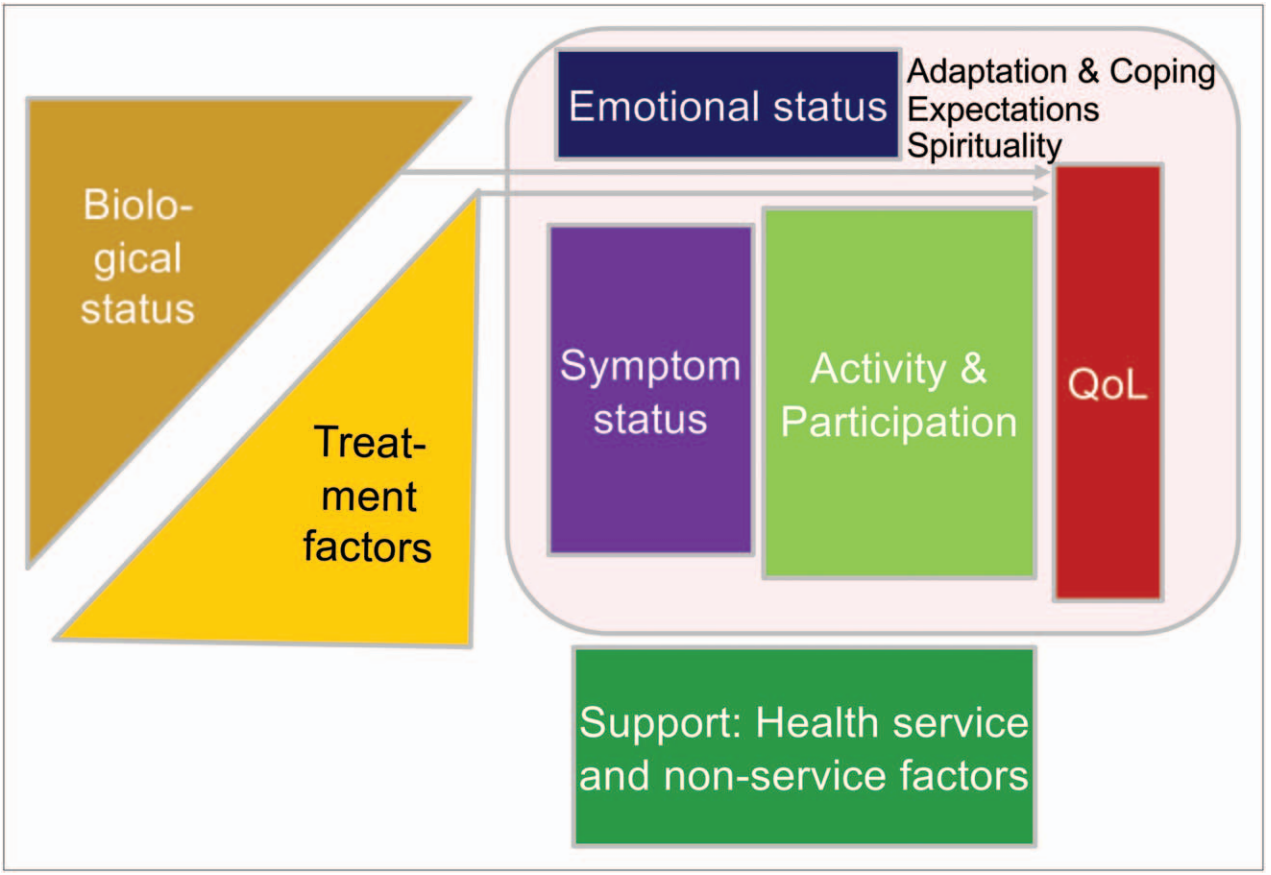

FIGURE 4. Theoretical model of quality of life and fitness preservation.

whether patients rated fit vs. frail via simplified IMWG frailty score [18] profit equally from novel combination therapies, such as Daratumumab, Bortezomib, Melphalan and Prednisone (Dara-VMP), Isatuximab, Pomalidomide and Dexamethasone (Isa-Pd) or Selinexor, Bortezomib and Dexamethasone (SVd). The latter difficulty is, that the CCI was not available retrospectively and was estimated as low in both fit and frail groups. Thus, poorly separating multiple myeloma patients were defined as fit or frail rather via age and ECOG alone than via simplified IMWG frailty score [36,37▪,38].

As shown in Fig. 4, both biological and treatment factors influence patients' symptoms and emotional status, their activity in daily life and QoL. Frailty scores and geriatric assessments may help to assess the complex patient status before and during therapeutic interventions, leading at best to supportive steps that allow patients to cope with their frailty, comorbidity burden and therapy. With an increasing number of elderly multiple myeloma patients, frailty needs should be identified and addressed in clinical trials, some representative of those being described in Table 1 [11].

Most oncologic procedures are based on findings of multicenter, randomized clinical trials but the patients enrolled in these studies are generally younger and healthier than the typical elderly and eventually frail multiple myeloma patient with comorbidities [9]. Therefore, physicians may administer novel agents to elderly and frail patients rather restrained, until clinical trials have shown efficacy and safety in elderly patients as much as in younger patients (Table 1) [11]. The simplified IMWG-frailty index [18] incorporating age, ECOG performance status and CCI, suggested an easier applicability than the original IMWG-frailty index with ADL and IADL inclusion. Here, the CCI was based on the retrospectively assessed comorbidity enumeration within the FIRST trial [18]. This led to low CCI values, therefore, the simplified IMWG-frailty index heavily relies on age and performance status alone [27]. Consequently, retrospectively performed 'ad hoc' analyses of the Alcyone, Icaria and Boston trials have suggested alike to the FIRST study [40], that fit and frail multiple myeloma patients profit from Dara-VMP, Isa-Pd and SVd similarly, albeit differences in the risk groups were small and prospective frailty assessment should have preferably been incorporated upfront into these clinical trials (Table 1) [39–41,42▪,43▪]. Frailty scores, should therefore, be prospectively planned to be included in research projects to get a

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much better understanding of how novel agents and treatment interventions can serve both fit and frail multiple myeloma patients [9], like ongoing representative studies do as summarized in Table 1.

FRAILTY SCORES AND QUALITY OF LIFE

Frailty may often be associated with lower QoL [20]. QoL is a complex model, influenced by the balance of symptoms, comorbidities, treatment-related toxicity and response to therapy. This model includes additional issues involving the biological status, emotional well being, possible physical activity, support by family, health service and nonservice factors at and during the disease course (Fig. 4).

Among cancer survivors, multiple myeloma patients have shown low QoL scores, highlighting the importance of the periodic assessment and interventions to improve QoL [1▪,20]. In principle, treatment response may induce or be associated with improved QoL as pain, anemia and organ impairment may subside, and strength, energy and physical activity may increase again, which we had indeed observed in follow-up analyses, specifically in responding (≥PR) and more strikingly in 70 year- or less vs. more than 70 year-old multiple myeloma patients [14▪▪].

Nevertheless, receiving the most effective treatment may not always guarantee patients' well being as emotional and socioeconomic factors influence patients likewise [44]. It is known, that anxiety and pain decrease QoL more than clinical characteristics [45▪▪]. Therefore, if QoL in any multiple myeloma patient does not improve during therapy, even though treatment response has been achieved, the evaluation of the R-MCI has shown to facilitate decisions on treatment adaptations or supportive interventions a patient might need [20,31].

CONCLUSION

Advanced age, frailty/myeloma-specific comorbidities and vulnerability/treatment tolerability are challenging to balance and may increasingly affect our patient management. Integrating frailty scores and geriatric assessments to support individual treatment decisions and dose adjustments may allow to improve clinical outcome and enhance patients' QoL to an even larger extend. To date, objective frailty and senescence markers remain to be exactly defined and it has to be determined, which can be reliably implemented into clinical practice to identify possible risks. Furthermore, reassessing patients' status during the treatment course seems important to determine, if patients' QoL improves, remains the same or deteriorates, therefore if the patient may need therapy adjustments [14▪▪]. Multifactorial interventions of comprehensive cancer centers today, combining physical activity, nutrition, cognitive training and other supportive measures seem necessary tools to preserve or at best improve patients' physical function. More prospective studies that include frailty scores and geriatric assessments in antimyeloma treatment and broader range of multicenter clinical trials that allow to enroll elderly multiple myeloma patients with various comorbidities are eagerly awaited and clinically needed. These should further determine, if and to what extend multiple myeloma patient and disease management have indeed improved and what can be done to foster this in the future.

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Conflicts of interest

There are no conflicts of interest.

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