






POSITION PAPER

The importance of frailty assessment in multiple myeloma: a position statement from the Myeloma Scientific Advisory Group to Myeloma Australia

Shirlene Sim ¹, Anna Kalff,² Gina Tuch,³ Peter Mollee,^{4,5} P. Joy Ho,^{6,7} Simon Harrison,^{8,9} Simon Gibbs ^{10,11}, H. Miles Prince,^{8,9,12} Andrew Spencer,² Douglas Joshua,^{6,7} Cindy Lee,¹³ Silvia Ling,¹⁴ Nick Murphy,¹⁵ Ferenc Szabo,¹⁶ Jeff Szer ^{8,9}, Nicholas Weber,¹⁷ Christopher Ward,¹⁸ Dipti Talaulikar ¹⁹, Andrew Zannettino ²⁰ and Hang Quach^{1,9}

¹Department of Haematology, St Vincent's Hospital, ²Department of Haematology, Alfred Hospital, ³Department of Geriatric Medicine, Alfred Health, ⁸Department of Haematology, Peter MacCallum Cancer Centre and The Royal Melbourne Hospital, ⁹Department of Medicine, The University of Melbourne, ¹⁰Department of Haematology, Eastern Health, ¹¹Department of Medicine, Monash University, and ¹²Department of Haematology, Epworth Healthcare, Melbourne, Victoria, ⁴Department of Haematology, Princess Alexandra Hospital, ⁵Department of Medicine, University of Queensland, and ¹⁷Department of Haematology, Royal Brisbane Hospital, Brisbane, Queensland, ⁶Department of Haematology, Royal Prince Alfred Hospital, ⁷Department of Medicine, University of Sydney, ¹⁴Department of Haematology, Liverpool Hospital, and ¹⁸Department of Haematology, Royal North Shore Hospital, Sydney, New South Wales, ¹³Department of Clinical Haematology, Royal Adelaide Hospital, and ²⁰Department of Experimental Haematology, University of Adelaide, Adelaide, South Australia, ¹⁵Department of Clinical Haematology, Royal Hobart Hospital, Hobart, Tasmania, ¹⁶Department of Haematology, Royal Darwin Hospital, Darwin, Northern Territory, and ¹⁹Department of Haematology, The Canberra Hospital, Canberra, Australian Capital Territory, Australia

Key words

frailty, elderly, treatment, multiple myeloma.

Correspondence

Hang Quach, Department of Haematology, Level 3 Daly Wing, St. Vincent's Hospital Melbourne, 41 Victoria Parade, Fitzroy, VIC 3065, Australia.
Email: hang.quach@svha.org.au

Received 14 April 2022; accepted 13 February 2023.

Abstract

Multiple myeloma (MM) is a disease of older people, yet factors relating to comorbidity and frailty may threaten treatment tolerability for many of this heterogeneous group. There has been increasing interest in defining specific and clinically relevant frailty assessment tools within the MM population, with the goal of using these frailty scores, not just as a prognostic instrument, but also as a predictive tool to allow for a frailty-adapted treatment approach. This paper reviews the various frailty assessment frameworks used in the evaluation of patients with MM, including the International Myeloma Working Group Frailty Index (IMWG-FI), the Mayo Frailty Index and the simplified frailty scale. While the IMWG-FI remains the most widely accepted tool, the simplified frailty scale is the most user-friendly in busy day-to-day clinics based on its ease of use. This paper summarises the recommendations from the Myeloma Scientific Advisory Group (MSAG) of Myeloma Australia, on the use of frailty assessment tools in clinical practice and proposes a frailty-stratified treatment algorithm to aid clinicians in tailoring therapy for this highly heterogeneous patient population.

Background

The median age of diagnosis of multiple myeloma (MM) is 70 years. Older transplant-ineligible (TIE) patients, particularly those >75 years old, have the poorest outcomes attributable to comorbidities and age-related organ dysfunction. The higher rate of treatment-

related toxicity and early treatment discontinuation is predictive of poorer survival in these patients.¹

With the advent of novel therapies that are more effective with lower toxicity profiles, there has been improved overall survival (OS) in older patients.² Deep and/or durable responses with novel agents are now attainable in TIE patients, as demonstrated in the Frontline Investigation of Revlimid and Dexamethasone Versus Standard Thalidomide combination therapy (FIRST) and Multiple Myeloma Ineligible for Transplant (MAIA) studies, which showed

Conflict of interest: None.

improved progression-free survival (PFS) even with dose modifications.^{3,4} This emphasises the importance of a tailored treatment approach in older patients, where tolerability is, arguably, the most important factor in deciding on the most optimal treatment regimen.

As such, there is growing interest in advancing the use of myeloma-specific frailty scores as a predictive tool. Older patients are a highly heterogenous population that vary significantly in their cognitive and physical abilities and, hence, their physiological reserve. Upfront assessment and stratification of patients across the fitness spectrum will allow for an individualised, frailty-adapted treatment approach. Older, fitter patients can receive more intensive treatment; a highly select subgroup may even benefit from autologous stem cell transplant.⁵ Conversely, treatment doses can be adjusted prospectively in frail patients to give them the best chance of continuing treatment or, alternatively, offering supportive care and palliation as the primary intervention.

Here, we present several frailty assessment frameworks and provide treatment recommendations for older patients.

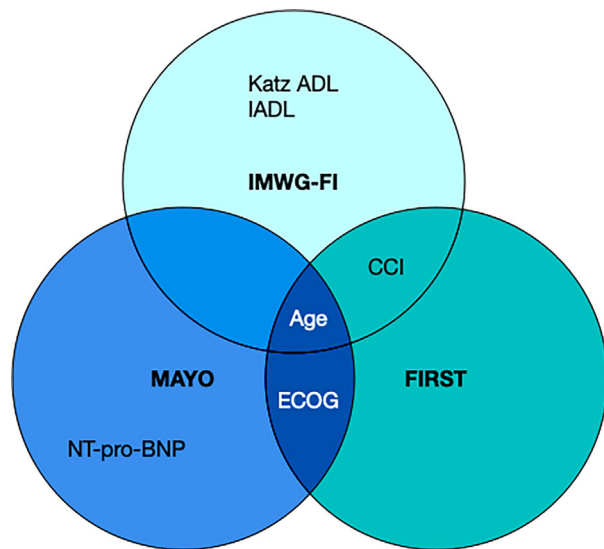


Figure 1 Frailty assessments in multiple myeloma. Several of the major frailty assessments have overlaps in their components, including age and the Charlson Comorbidity Index (CCI); however, they differ in their choice of performance status and other measures. Attributable to their different components, there are differences in the complexity and length of time required to administer these assessments. ADL, Katz activity of daily living; CCI, Charlson Comorbidity Index; ECOG, Eastern Cooperative Oncology Group performance status; FIRST, simplified frailty scale; IADL, Lawton instrumental activity of daily living; IMWG-FI, International Myeloma Working Group Frailty Index; NT-proBNP, N-terminal fragment of the type-B natriuretic peptide; MAYO, Mayo Frailty Index.

How is frailty assessed?

Frailty is characterised by a cumulative decline in multiple physiological systems culminating in a state of vulnerability and loss of reserve to stressors, all of which result in increased morbidity and mortality. Various tools utilise phenotypic and deficit-accumulation scores to index this state of vulnerability.⁶

There has been a push to develop myeloma-specific geriatric assessment tools (Fig. 1). Table 1 summarises the components and scoring system of each tool.

The International Myeloma Working Group Frailty Index (IMWG-FI)

In a pooled analysis of 869 patients, the IMWG established a frailty score in which patients were

Table 1 Summary of frailty assessment tools

Frailty assessments	Components	Score	Total score	stratification
IMWG-FI ¹	Age, years			
	≤75	0		
	76–80	1		
	>80	2		
	ADL		0	Fit
	>4	0		
	≤4	1	1	Intermediate fit
IADL	>5	0	≥2	Frail
	≤5	1		
	CCI			
	≤1	0		
	>1	1		
	Mayo Frailty Index ⁹		0	Stage I
Age, years	≥70	1		
	ECOG-PS		1	Stage II
	≥2	1		
NT-proBNP	≥300 ng/L	1	2	Stage III
			3	Stage IV
Simplified frailty scale ¹⁰	Age, years			
	≤75	0		
	76–80	1		
	>80	2		
	CCI		0–1	Non-frail
	≤1	0		
	>1	1	≥2	Frail
ECOG-PS	0	0		
	1	1		
	≥2	2		

ADL, Katz activity of daily living; CCI, Charlson Comorbidity Index; ECOG-PS, Eastern Cooperative Oncology Group performance status; IADL, Lawton instrumental activity of daily living; IMWG-FI, international Myeloma working group frailty index; NT-proBNP, N-terminal fragment of the type-B natriuretic peptide.

stratified into three categories: fit, intermediate-fit and frail.¹ This score was shown to be an independent predictor of OS, non-haematological adverse events and early drug discontinuation, irrespective of staging and treatment regimen.¹ This is the most accepted frailty assessment in MM and has undergone validation in a real-world setting.⁷

One of the concerns of the IMWG-FI is its high dependence on chronological age. Patients aged >80 years are automatically classified as frail. However, a recent analysis of the original cohort demonstrated that the presence of geriatric impairments was able to predict an inferior OS in patients aged ≤80 years, but not in those >80 years,⁸ thus confirming that patients aged >80 years should be classified as frail irrespective of the presence or absence of functional limitations and/or comorbidities.

The IMWG-FI is still underutilised in the clinical setting. This is likely attributable to its multiple elements and the perceived difficulty of incorporating a potentially time-consuming tool into busy clinics.

Mayo Frailty index

The Mayo Frailty Index was developed with the aim of providing an easily applicable and objective frailty tool.⁹ It includes the serum biomarker N-terminal fragment of the type-B natriuretic peptide (NT-proBNP), which is reflective of cardiac and renal function. Using a cut-off of ≥300 ng/mL, NT-proBNP was able to classify those at higher risk of dying, independent of the Revised Multiple Myeloma International Staging System (R-ISS) score. Patients were assigned a score of 1 for each variable of age, Eastern Cooperative Oncology Group-Performance Status (ECOG-PS) and NT-ProBNP, and stratified into four stages. Median OS was not reached in Stage I patients versus 18 months for Stage IV patients ($P < 0.0001$). This index has not yet been validated. Comparison with the IMWG-FI is difficult as the Mayo Frailty Index used a retrospective calculation of the Charlson Comorbidity Index (CCI) and did not include Lawton Instrumental Activity of Daily Living (IADL) data. This was a single-centre study, and participants were on average 10 years younger than the IMWG study.

Simplified frailty scale

Given the need for a more accessible tool, Facon *et al.* retrospectively analysed 1600 patients from the FIRST trial and proposed a simplified scale based on age, CCI and ECOG-PS.¹⁰ This abbreviated scoring system stratified patients into two categories, frail and non-frail, which the authors felt would be more relevant in clinical

Box 1 Summary of recommendations for the management of older patients

- All older patients should have a frailty assessment at diagnosis.
- Frailty stratification helps to define treatment goals at the outset and allows for upfront dose attenuation (see Table 2).
- MSAG recommends the IMWG-FI as the instrument of choice for frailty assessment.
- The simplified frailty score is an alternative, more convenient assessment tool in busy day-to-day clinics, although it has not been directly compared with the IMWG-FI.
- Frailty-adapted clinical trials are under way which will inform clinicians on how best to tailor therapy based on frailty scores.

practice. While this simplified scale has not been directly compared with the IMWG-FI, it has been validated independently in a trial population.¹¹ Using this tool, those aged >80 years are also automatically categorised as frail.

MSAG recommendations for treatment of older patients

We recommend using the IMWG-FI instrument to stratify patients at diagnosis and consideration of a geriatrician referral for a comprehensive geriatric assessment. Frailty stratification is important to define treatment goals from the outset. Fit patients should receive treatment that prioritises efficacy with the aim of achieving deep remission, while intermediate-fit patients should receive treatment that adequately balances efficacy and toxicity.¹² Frail patients require a conservative approach, with priority given to toxicity minimisation.¹²

The following sections outline the general principles of treatment, and our recommendations on regimen choice and dose adjustments based on frailty assessment. Box 1 summarises our key recommendations. For a comprehensive review of the treatment options for NDMM-TIE patients, please refer to the MSAG Clinical Practice Guidelines.¹³

Triplet versus doublet therapy

While there is no 'one-size-fits-all' paradigm in older patients, it is accepted that more intensive treatment is not necessarily beneficial. Post hoc analysis of the EMN01 trial demonstrated that the addition of an alkylator to doublet therapy had no advantage in terms of response for the intermediate-fit and frail patients.¹⁴ Similarly, a trial comparing three different upfront bortezomib-based regimens concluded that bortezomib-dexamethasone was better

Table 2 Suggested upfront dose adjustments as per frailty stratification¹²

Agent	Simplified frailty score	Non-frail	Frail
	IMWG-FI [†]	Fit	Intermediate-fitness or frail
	Starting dose		
Bortezomib (subcutaneous route preferred over intravenous)		1.3 mg/m ² ‡	1.0–1.3 mg/m ² weekly
Lenalidomide		25 mg	10–15mg§20
Thalidomide		100 mg	50–100 mg
Dexamethasone (weekly)		40 mg	10–20 mg
Melphalan (Days 1–4)		0.25 mg/kg	0.12–0.18 mg/kg
Cyclophosphamide (weekly)		300 mg/m ²	150 mg/m ²

[†]<http://www.myelomafrailtyscorecalculator.net/>

‡If a twice-weekly bortezomib schedule is used per the IFM 2009 or PETHEMA studies, vigilance is required for the development of peripheral neuropathy. Prompt withholding of bortezomib and/or dose reduction is required in the event of Grade 3 (Common Terminology Criteria for Adverse Events) peripheral neuropathy, particularly upon burning/pain, or cessation to avoid irreversibility. Alternatively, a weekly schedule of bortezomib is recommended at the outset.

§Older patients are more susceptible to lenalidomide-induced myelosuppression attributable to renal impairment. Suggest close monitoring at commencement of treatment and prompt dose reduction in event of toxicity. A lower starting dose is required for all patients with CrCl ≤ 60 mL/min.

tolerated with fewer discontinuations compared with triplet therapy, with no difference in outcomes.¹⁵

Based on the findings of the SWOG S0777 study,¹⁶ triplet bortezomib-lenalidomide-dexamethasone (VRd) was reimbursed by the Australian Pharmaceutical Benefits Scheme in June 2020 for NDMM-TIE patients. However, a significant proportion of patients in this study were more appropriately designated transplant-delayed rather than truly TIE. Treatment toxicity was significant and survival benefit was not seen in patients >65 years. VRd-lite with weekly bortezomib appears to have comparable efficacy with reduced toxicity but has only been investigated in a small Phase II study and has not been compared with Rd.¹⁷

An exception to the notion of ‘more is not necessarily better’ is the triplet combination of an immunomodulatory drug, daratumumab and dexamethasone, which appears to be well tolerated in TIE patients. In the MAIA study, daratumumab-lenalidomide-dexamethasone (D-Rd) was associated with longer PFS and tripling of minimal residual disease negativity rates compared with Rd.⁴

Another important consideration in older patients is the planned reduction in treatment intensity. Larocca *et al.* demonstrated that dose/schedule-adjusted Rd followed by maintenance lenalidomide alone (Rd-R) was equivalent to Rd continuous in terms of PFS and OS, but with superior event-free survival in patients of intermediate fitness.¹⁸

Boyle *et al.*¹⁹ have recently published real-world data from the Australasian Myeloma and Related Diseases Registry (MRDR), demonstrating that receiving four or fewer cycles of bortezomib-based induction therapy in TIE patients is an independent predictor of inferior survival. The inferior survival was not attributable to higher-stage disease, but rather because of early treatment cessation

from toxicity in a group of older patients with worse performance status. They highlighted the need for prospective studies utilising frailty-adapted dosing strategies. Indeed, results from clinical trials do not always translate to real-world contexts, as trial participants are a highly select group, and there is an under-representation of more frail patients than seen in clinical practice.

Upfront treatment dose attenuation according to frailty classification

The ongoing challenge is determining how we can best tailor therapy based on frailty scores. Frailty tools are only just beginning to be incorporated into treatment algorithms. There are currently ongoing clinical trials that are using frailty-adjusted therapy (trials identifier: ACTRN12619001199101 and NCT03720041). Table 2 details our current suggestions on upfront dose adjustments according to the IMWG-FI and the simplified frailty score.^{12,13}

Supportive care

Particular vigilance should be given to supportive care in order to optimise treatment tolerability and quality of life. This includes granulocyte colony stimulating factor (G-CSF) use (particularly at treatment initiation in patients with high marrow disease burden), immunoglobulin replacement, anti-microbial prophylaxis, bisphosphonate therapy, proton pump inhibitors and early involvement of the allied health multidisciplinary team.

Conclusion

Objective and applicable frailty assessment tools are an integral component of clinical care for patients with MM, especially older patients. While the role of these tools in prognostication is well established, the future lies in validating and incorporating their use as a predictive tool in the clinical context. As the treatment landscape in myeloma continues to expand with the ultimate aim of improving survival and quality of life not only for younger but also for older patients, it is important to have frailty-adapted treatment strategies for this highly

heterogenous population in order to aid clinicians in achieving the optimal balance between treatment efficacy, tolerability and quality of life.

Acknowledgements

Open access publishing facilitated by The University of Melbourne, as part of the Wiley - The University of Melbourne agreement via the Council of Australian University Librarians.

References

- Palumbo A, Bringhen S, Mateos MV, Larocca A, Facon T, Kumar SK *et al*. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an international myeloma working group report. *Blood* 2015; **125**: 2068–74.
- Kumar SK, Dispenzieri A, Lacy MQ, Gertz MA, Buadi FK, Pandey S *et al*. Continued improvement in survival in multiple myeloma: changes in early mortality and outcomes in older patients. *Leukemia* 2014; **28**: 1122–8.
- Facon T, Dimopoulos MA, Dispenzieri A, Catalano JV, Belch A, Cavo M *et al*. Final analysis of survival outcomes in the phase 3 FIRSST trial of up-front treatment for multiple myeloma. *Blood* 2018; **131**: 301–10.
- Kumar SK, Facon T, Usmani SZ, Plesner T, Orlowski RZ, Touzeau C *et al*. Updated analysis of daratumumab plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) in patients with transplant-ineligible newly diagnosed multiple myeloma (NDMM): the phase 3 Maia study. *Blood* 2020; **136**: 24–6.
- McCaughan GJ, Tran S, Durrant S, Harrison SJ, Morton J, Horvath N *et al*. Trends in outcomes in Australia and New Zealand in autologous stem cell transplantation in older patients with multiple myeloma: an Australasian bone marrow transplant recipient registry study. *Blood* 2020; **136**: 11–2.
- Isaacs A, Fiala M, Tuchman S, Wildes TM. A comparison of three different approaches to defining frailty in older patients with multiple myeloma. *J Geriatric Oncol* 2020; **11**: 311–5.
- Engelhardt M, Dold SM, Ihorst G, Zober A, Moller M, Reinhardt H *et al*. Geriatric assessment in multiple myeloma patients: validation of the international myeloma working group (IMWG) score and comparison with other common comorbidity scores. *Haematologica* 2016; **101**: 1110–9.
- D'Agostino M, Larocca A, Offidani M, Liberati AM, Gaidano G, Petrucci MT *et al*. Octogenarian newly diagnosed multiple myeloma patients without geriatric impairments: the role of age >80 in the IMWG frailty score. *Blood Cancer J* 2021; **11**: 73.
- Milani P, Vincent Rajkumar S, Merlini G, Kumar S, Gertz MA, Palladini G *et al*. N-terminal fragment of the type-B natriuretic peptide (NT-proBNP) contributes to a simple new frailty score in patients with newly diagnosed multiple myeloma. *Am J Hematol* 2016; **91**: 1129–34.
- Facon T, Dimopoulos MA, Meuleman N, Belch A, Mohty M, Chen WM *et al*. A simplified frailty scale predicts outcomes in transplant-ineligible patients with newly diagnosed multiple myeloma treated in the FIRSST (MM-020) trial. *Leukemia* 2020; **34**: 224–33.
- Stege CAM, van der Holt B, Dinmohamed AG, Sonneveld P, Levin MD, van de Donk N *et al*. Validation of the FIRSST simplified frailty scale using the ECOG performance status instead of patient-reported activities. *Leukemia* 2020; **34**: 1964–6.
- Larocca A, Dold SM, Zweegman S, Terpos E, Wäsch R, D'Agostino M *et al*. Patient-centered practice in elderly myeloma patients: an overview and consensus from the European myeloma network (EMN). *Leukemia* 2018; **32**: 1697–712.
- Quach H, Prince HM. Medical Scientific Advisory Group (MSAG) - Clinical Practice Guideline Multiple Myeloma; MSAG Update: Bortezomib, Lenalidomide and Dexamethasone (VRd) for initial treatment of multiple myeloma. Updated March 2017 and July 2020, 3 December 2021.
- Bringhen S, D'Agostino M, Paris L, Ballanti S, Pescosta N, Spada S *et al*. Lenalidomide-based induction and maintenance in elderly newly diagnosed multiple myeloma patients: updated results of the EMN01 randomized trial. *Haematologica* 2020; **105**: 1937–47.
- Niesvizky R, Flinn IW, Rifkin R, Gabrail N, Charu V, Clowney B *et al*. Community-based phase IIIB trial of three UPFRONT bortezomib-based myeloma regimens. *J Clin Oncol* 2015; **33**: 3921–9.
- Durie BG, Hoering A, Sexton R, Abidi MH, Epstein J, Rajkumar SV *et al*. Longer term follow-up of the randomized phase III trial SWOG S0777: bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients (pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT). *Blood Cancer J* 2020; **10**: 1–11.
- O'Donnell EK, Laubach JP, Yee AJ, Chen T, Huff CA, Basile FG *et al*. A phase 2 study of modified lenalidomide, bortezomib and dexamethasone in transplant-ineligible multiple myeloma. *Br J Haematol* 2018; **182**: 222–30.
- Larocca A, Bonello F, Gaidano G, D'Agostino M, Offidani M, Cascavilla N *et al*. Dose/schedule-adjusted Rd-R vs continuous Rd for elderly, intermediate-fit patients with newly diagnosed multiple myeloma. *Blood* 2021; **137**: 3027–36.
- Boyle S, Wellard C, Moore EM, Blacklock H, Harrison SJ, Ho PJ *et al*. Receiving four or fewer cycles of therapy predicts poor survival in newly

diagnosed transplant-ineligible patients with myeloma who are treated with bortezomib-based induction. *Eur J Haematol* 2021; **107**: 497–9.

20 Quach H, Fernyhough L, Henderson R, Corbett G, Baker B, Browett P *et al.* Upfront lower dose lenalidomide is less toxic and does not compromise efficacy

for vulnerable patients with relapsed refractory multiple myeloma: final analysis of the phase II RevLite study. *Br J Haematol* 2017; **177**: 441–8.