Myeloma in Focus:
A newsletter for healthcare providers

Frailty in multiple myeloma

Welcome to the third edition of the Sanofi 2024 newsletter! These newsletters, created by Sanofi, aim to provide education to healthcare providers in relevant topics in multiple myeloma (MM). This edition will provide an overview of frailty in MM, highlighting the need for clinical trials to further investigate outcomes in this population and the importance of robust frailty assessment methods to inform treatment decision-making.

Introduction

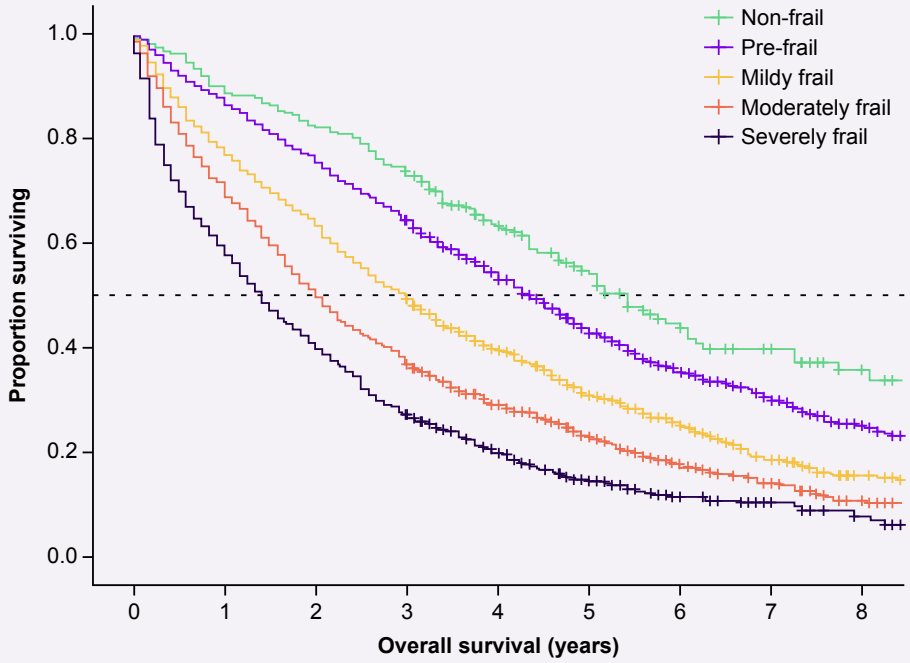
Frailty is an important consideration in the management of multiple myeloma (MM); however, there is limited guidance on the optimal approach to managing frail patients.[1,2] Increased frailty is linked to poorer outcomes, as well as higher rates of treatment toxicity and discontinuation.[3,4] Around one third of MM patients are considered frail at the time of diagnosis; however, frailty levels can change over time, a concept introduced as dynamic frailty in recent studies.[5,6] MM is primarily a disease of the older population, with a median age of diagnosis at 69 years.[1] Older patients have an increased incidence of frailty, and while age is an important factor in determining frailty status, many other patient characteristics must be considered in a comprehensive frailty assessment.[1] There are several frailty scoring systems available, and although these can be useful, they are inconsistently used in clinical practice due to a number of limitations. Refinement of frailty assessment tools remains an unmet medical need; a comprehensive understanding of individual patient needs is required to optimize treatment decision-making and patient outcomes.[1–3]

In this issue

The impact of frailty

Frailty refers to a decline in physiological function, leading to dependency, vulnerability to stressors, and high risk of poor health-related outcomes.[7] Frailty is increasingly being recognized as a critical factor in the management of MM, significantly influencing treatment outcomes. Those who are more frail are at higher risk for poorer survival outcomes (Figure 1).[3]

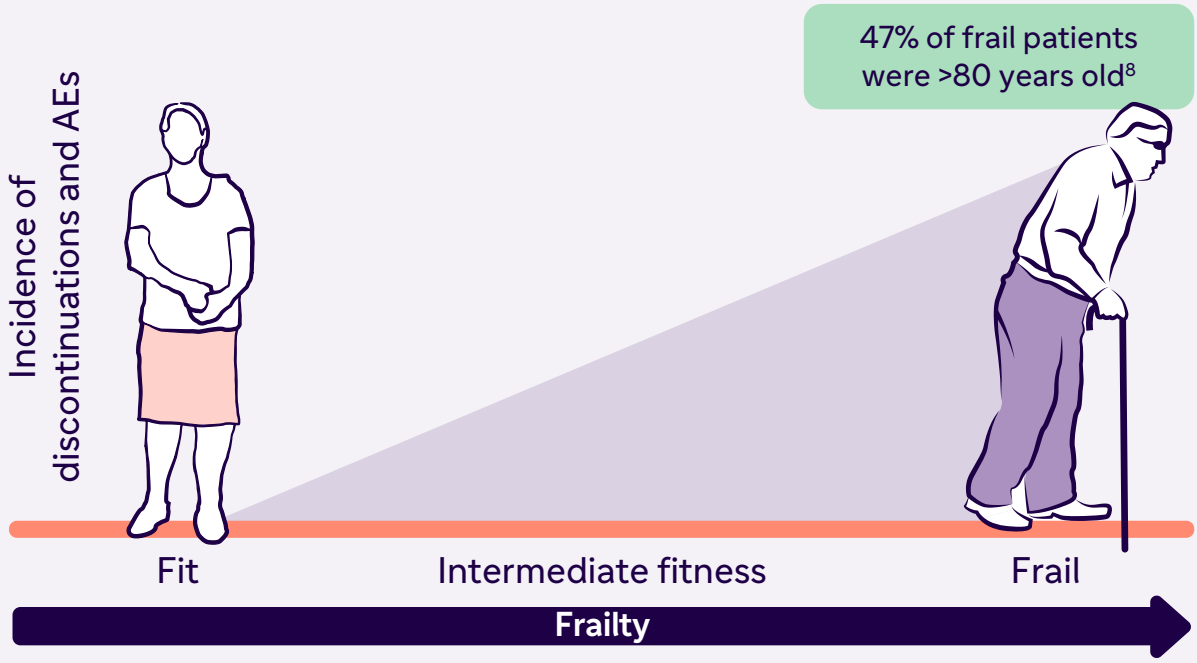
Figure 1. Survival of patients with MM based on frailty[3]



MM, multiple myeloma

Additionally, frailty is linked to higher rates of toxicity and treatment discontinuation (Figure 2).[2,4] Recognizing frailty in MM patients is a key consideration in optimizing treatment, while minimizing adverse events and preventing treatment discontinuation.[1] Close monitoring for tolerability to treatment in frail patients can help guide treatment modifications where required in order to prevent treatment discontinuation.[2] Health-related quality of life (HRQOL) is important to monitor in this population; susceptibility to therapy-related toxicity underscores the need for robust data on the safety and HRQOL of novel combinations in frail patients to help guide management of MM.[2]

Figure 2. Frailty predicts treatment toxicity in elderly patients with MM[4]



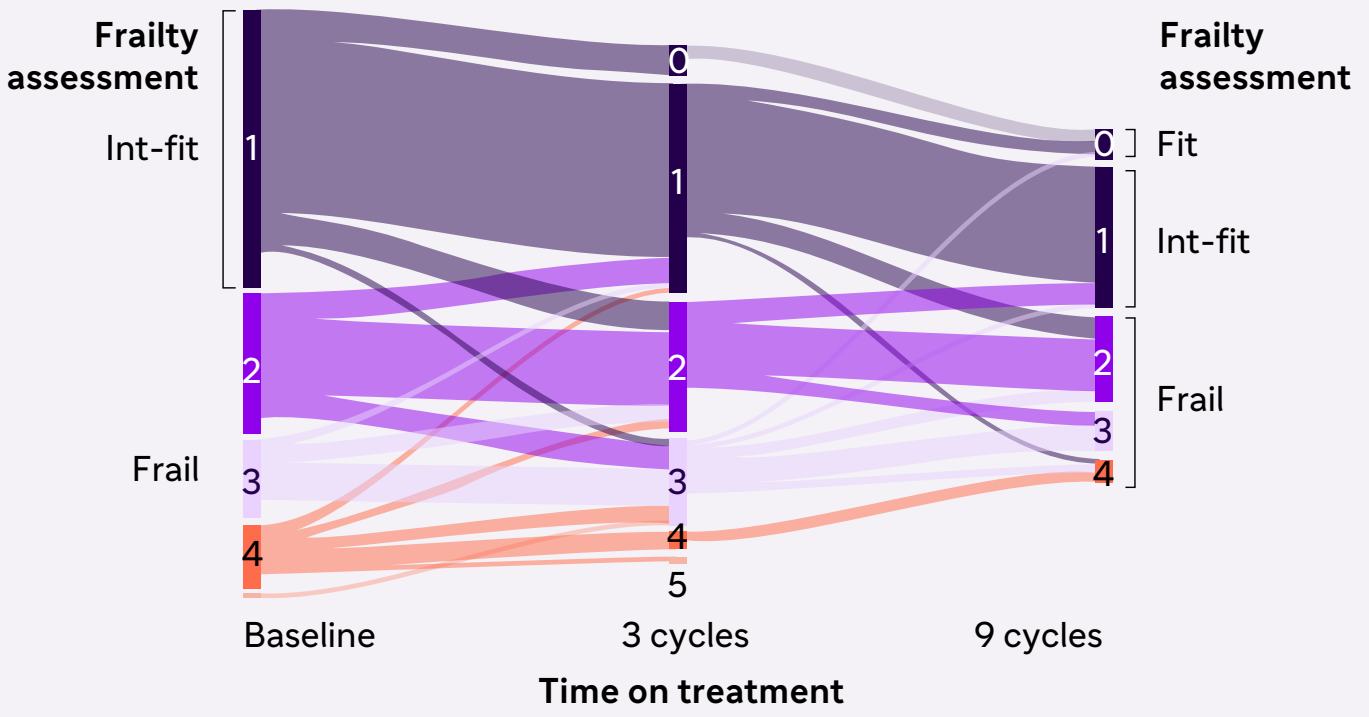
AE, adverse event; MM, multiple myeloma

Factors contributing to frailty

Many factors contribute to the assessment of frailty status, including age, comorbidities, MM disease burden, performance status (PS), and ability to complete activities of daily living (ADL).[8,9] Due to the increased incidence of frailty in older patients, age is central across all commonly used frailty scoring systems; however, age alone does not capture the complexities of frailty.[1] Besides chronological age, older patients typically have declining organ function and increased incidence of comorbidities, which may affect their ability to perform ADL and contribute to a lower PS.[10] Some studies have shown that patients considered frail based on age alone have better clinical outcomes than those with geriatric impairments and comorbidities.[1,11] Additionally, myeloma-related factors including burden of disease and response to treatment contribute to frailty status.[9] The purpose of frailty assessment is to inform treatment decision-making and improve patient outcomes.[8]

Recent studies have introduced the concept of dynamic frailty, presenting frailty as a parameter that changes over time (Figure 3).[6] A systematic review of 4617 patients showed that among those with 3 years of follow-up, frailty status had changed in 93% of patients; 78% had improved and 72% had worsened.[3] Understanding changes in frailty over a patient's disease trajectory, by assessing frailty throughout the treatment period, can inform dynamic treatment delivery to maximize disease control and minimize toxicity.[3,8]

Figure 3. Change in frailty over time in transplant-ineligible NDMM patients[6]



Int, intermediate; NDMM, newly diagnosed multiple myeloma

Frailty assessment and limitations of current frailty scores

There are several frailty scoring tools and geriatric scales in MM that aim to encompass the most important factors to evaluate a patient's frailty (Figure 4). The Charlson Comorbidity Index (CCI), which appears in the IMWG and Simplified IMWG (IFM) frailty scores, predicts the mortality of patients based on comorbidity prevalence.[8,12]

Functional status is captured through a variety of approaches in different frailty scores, including ADL/instrumental ADL (IADL), ECOG PS, Karnofsky PS and WHO PS. Some scores classify patients as either frail or non-frail, where others categorize patients by frailty severity or risk.[8]

Figure 4. Comparison of commonly used frailty scoring tools in MM[8]

	IMWG frailty score	Simplified IMWG (IFM) score	R-MCI	UK MRP	Mayo frailty index
Biological/clinical components	Age CCI	Age CCI	Age eGFR PFTs Frailty cytogenetics	Age R-ISS CRP	Age NT-proBNP
Functionality tests	ADL/IADL	PS (ECOG)	PS (Karnofsky)	PS (WHO)	PS (WHO)
Frailty groups	Fit Intermediate fit Frail	Non-frail Frail	Fit Intermediate fit Frail	Low-risk Medium-risk High-risk	I II III IV

ADL, Activities of Daily Living; CCI, Charlson Comorbidity Index; ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; IADL, Instrumental Activities of Daily Living; IFM, Intergroupe Francophone du Myelome; IMWG, International Myeloma Working Group; MM, multiple myeloma; MRP, Myeloma Risk Profile; NT-proBNP, N-terminal pro-brain natriuretic peptide; PFTs, pulmonary function tests; PS, performance status; R-ISS, Revised International Staging System; R-MCI, Revised Myeloma Comorbidity Index; WHO, World Health Organization

Frailty scores are useful, but have a number of limitations that are a barrier to use in clinical practice, such as subjectivity and inconsistency between scoring systems, and being time-consuming to assess.[1] As a result, many physicians will choose to assess frailty in their patients using clinical judgement, primarily based on age.

However, it may be challenging to distinguish between frail and fit older patients with this approach.[1,8] The development of a convenient and objective frailty scoring system with robust parameters based on clinical evidence is a substantial need, and ongoing research continues to refine frailty assessment methods.[1,2]

Inclusion of frailty in clinical trials

Due to stringent eligibility criteria, frail patients are underrepresented across clinical trials for MM, which has limited treatment recommendations for this population. Exclusion of frailty from clinical trials is largely due to predefined upper age limits, poor performance status, comorbidities, renal impairment, and concomitant use of multiple medications, all of which are prevalent in frail patients.[1,8] The real-world patient population is older and more frail than those included within the majority of clinical trials, underscoring the need for broader inclusion criteria in future trials.[1]

However, more recently, a number of large clinical trials have included frail patients and explored the impact of frailty on treatment outcomes through subgroup analyses.[7] The increased focus on frailty in recent trials will contribute valuable insight into the tolerability and response to different regimens, helping to determine which treatment options should be used in frail patients.[1,2]

Summary

While frailty is highly prevalent in MM and is a key consideration in patient management, currently available assessment tools have limitations. The need for robust, comprehensive frailty assessment remains an unmet need in MM. Ongoing research continues to refine frailty assessment methods, which is necessary for an improved understanding of individual patient needs to help physicians make informed, personalized treatment decisions.[1,2,13] Clinical trial data for the frail population are needed to contribute to our understanding of the needs of frail patients, in addition to the efficacy and safety of available treatment regimens in this population, which is of paramount importance within the evolving MM treatment landscape.[2]

Abbreviations:

ADL, Activities of Daily Living; CCI, Charlson Comorbidity Index; ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; HRQOL, health-related quality of life; IADL, Instrumental Activities of Daily Living; IFM, Intergroupe Francophone du Myelome; IMWG, International Myeloma Working Group; MM, multiple myeloma; MRP, Myeloma Risk Profile; NDMM, newly diagnosed multiple myeloma; NT-proBNP, N-terminal pro-brain natriuretic peptide; PFTs, pulmonary function tests; PS, performance status; R-ISS, Revised International Staging System; R-MCI, Revised Myeloma Comorbidity Index; WHO, World Health Organization.

References:

1. Facon T, et al. Blood 2024;143:224–32
2. Lipof JJ, et al. Curr Oncol Rep 2024;1–10
3. Mian H, et al. Blood Cancer J 2023;13:76
4. Palumbo A, et al. Blood 2015;125:2068–74
5. Möller MD, et al. Curr Opin Oncol 2021;33:648–57
6. Smits F, et al. ASH 2023; Oral Abstract #342
7. Cook G, et al. Leukemia 2020;34:2285–94
8. de Ramon O, et al. Healthbook TIMES Onco Hema 2024;20:86–93
9. Grant SJ, et al. Hematology Am Soc Hematol Educ Program 2021;2021:46–54
10. Palumbo A, et al. J Clin Oncol 2014;32:587–600
11. Stege CA, et al. J Clin Oncol 2021;39:2758–67
12. Charlson ME, et al. Psychother Psychosom 2022;91:8–35
13. Miller HL, Sharpley FA. Hematol Rep 2023;15:151–6