Advances in the application of frailty scoring in the diagnosis and management of elderly patients with multiple myeloma (Review)

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Abstract. Multiple myeloma (MM) is a hematological malignancy that disproportionately affects elderly populations, with age being a key risk factor for disease progression and adverse outcomes. Frailty, a multifaceted geriatric syndrome characterized by reduced physiological reserve and increased vulnerability to stressors, is recognized as a pivotal factor influencing the diagnosis, prognosis and therapeutic management of elderly patients with MM. The present review explores the complex interplay between frailty and MM, discussing the underlying mechanisms, such as chronic inflammation, sarcopenia and immune dysfunction, that link these conditions. In addition, the clinical implications of frailty, including its association with higher treatment toxicity, prolonged hospitalization and diminished survival rates, are reviewed. The present study also aimed to evaluate commonly used frailty assessment tools, such as the International Myeloma Working Group frailty score and the Geriatric Assessment, and their use in guiding clinical decision-making. Recent advancements in frailty scoring systems, which enable more precise risk stratification, are highlighted, emphasizing their role in tailoring individualized treatment strategies to balance efficacy and safety. Finally, the present review addresses current challenges in integrating dynamic frailty monitoring into routine clinical practice and outlines future directions, including the development of novel biomarkers and digital tools to enhance frailty assessment and improve long-term patient outcomes.

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1. Introduction

The present review summarizes the current understanding of frailty in elderly patients with multiple myeloma (MM), focusing on mechanisms, assessment tools, clinical implications and recent advances. A critical overview of the literature is provided, controversies and research gaps are highlighted, and future directions for research and clinical practice are discussed.

MM is a malignant disorder marked by clonal plasma cell proliferation, which leads mainly to immunodeficiency and bone destruction (1,2). MM is the second most common hematological malignancy (3), affecting mostly middle-aged and elderly individuals, with a median onset age of 55-59 years, and is rare in individuals aged <40 years (4). Despite advances in therapy, MM remains incurable (5,6). Recent treatment optimization has led to the use of immunotherapy for MM (7,8), markedly improving survival rates. The IMROZ trial conducted by Manier *et al* (9), confirmed that the isatuximab + bortezomib/lenalidomide/dexamethasone (VRd) regimen notably

improved progression-free survival (PFS) with a manageable safety profile in frail, transplant-ineligible patients with newly diagnosed MM (NDMM). In addition, the IFM2017-03 trial completed by Manier *et al* (10) showed that the dexamethasone-sparing regimen (daratumumab + lenalidomide) could extend PFS to 53.4 months compared with traditional regimens, providing a safer option for elderly frail patients. The GEM-2017FIT trial led by Mateos *et al* (11) demonstrated that the carfilzomib-lenalidomide-dexamethasone and daratumumab-carfilzomib-lenalidomide-dexamethasone regimens were superior compared with bortezomib-melphalan-prednisone (VMP) and lenalidomide-dexamethasone in terms of minimal residual disease (MRD) negativity rate, thus providing evidence for regimens adapted to different frailty statuses. However, drug resistance continues to drive disease progression (12-14).

Conventional prognostic methods, such as the Second Revised International Staging System (R2-ISS) (15) and the Mayo additive staging system (16), do not fully capture prognosis due to high interpatient variability, particularly among elderly patients (15-17). In this context, it is important to note that age alone is not the most important prognostic factor in elderly patients with MM (18,19). For example, individuals aged >65 years with good organ function and physical status may undergo intensive chemotherapy and autologous transplantation, whereas some individuals aged <65 years with comorbidities and limited psychological resilience might not tolerate such treatment. As a result, frailty assessment has become an important and objective tool to guide treatment selection and predict prognosis in MM (20-23).

Frailty is a nonspecific clinical syndrome that impairs homeostasis across several physiological systems, including neurological, metabolic-endocrine and immune domains, and sarcopenia forms a core element (24). Frailty lowers physiological reserves, reduces resilience to stress and limits recovery, and is considered the most clinically notable geriatric syndrome (25,26). Notably, frailty increases the risk of poor outcomes, including longer hospital stays, increased treatment toxicity and mortality (27). Clinicians most widely use the Fried Frailty Phenotype criteria (19,28) as clinical diagnostic standards, and the criteria are defined as follows: i) Unexplained weight loss: ≥5% weight loss or >4.5 kg weight loss within 1 year (excluding deliberate dieting or other disease-related causes); ii) fatigue: Feeling exhausted even after simple activities (such as walking and household chores); iii) decreased muscle strength: Reduced handgrip strength (such as difficulty wringing out a towel); iv) reduced activity level: Avoiding going out and decreased physical activity; and v) slow walking speed: A walking speed of ≤0.8 m/sec (for example, being unable to cross the street before the green light changes). Meeting three or more of these criteria indicates frailty, meeting one or two indicates pre-frailty and meeting none indicates a healthy status.

2. Assessment of myeloma-related frailty

Approximately two-thirds of elderly patients (patients aged >70 years at diagnosis) with MM have frailty, with ≥40% experiencing severe forms (29). This condition greatly reduces quality of life (21,22,30-32), and can lead to longer hospitalization, increased treatment toxicity and a higher risk of mortality. Frailty is a dynamic and possibly reversible process (33,34); early identification allows interventions such as exercise, nutrition and disease management to delay its progression and reduce associated risks. In MM, frailty typically includes physical decline, fatigue and decreased activity, and is often complicated by comorbidities or reduced daily functioning. Assessment of myeloma-related frailty can be performed by the methods described in this section.

Frailty index (FI) assessment. The cumulative deficit FI (35) calculates frailty by evaluating six daily activities: Dressing, eating, bathing, toileting, walking and climbing stairs, and several comorbidities, including vascular disease, renal insufficiency, diabetes and chronic obstructive pulmonary disease (10 items in total). Each item is considered a deficit if the patient is unable to perform it independently or has the specific comorbidity. The number of deficits is divided by the total number of items to obtain the FI value. An FI of ≥0.15 is considered indicative of frailty (35).

Clinical manifestations and impact. Frail patients often experience fatigue, pain and reduced quality of life, which are associated with disease stage, anemia and poor physical performance. Frailty influences treatment tolerance and prognosis, and is associated with reduced survival (36,37).

Characteristics of dynamic changes. Frailty status may change over time or with treatment progress, requiring regular assessment (38). Some patients improve following therapy, whereas others may experience worsening due to disease progression or treatment side effects (38).

3. Factors influencing frailty

Frailty in the elderly is an age-related syndrome associated with MM. The influencing factors are complex and diverse (39), and have been categorized in the present review as uncontrollable, controllable and other.

Uncontrollable factors. The uncontrollable factors that influence frailty include: i) Genetic factors: Genetic polymorphisms [such as interleukin (IL)-6 and angiotensinogen genes] may influence susceptibility to frailty (40,41); ii) age: With advancing age, organ function declines and physiological reserves decrease, notably increasing the risk of frailty (42); and iii) sex: Women have higher frailty rates than men, mostly due to postmenopausal estrogen decline that affects muscle and nerve function (43).

Controllable factors. The controllable factors that influence frailty include: i) Lifestyle: Unhealthy habits such as smoking, excessive alcohol consumption and physical inactivity increase frailty risk (44); ii) chronic conditions, including hypertension, diabetes, coronary heart disease, chronic obstructive pulmonary disease and arthritis, as well as the presence of multiple coexisting conditions (five or more comorbidities) are major contributors (45-47); iii) medications: Inappropriate drug use (such as anticholinergic agents or antipsychotics) or polypharmacy may contribute to the onset of frailty (48);

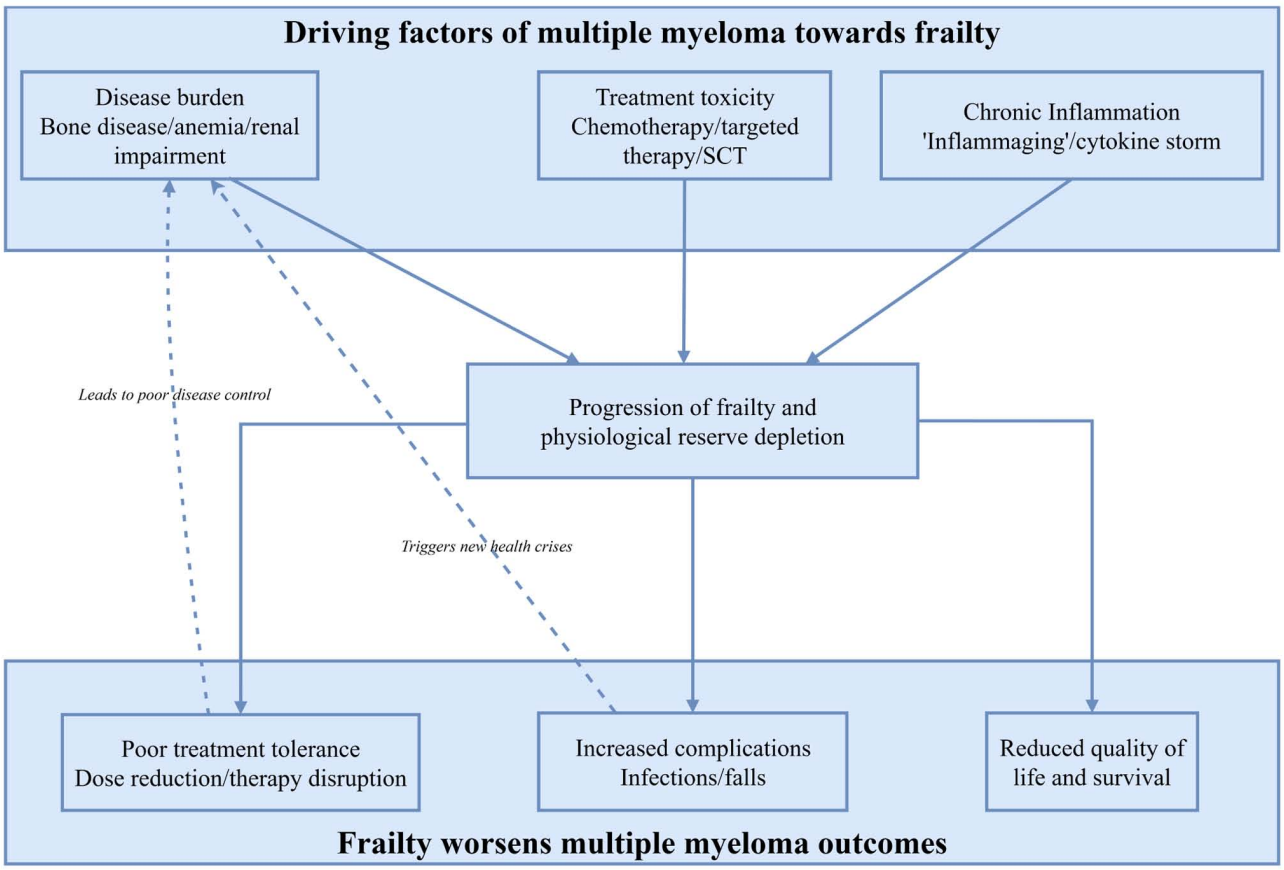

Figure 1. Driving factors of multiple myeloma-induced frailty and its adverse clinical outcomes. SCT, stem cell transplantation.

iv) psychological factors, such as anxiety, depression and sleep disorders interact with frailty (49,50); and v) socioeconomic factors: Inadequate social support, being unmarried, living alone, financial hardship or low educational attainment may elevate frailty risk (51).

Other factors. Malnutrition can influence frailty as deficiencies in nutrients, such as protein, vitamin D and calcium, or inadequate intake caused by decreased appetite or dysphagia, may accelerate muscle wasting and functional decline (52). In addition, immune dysfunction, including abnormal inflammatory responses [such as elevated IL-6 and C-reactive protein (CRP) levels] are closely associated with frailty (53). MM and frailty also influence each other (Fig. 1). The disease and its treatment reactions can cause frailty, which in turn can worsen disease severity (54). MM can often lead to other conditions such as anemia, osteolytic lesions and renal issues (55); in turn, anemia can lead to fatigue and dizziness, whereas osteolytic lesions contribute to pain and fractures, increasing activity avoidance and muscle loss (56). Renal failure may exacerbate anemia, bone damage and metabolic problems, further increasing frailty (24). A balanced diet, regular exercise, health checkups, chronic disease management, appropriate medication and attention to mental health can help reduce frailty risk.

4. Clinical assessment tools for frailty

Elderly patients with MM display wide variability in physiological and functional status, necessitating individualized treatment. Transplant-eligible patients should receive intensive therapies, whereas frail patients require regimens with adjusted doses or schedules (57). MM may impair physical function due to disease complications, although effective initial therapy can reverse these effects, and additional interventions may be introduced as needed (34,58).

The Comprehensive Geriatric Assessment (CGA) is the most sensitive tool used to identify frailty (59); however, clinical practice is limited by lack of time and resources (60). The CGA is time-intensive, complex and requires a multidisciplinary team (a group of healthcare professionals such as doctors, nurses, social workers and therapists working together). Recognizing that MM has unique characteristics and the need for a special frailty assessment model has led to the development of the MM frailty model (60,61).

To identify frail patients more accurately, the International Myeloma Working Group (IMWG) established the IMWG Frailty Score (IMWG-FS) in 2015, based on three prospective international multicenter clinical studies (60). This system assigns patients to three groups, including fit (score, 0), intermediate-fit (score, 1) and frail (score, ≥2), based on a composite score derived from age, activities of daily living (ADL), instrumental ADL (IADL) and the Charlson Comorbidity Index (CCI) (62). This scoring system can predict the overall survival (OS) and PFS of patients with MM, and can predict the incidence of adverse events (AEs) and drug discontinuation (62). Multiple studies (36,63-67) have confirmed that patients assessed as frail using the IMWG-FS exhibit shorter OS, higher rates of severe AEs and increased

risk of treatment discontinuation. Given differing priorities in frailty assessment across clinical contexts (such as emphasis on comorbidities or need for rapid evaluation), a single assessment tool cannot meet all requirements. Consequently, multiple alternative frailty assessment systems have been developed and applied clinically. Beyond the IMWG-FS, the Revised MM Comorbidity Index (R-MCI) (68,69), the UK Myeloma Research Alliance Risk Profile (MRP) (70), the Mayo Clinic fraity index (Mayo-FI) (71), the Freiburger Comorbidity Index (72) and the Geriatric Assessment in Hematology (73) are also commonly used frailty assessment systems in clinical practice. These systems incorporate combinations of age, comorbidities, physical performance status and laboratory parameters. Additionally, the Timed Up and Go test and Mini Nutritional Assessment-Short Form (TM) Frailty Score (74-76), Carolina FI (77), Electronic Frailty Score (36) and cumulative deficit FI (35,78) are also commonly used frailty scoring systems for elderly patients.

The Chinese TM Frailty Score system categorizes elderly patients with MM into three groups, including good, fair and frail, using the Timed Up and Go (TUG) test and the Mini Nutritional Assessment Short Form (MNA-SF), demonstrating good assessment efficacy (79). The model was developed and internally validated in 167 consecutive Chinese patients with MM (June 2019-September 2021; First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China), with 135 completing an eight-domain CGA for core analysis. The cohort (median age, 68 years; range, 60-85 years) aligns with the target elderly MM population and key predictive metrics demonstrate its robustness, including the TM score (combining TUG and MNA-SF), which achieved C-indices of 0.741 (grade ≥3 AEs; P<0.001), 0.690 (treatment discontinuation, P<0.001) and 0.702 (OS; P=0.001), outperforming the IMWG Geriatric Assessment (IMWG GA) (0.662, 0.636 and 0.631) and IMWG GA Plus (0.701, 0.656 and 0.618). Kaplan-Meier analysis confirmed significant stratification of grade ≥3 AE and OS risks between fit and frail groups (P<0.05). Regarding consistency with the IMWG GA, the TM score enhanced risk discrimination within the IMWG GA intermediate fit group, identifying subgroups with higher grade ≥3 AE risk (P<0.05), while retaining consistent prognostic alignment for frail patients (poorer outcomes vs. fit groups, P<0.05). Although external validation was not included in the initial abstract due to length constraints, internal validation in a real-world Chinese MM cohort provides solid preliminary evidence (79). A multicenter external validation study is ongoing to further confirm its generalizability, strengthening the credibility of the TM score as a locally tailored tool for Chinese patients with MM (79).

Given that the parameters included in each assessment system are not entirely consistent, the expected survival of identified frail patients varies. To explore the consistency among frailty assessment systems, Li *et al* (80,81) retrospectively analyzed the clinical data of 84 patients aged ≥60 years with NDMM. The authors systematically evaluated the patients using the IMWG-FS, Mayo-FI, Intergroupe Francophone du Myélome (IFM) simplified score and MRP score, and compared the PFS and OS of the patients based on different assessment tools. The results showed low consistency among the four frailty assessment tools, with 64 patients (76.2%) defined as frail by at least one tool. Among these, 48 patients (75.0%) were identified as frail by at least two tools, whereas only 14 patients (21.9%) were classified as frail by all four tools. Compared with the Mayo-FI and IFM simplified score, the MRP score and IMWG-FS demonstrated higher consistency and superior prognostic stratification efficacy. The IMWG-FS assessed a median OS of 15.5 months (P=0.01) vs. not reached for the non-frail and frail groups, respectively, with a median PFS of 42.5 vs. 10.0 months (P=0.011). The MRP score showed a median OS of not reached and 15.0 months (P<0.001) for the non-frail and frail groups, respectively, with a median PFS of 42.5 and 9.0 months (P<0.001). Therefore, combining MRP scoring with IMWG-FS may effectively enhance the identification of frail elderly patients with NDMM (82,83). For elderly patients with MM, dynamic frailty assessment holds greater prognostic value than static frailty assessment, necessitating treatment adjustments based on such evaluations (33,63).

The prospective MFRAIL study carried out by Haider *et al* (84) confirmed that 13.8-37.1% of patients experienced changes in frailty status within 1 year as evaluated by four commonly used frailty assessment tools, and continuous scores were shown to be more sensitive to capturing early improvements or deteriorations in frailty that may be missed by categorical frailty assessments. The long-term follow-up of the HOVON 143 trial completed by Smits *et al* (85) revealed the heterogeneity of frail subgroups, with ultra-frail patients and those frail due to geriatric impairments having worse prognoses, emphasizing the importance of precise stratification. The GETH-TC study conducted by Tolosa-Ridao *et al* (86) showed that the frailty status of patients undergoing autologous hematopoietic cell transplantation evolves dynamically throughout the treatment process, requiring continuous monitoring to optimize care. The combination of MRP scores with IMWG-FS, alongside simple, easily measurable and readily available assessment methods such as gait speed and grip strength, demonstrates potential in frailty assessment, particularly in dynamic evaluation (81). During treatment, starting with low-intensity therapy and adjusting treatments based on dynamic frailty assessments can ensure efficacy and safety, further improving survival outcomes for frail patients (81). The frailty assessment tools included in the present study possess distinct advantages and limitations in various clinical settings due to differences in their research and development backgrounds, assessment dimensions, operational complexity and applicable populations (81). The specific selection strategies are shown in Table I (36,60,70,71,74,87).

With the advent of novel therapies for MM, current frailty assessment systems are increasingly limited in their ability to address the complexities of patient care (60,70,71,88). There is a need to develop more comprehensive frailty assessment tools to support personalized treatment strategies for patients with MM.

5. Overview of newly developed frailty assessment tools in recent years

Composite models integrating functional and hematopoietic dimensions. The Hemo-IMWG GA was developed by Chen *et al* (89), and dynamically combines IMWG GA and Hematopoietic Score (HS), enhancing the prediction

Table I. Comparison of commonly used frailty assessment tools in elderly patients with multiple myeloma.

First author, year	Tool name	Categorization	Key advantages	Key limitations	Core components/ domains	Suitable healthcare settings	Sensitivity range	Specificity range	(Refs.)
Palumbo *et al*, 2015	IMWG-FS	Fit (0), intermediate-fit (1), frail (≥2)	International gold standard; prospectively validated; predicts OS, PFS and AEs	Time-consuming; includes subjective components	Age, ADL, instrumental ADL, Charlson Comorbidity Index	Tertiary hospitals (hematology/geriatric oncology), transplant centers	0.72-0.81	0.68-0.76	(60)
Engelhardt *et al*, 2017	R-MCI	Score-based risk groups	Focuses on comorbidities; validated for prognosis	Does not directly incorporate functional status	Age, organ function, pulmonary function, etc.	Tertiary hospitals (hematology/intensive care medicine), transplant centers (pre-transplant comorbidity assessment)	0.75-0.83	0.70-0.78	(87)
Cook *et al*, 2019	UK MRP	Risk stratification groups	Incorporates inflammation; predicts PFS and early mortality	Requires laboratory data	C-reactive protein, age, WHO performance status, ISS Stage	Tertiary hospitals (hematology), myeloma specialty centers	0.66-0.72	0.63-0.70	(70)
Milani *et al*, 2016	Mayo-FI	Simple scoring system	Quick and simple; integrates a cardiac biomarker	Not MM-specific	NT-proBNP, age, ECOG performance status	Tertiary hospitals (hematology/cardiology joint assessment), community healthcare	0.68-0.75	0.65-0.73	(71)
Chen *et al*, 2023	TM frailty score	Robust, pre-frail, frail	Combines physical performance and nutrition; developed for the Chinese population	Requires in-person testing	Timed Up and Go test, Mini Nutritional Assessment Short-Form	Tertiary hospitals (hematology, with physical fitness testing conditions), myeloma specialty centers (targeted assessment for Chinese population)	0.79-0.85	0.74-0.80	(74)
Chan *et al*, 2021	e-FRAIL	Likely-frail vs. non-frail	Uses routine electronic data; objective and potentially automatable	Retrospectively derived; requires further validation	History of falls, geriatric referral, cognitive impairment polypharmacy (≥6, drugs), hospitalization/ need for support	Community healthcare, tertiary hospitals (geriatrics/hematology)	0.70-0.78	0.66-0.74	(36)

ADL, activities of daily living; AEs, adverse events; ECOG, Eastern Cooperative Oncology Group; e-FRAIL, Electronic Frailty Score; ISS, International Staging System; Mayo-FI, Mayo Clinic Frailty Index; MWG-FS, International Myeloma Working Group Frailty Score; NT-proBNP, N-terminal pro-B-type natriuretic peptide; OS, overall survival; PFS, progression-free survival; R-MCI, Revised Multiple Myeloma Comorbidity Index; UK MRP, UK Myeloma Research Alliance Risk Profile; WHO, World Health Organization.

of total/non-hematological toxicity (area under the curve, 0.600-0.646) and hematological AEs (HR, 9.91; P<0.001). The Fmodel, proposed by Tian *et al* (90), integrates age, hematopoietic cell transplantation comorbidity index (HCT-CI), Eastern Cooperative Oncology Group performance status (ECOG-PS), ISS and prognostic nutritional index, and outperforms traditional models [simplified frailty model (91) and Revised International Staging System (92)] in predicting OS, PFS and grade ≥2 non-hematological AEs.

Simplified clinically practical tools. The Simplified Frailty Scale (age/CCI/ECOG-PS), established by Facon *et al* (93), enables rapid prognostic stratification of transplant-ineligible patients with NDMM with high repeatability. The Korean Cancer Study Group Geriatric Score, developed by Lee *et al* (94) for elderly patients with MM (≥70 years), effectively predicts grade 3-4 non-hematological toxicity (HR, 2.43; P=0.043) and tracks dynamic vulnerability changes.

Patient-centered subjective tools. The patient-reported frailty phenotype (PRFP) was developed by Krepper *et al* (95) based on patient-reported outcomes, and the European Organisation for Research and Treatment of Cancer Quality of Life Multiple Myeloma Questionnaire/the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, and captures subjective frailty experiences (fair agreement with IMWG-FS, weighted κ=0.27) and complements objective assessments.

Dynamic assessment tools. Cumulative deficit FI was calculated by Abdallah *et al* (78) (FI ≥0.15 for frailty), and reveals dynamic frailty changes (25% worsening, <10% improvement in 3-12 months) and incorporates social support prognostic value.

Specialized optimized tools. The 40-Item Rockwood FI was validated by Muzyka *et al* (96) in elderly patients with MM, and outperforms IMWG-FS in predicting long-term mortality (C-index, 0.775 vs. 0.749) with multi-dimensional health deficit coverage.

6. Treatment implications of frailty

Due to multiple comorbidities and poor chemotherapy tolerance, elderly patients with MM are generally considered unsuitable recipients for transplantation if aged ≥75 years (70). Treatment selection requires consideration of multiple factors, including disease-specific factors such as disease stage and cytogenetic abnormalities, and patient-specific factors including age, comorbidities, organ function status and frailty status (97). Initial treatment regimens should be selected based on shared decision-making between physicians and patients.

Additionally, initial treatment dosages for elderly patients should be individualized (98). For example, elderly patients or those with multiple comorbidities should receive low-dose anti-MM agents as initial therapy (97). For patients aged ≥75 years, the starting dose of dexamethasone is 20 mg weekly. For frail patients, a further dose reduction (8-20 mg weekly) may be considered, with subsequent adjustments based on response and treatment tolerance. In addition (98), renal impairment is common in the elderly, necessitating dose adjustments for lenalidomide (99).

The National Comprehensive Cancer Network (100), the European Myeloma Network (EMN) (58), the American Society of Clinical Oncology (ASCO) (101) and the European Society for Medical Oncology (ESMO) (3) all emphasize the importance of stratified treatment. Frailty assessment is a primary strategy for patient stratification, and at present, EMN and ESMO recommend using the IMWG-FS and R-MCI as tools for frailty assessment to guide treatment for elderly patients with MM.

Research indicates that frailty is highly associated with mortality risk, serving as an independent predictor of all-cause mortality in patients with MM. The severity of frailty is directly associated with increased mortality risk (102,103). In terms of accuracy and sensitivity for assessing mortality risk, frailty assessment tools demonstrate notable superiority over measures evaluating cognition, function or comorbidities (104). Frailty assessment tools can predict 3-year OS rates for patients with MM with varying degrees of frailty. Using the R-MCI, the 3-year survival rates for patients without frailty, and those in pre-frailty and frailty states were 91, 77 and 47%, respectively, indicating the notable discriminatory power of the scale (105). It can also provide evidence for establishing novel clinical or biological prognostic factors (106). Similarly, the IMWG-FS can effectively predict survival outcomes in patients with MM with varying frailty levels. The 3-year survival rates were 84% for non-frail patients, 76% for pre-frail patients and 57% for frail patients (60). Thus, frailty serves as a sensitive predictor of survival in patients with MM.

In drug therapy for patients with MM, frail patients experience greater drug-related toxicity during treatment, higher discontinuation rates and poorer efficacy (63,107). Using frailty as a screening indicator to predict drug toxicity reactions, and as a basis for adjusting medication choices or dosages can maximize patient benefits regarding both efficacy and quality of life (99).

A 2025 study by Abdallah *et al* (78) identified the independent prognostic value of the cumulative deficit FI combined with social support status for survival. The Hemasphere study completed by Bruins *et al* (108) revealed that baseline immune characteristics (such as naive $CD8^+$ T-cell counts) can predict treatment outcomes independently of frailty status, providing a new dimension for personalized regimen selection.

7. NDMM suitable for transplantation

ASCO (101) recommends considering reduced melphalan doses (100-140 mg/m^2) for patients aged >70 years, and/or with renal impairment (chronic kidney disease stages 3-5), and/or Karnofsky Performance Status (KPS) <90%, and/or R-MCI 4-6. The EMN recommends appropriately reducing the induction dose of melphalan (140 mg/m^2) for patients aged ≥65 years, with KPS <90%, R-MCI 4-6 or HCT-CI 1-2 (15). Full-dose melphalan (200 mg/m^2) may be administered to healthy patients not meeting these criteria (15). Induction therapy is recommended with the following three- or four-drug combinations: VRd, bortezomib-cyclophosphamide-dexamethasone (VCd) or bortezomib-thalidomide-dexamethasone (15). If

financially feasible, CD38 monoclonal antibodies may be added to these regimens, or second-generation proteasome inhibitors may replace them if neuropathy occurs (15). For transplant patients with MM, early identification of frailty enables timely screening of high-risk groups for transplant complications (68). Frailty assessment can evaluate physiological reserve and predict transplant risks in patients with MM (67), providing a crucial reference for adjusting safe and effective treatment strategies. Recently multiple studies have demonstrated that different doses of melphalan (100/140/200 mg/m^2) exert distinct impacts on OS, PFS and transplantation-related mortality across different frailty stratifications (Table II) (109-115).

8. NDMM unsuitable for transplantation

For patients ineligible for transplantation, the focus should be on achieving deeper remission, prolonging OS and PFS, and improving quality of life (116,117). In a frail state, elderly patients with MM experience reduced muscle strength and immunity, leading to increased infections and other complications (such as organ damage, renal impairment and anemia), longer hospital stays and higher costs (118). This not only impacts hospital bed turnover rates and constrains the full utilization of public health resources, but also diminishes social and economic benefits (118). Therefore, frailty assessment in elderly patients with MM should guide the balancing of efficacy and toxicity to deliver appropriate medical care, maximizing therapeutic benefits while minimizing treatment risks to improve patient outcomes (119). Concurrently, strengthening family and social support, implementing standardized management for outpatients, ensuring timely healthcare responses and fostering clinician-patient collaboration are essential to optimize resource utilization efficiency and equity.

The specific treatment plan is recommended as follows: For induction therapy in patients with good performance status, triple or even quadruple combination regimens are recommended, including daratumumab-lenalidomide-dexamethasone (107), VRd (120), VCd and daratumumab-VMP (121). For patients with moderate performance status, treatment should balance efficacy and safety, aiming for a deep response while maintaining good safety (122). Dose-reduced triple or dual regimens are recommended (123), including: Dose-reduced VRd-Lite (124) VMP/VCd (once weekly) (125), induction-lenalidomide maintenance (126), bortezomib-dexamethasone (Vd) and lenalidomide-dexamethasone (Rd) (101,123). For frail patients, priority should be given to enhancing independence and improving quality-of-life-related aspects. The primary goal is to alleviate symptoms as much as possible without worsening the disease and to prolong survival. Reduced-dose, low-toxicity two-drug combinations (Rd and Vd) are recommended (Fig. 2; Table III) (98,105,107,120,121,125,127,128).

9. Relapsed/refractory MM (RRMM)

The clinical management of RRMM is challenging (129). Frailty, as a key factor affecting the treatment tolerance and prognosis of patients, has become the core of research regarding the clinical value and intervention logic of its assessment tools (130,131). The IMWG-FS can effectively distinguish different health-related quality of life profiles among patients with RRMM (132). Through multi-dimensional assessments including the CCI and the Katz Activity of Daily Living Scale, it can clearly identify notable differences in physical functioning, fatigue, insomnia, dyspnea and other aspects among frail patients (67). Notably, the incidence of pain in frail patients reaches 70.9%, which is higher than that in fit or intermediate-fit patients (67). The PRFP, a novel patient-centered tool, shows fair agreement with IMWG-FS (weighted Cohen's κ=0.27), and better captures subjective treatment side effects and disease symptoms (95). This previous study extends frailty assessment to novel therapy selection and toxicity management for RRMM, improving full-course frailty intervention logic (95).

In terms of the efficacy of novel treatment regimens, multiple studies have confirmed that various therapies exhibit clinical value in frail patients with RRMM. Real-world data on B cell maturation antigen (BCMA)-directed chimeric antigen receptor T cell (CAR-T) therapy showed that 61% of frail patients achieved a median PFS of 6.9 months and a median OS of 14 months after treatment. Although these outcomes are inferior to those in non-frail patients, no excessively severe toxicities were detected, indicating a controllable risk-benefit ratio (133,134). Among chemo-targeted combinations, the pomalidomide, bortezomib and dexamethasone (PVd) regimen has been shown to achieve an objective response rate (ORR) of 79.6% and a median PFS of 9.7 months in frail patients, which were significantly superior compared with those in patients treated with the traditional Vd regimen (135). Furthermore, dose adjustment of bortezomib can further prolong treatment duration and PFS (135). Post-marketing surveillance data from Japan show that the isatuximab plus pomalidomide and dexamethasone (Isa-Pd) regimen achieved an ORR of 38.5% in frail patients, with a treatment discontinuation rate due to disease progression similar to that of fit/intermediate-fit patients, confirming its real-world effectiveness (136).

In terms of toxicity management, the toxicity profiles of different regimens provide clear directions for individualized interventions in frail patients. For CAR-T therapy, the incidence of immune effector cell-associated neurotoxicity syndrome (ICANS) in frail patients (39%) was higher than that in non-frail patients (17%), but there was no difference in the incidence of all-grade or high-grade cytokine release syndrome (CRS) between the two groups. This suggests that close monitoring of ICANS is crucial rather than excluding the treatment (133). Although the PVd regimen increased the incidence of grade ≥3 treatment-emergent AEs in frail patients, with a treatment discontinuation rate (30.1%) higher than that in non-frail patients (19.2%), ~70% of patients could complete the treatment without clustering of fatal toxicities, and dose adjustment is a key safety guarantee (135). In response to the Isa-Pd regimen, frail patients have been reported to exhibit higher incidences of myelosuppression and infectious diseases, but no new serious safety signals were observed (136). By contrast, the bispecific antibodies regimen has a milder toxicity profile, and no notable differences in CRS, ICANS or treatment-related mortality have been reported between frail

Table II. Evidence-based clinical outcomes of different melphalan doses in autologous stem cell transplantation for multiple myeloma across frailty stratifications.

First author, year	Frailty stratification	Melphalan dose, mg/m^2	OS	PFS	TRM	Applicable scenarios and dose selection basis	(Refs.)
Palumbo *et al* 2010	Fit	200	5-year OS rate, 61.8%	Median PFS, 31.4 months	3.1%	Standard for autologous transplantation in fit patients <65 years; achieves longer remission duration (15% CR rate, 79% ORR) than using lower melphalan doses	(109)
Rodriguez *et al*, 2016	Fit	140	1-year OS, 93%	1-year PFS, 90%	0%	Alternative for fit patients; combined with busulfan and bortezomib reduces relapse risk compared with MEL200 regimen (10% vs. 21% at 1 year)	(110)
Palumbo *et al*, 2010	Fit	100	Median, 60 months	Median, 26.2 months	2.9%	For fit patients ≥65 years or mild comorbidities; lower toxicity compared with MEL200 regimen (reduced severe thrombocytopenia/mucositis)	(109)
Brioli *et al*, 2021	Intermediate-fit	200	Median, 103 months	Median, 39 months	No notable increase compared with lower dose	Suitable for intermediate frailty patients <60 years with adequate organ function; preserves efficacy	(111)
Bostankolu Değirmenci *et al*, 2024	Intermediate-fit	140	2-year OS rate, 22.1%	Median, 17.9 months	Slightly lower than 200 mg/m^2	For intermediate frailty with renal/cardiac comorbidities; reduces nonhematological toxicities compared with MEL200 regimen	(112)
Straka *et al*, 2021	Intermediate-fit	100	Similar to 140 mg/m^2	Similar to 140 mg/m^2	Lower than 200 mg/m^2	For patients with intermediate frailty ≥65 years or multiple comorbidities; prioritizes safety	(113)
Badros *et al*, 2001	Severe frailty	200	Median, 14-16 months; 3-year OS rate, ≤12%	Median, 7-8 months; 3-year PFS rate, ≤7%	25-30%	Reserved for selected severely frail patients with intact organ function, albumin ≥35 g/l, prior chemotherapy ≤12 months and intensive supportive care	(114)
Badros *et al*, 2001	Severe frailty	140	Median, 16 months; 3-year OS rate, ≤15%	Median, ~8 months; 3-year PFS rate, ≤8%	8-10%	Recommended as preferred dose for severely frail patients (≥70 years, albumin <35 g/l, prior chemotherapy >12 months, renal impairment)	(114)
Dimopoulos *et al*, 2016	Severe frailty	100	No median reported	No median reported	Lowest risk	Applicable for very frail patients with multiple comorbidities (dialysis-dependent renal failure, KPS <80) who cannot tolerate 140 mg/m^2	(115)

CR, complete remission; KPS, Karnofsky Performance Status; MEL200, melphalan 200 mg/m^2; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TRM, transplant-related mortality.

and non-frail patients, thus indicating that it is a safer option for frail patients (134).

In summary, tools such as the IMWG-FS and PRFP provide reliable support for frailty assessment in patients with

Table III. Recommended initial treatment strategies based on frailty status.

A, Transplant-eligible

Frailty status	Treatment goal	Example regimens	Dosing principle	(Refs.)
Fit	Deep response, preparation for ASCT	VRd, VTd, VCd, ± CD38 monoclonal antibody	Standard dosing	(98,107,127)
Intermediate-fit	Balance efficacy and safety	Triplet therapy (for example, VRd)	Consider reduced melphalan dose (140 mg/m^2)	(98,107)
Frail	Minimize transplant-related toxicity	Carefully assess transplant feasibility	Strongly recommend reduced melphalan dose (100-140 mg/m^2)	(98,107)

B, Transplant-ineligible

Frailty status	Treatment goal	Example regimens	Dosing principle	(Refs.)
Fit	Maximize OS and PFS	D-Rd, VRd, D-VMP	Standard or minimally reduced dosing	(105,120,128)
Intermediate-fit	Deep response with maintained safety	Reduced-intensity triplet or doublet therapy (for example, VRd-lite, Rd)	Dexamethasone 20-40 mg/week, adjust according to tolerance	(98,121,125)
Frail	Preserve quality of life, alleviate symptoms	Reduced-dose, low-toxicity doublet (for example, Rd, Vd)	Dexamethasone 8-20 mg/week, lenalidomide 10 mg start	(98,121)

ASCT, autologous hematopoietic stem cell transplantation; D-Rd, daratumumab-lenalidomide-dexamethasone; D-VMP, daratumumab-bortezomib-melphalan-prednisone; OS, overall survival; PFS, progression-free survival; Rd, lenalidomide-dexamethasone; Vd, bortezomib-dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone; VTd, bortezomib/thalidomide/dexamethasone; VCd, bortezomib/cyclophosphamide/dexamethasone.

RRMM. Novel regimens including BCMA-directed immunotherapies, PVd and Isa-Pd have demonstrated acceptable safety and reasonable efficacy in frail populations.

10. Potential biological impact factors of frailty in different types of MM

N-terminal pro-B-type natriuretic peptide (NT-proBNP). Milani *et al* (71) reported that NT-proBNP can effectively predict OS in patients with MM, with an optimal cut off of 300 pg/ml. Notably, NT-proBNP serves as an independent predictor of survival in MM, particularly in patients with cardiac amyloidosis (137), and it can serve as a biomarker for assessing frailty severity in patients with NDMM (71). NT-proBNP is mechanistically linked to frailty via two key pathways (71), as it reflects ventricular dysfunction (from increased myocardial stress) and renal impairment (as it is kidney-cleared), capturing the two most common organ-related drivers of frailty in hematological malignancies [MM and amyloid light-chain (AL) amyloidosis]. Additionally, age-related declines in ventricular compliance and glomerular filtration rate independently elevate NT-proBNP, aligning it with 'biological age', a core component of frailty (71). Its disease-specific cut offs (300 ng/l for MM, 8,500 ng/l for AL amyloidosis) reflect varying organ involvement severity, and its independence from clinical factors (such as ECOG-PS and age) confirms it as an objective, actionable frailty biomarker (137). However, NT-proBNP is primarily used clinically as a key indicator for heart failure detection and is a nonspecific marker for frailty (138-140). When employing NT-proBNP to evaluate frailty severity, it must be integrated with the overall functional status of bodily organs and other criteria for a comprehensive assessment (141). In 2016, the Mayo Clinic established the Mayo-FI based on NT-proBNP, age and ECOG-PS (71). This system uses NT-proBNP, a key biomarker reflecting ventricular dysfunction, as a core component. The Mayo Frailty Score System is simple to implement and effectively predicts survival in elderly patients with MM (71).

Neutrophil-to-lymphocyte ratio (NLR). Additionally, studies have indicated that the NLR combines inflammation with cell cycle alterations, and is thus associated with frailty and OS in patients with MM (142,143). As a readily obtainable clinical laboratory biomarker, it serves as a reference indicator for identifying frailty in patients with MM. NLR links frailty to two foundational aging-related processes: i) Neutrophilia (marking chronic inflammation, which drives tissue dysfunction and reduced stress resilience) (142); and ii) lymphopenia (indicating immunosenescence and impaired infection/tumor defense) (142). In elderly patients with MM, high NLR (top quartile) is associated with frailty-related phenotypes (such

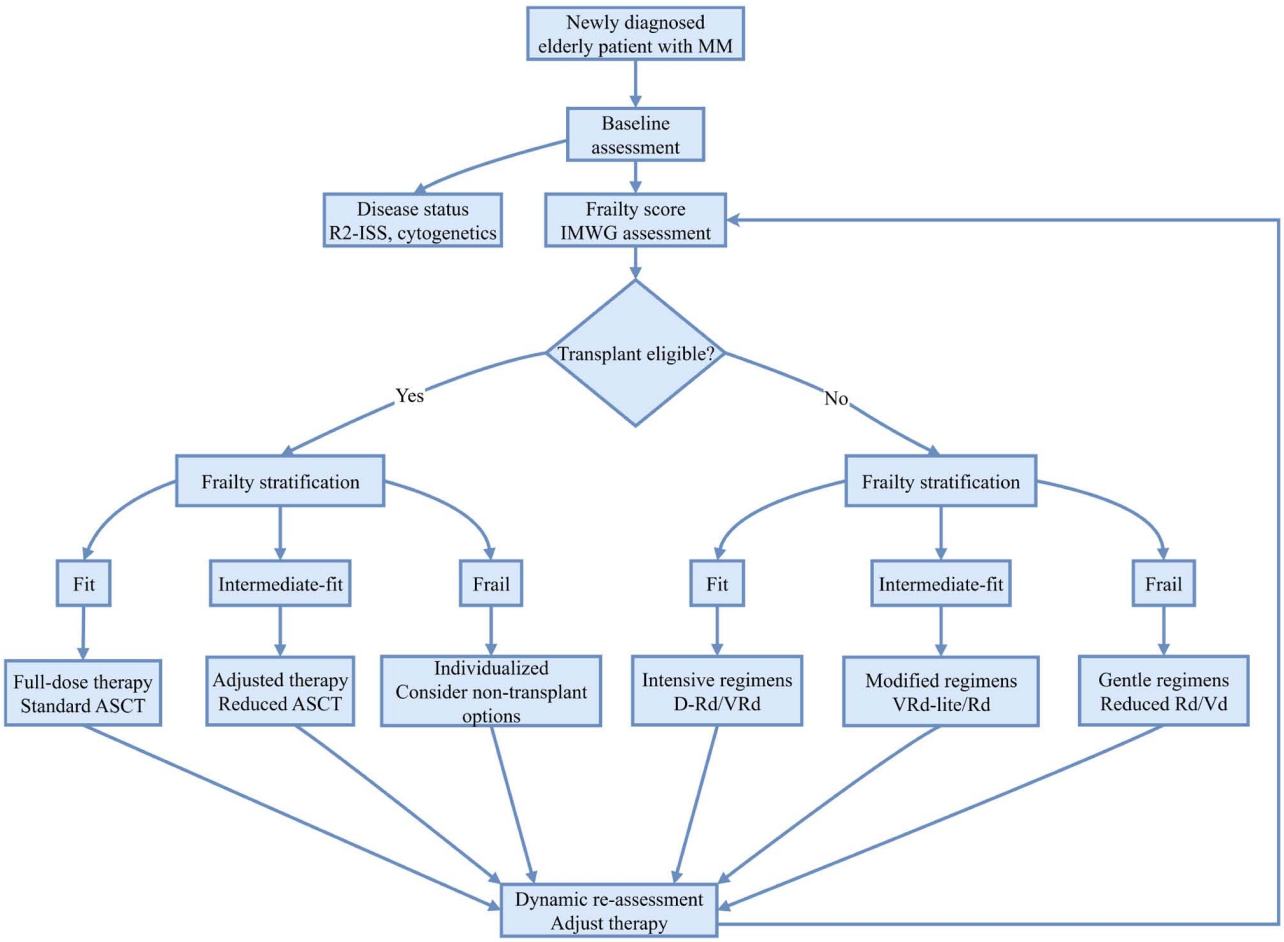

Figure 2. Clinical decision-making flow chart: Transplant eligibility and frailty stratification in elderly patients with MM. ASCT, autologous hematopoietic stem cell transplantation; D-Rd, daratumumab-lenalidomide-dexamethasone; IMWG, International Myeloma Working Group; MM, multiple myeloma; Rd, lenalidomide-dexamethasone; R2-ISS, Second Revised International Staging System; Vd, bortezomib-dexamethasone; VRd, bortezomib/lenalidomide/dexamethasone.

as ECOG-PS ≥2 and renal dysfunction) and predicts poor survival (142). By integrating inflammation and immunosenescence, intertwined pathways that exacerbate frailty, NLR serves as a simple, readily available biomarker that complements clinical frailty assessments, validating its use in identifying high-risk patients (142).

CRP. Chronic inflammatory responses represent characteristic alterations in organ aging (144,145). CRP is an inflammatory marker, and elevated levels of CRP have been reported to be associated with multiple age-related diseases, such as atherosclerosis, diabetes and sarcopenia, and to predict mortality risk (146-151). Studies have found that CRP can activate myeloma cells in the body, thereby promoting osteoclastogenesis and bone destruction, and suggest that CRP may serve as a therapeutic target for the prevention or treatment of myeloma-related bone diseases (152,153). Based on CRP, age, World Health Organization-PS and ISS staging, the UK Myeloma Research Consortium established a risk prediction model (MRP) in 2019 (70) capable of forecasting PFS and early mortality (EM).

While R2-ISS staging, which reflects MM biology, does not predict EM, frailty and organ function markers such as ECOG-PS, estimated glomerular filtration rate and NT-pro-BNP do predict EM risk, with NT-pro-BNP potentially being the most important independent factor (154). Therefore, incorporating these frailty biomarkers into the R2-ISS staging system holds promise for more precise prognostic stratification and EM prediction in elderly patients with MM. Frailty serves as a risk predictor in patients with MM. Studies have demonstrated that frailty is closely associated with mortality risk, acting as an independent factor for all-cause mortality in patients with MM, with increased frailty severity associated with higher mortality risk (155,156).

Notably, research on frailty-related biomarkers in MM has continued to expand. Beyond traditional indicators, a variety of emerging biomarkers have become the focus of research due to their clear mechanistic associations and clinical value, providing new dimensions for disease assessment.

IL-5. IL-5 is a key cytokine for distinguishing engraftment syndrome (ES) after autologous hematopoietic stem cell transplantation (ASCT). ES occurs in 24.0% of patients with NDMM post-ASCT. The IL-5 level on day 6, combined with the proportion of $CD8^+$ T cells and daratumumab treatment history, can accurately predict ES risk in 70.8% of patients (157). Its mechanism is related to IL-5-mediated immune-inflammatory imbalance, which is a core pathological basis for frailty (157).

Regulatory T cells (Tregs). A reduced proportion of Tregs at diagnosis is an important predictor of early relapse (within 18 months) and shortened PFS in patients with MM, and synergizes with adverse factors such as extramedullary disease to predispose patients to a functionally high-risk state (158). This may be due to the insufficient regulatory capacity caused by reduced Treg proportions, which fails to effectively inhibit abnormal inflammatory responses, thereby exacerbating systemic metabolic disorders and frailty (158).

Metabolomic markers. MM-related specific metabolites identified by high-throughput analysis can reflect frailty-related abnormalities in energy metabolism and inflammatory intensity, enabling non-invasive assessment of the systemic reserve function of patients (159). Combined with advances in blood testing technology, their integration with monoclonal protein structure analysis can improve the accuracy of frailty risk stratification (160).

Macrophage migration inhibitory factor (MIF). Serum MIF levels are markedly elevated in patients with NDMM (161). Notably, high MIF expression is associated with adverse features such as advanced staging and hypercalcemia, and serves as an independent risk factor for shortened PFS and OS (162). By promoting tumor proliferation and inflammatory disorders, it provides a reference for frailty risk assessment (163).

PET-CT imaging marker [splenic (68)Ga-Pentixafor uptake]. The splenic peak standardized uptake value (SUVpeak) measured by (68) Ga-Pentixafor-PET/CT is an important prognostic marker for pretreated patients with MM (164). A previous study has shown that patients with an SUVpeak of <3.35 have a median OS of 5 months, which is markedly shorter than the 62 months in those with an SUVpeak of >5.79 (164). This indicator is associated with disease progression and can reflect immune-inflammatory status, providing a non-invasive imaging basis for frailty-related prognostic assessment (164). The association strength between different biomarkers and frailty levels are shown in Fig. 3 This heatmap was generated to visualize the correlation strength between biomarkers and frailty status in MM. A total of 10 evidence-based biomarkers were selected from nine published studies, with frailty stratified into fit, intermediate-fit and frail according to MM geriatric assessment standards (142,154,157,158,162,165-168). Correlation values ranging from -1 to 1 were assigned based on quantitative and qualitative evidence from the literature. Spearman rank correlation was used to characterize the monotonic relationships between biomarker levels and frailty severity. The heatmap was constructed using GraphPad Prism (version 10; Dotmatics) with a diverging color scheme (dark blue, strong negative correlation; dark red, strong positive correlation) for clear visualization.

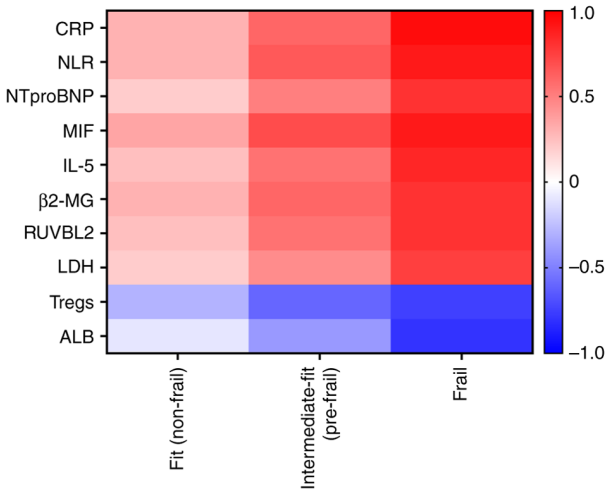

Figure 3. Association strength between different biomarkers and frailty levels. Color key indicates the strength of correlation: -1.0 represents strong negative correlation and 1.0 represents strong positive correlation. CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; NTproBNP, N-terminal pro-brain natriuretic peptide; MIF, macrophage migration inhibitory factor; IL-5, interleukin-5; β2-MG, β2-microglobulin; RUVBL2, RuvB-like 2; LDH, lactate dehydrogenase; Tregs, regulatory T cells; ALB, albumin.

11. Timing of frailty assessment

Although the IMWG-FS categorizes patients with MM into fit, intermediate-fit and frail groups and predicts OS, PFS, treatment discontinuation and non-hematologic toxicity, patient outcomes exhibit significant heterogeneity even within the same frailty subgroup (65).

Frailty is a dynamic state, however most existing studies lack detailed dynamic frailty scoring for specific subgroups, overlooking the impact of dynamic frailty assessment on clinical outcomes. Smits *et al* (38) conducted a prospective study on the dynamic changes of frailty and its impact on clinical outcomes in the HOVON 143 study, which involved patients with NDMM (NTE-NDMM) who were assessed as intermediate-fit and frail and not eligible for transplantation by the IMWG-FS. The HOVON 123 study confirmed that improvements in frailty scores are associated with longer OS, longer PFS and reduced 100-day mortality. During treatment, nearly half of frail patients showed improvement in IMWG-FSs, and integrating dynamic frailty assessment significantly enhances survival prediction. In most clinical settings, treatment modifications should not be based solely on a single frailty assessment. Relying solely on one assessment risks inadequate or excessive treatment, particularly due to underestimating frailty dynamics.

Early detection of frailty and timely intervention are key to slowing its progression (77). The International Conference on Frailty and Sarcopenia Research working group recommends a patient-centered, multidisciplinary team approach for CGA and management (169). In China, due to differences in medical and social environments, the primary approach is a multidisciplinary collaboration model. Teams comprising healthcare professionals from oncology, geriatrics, cardiovascular medicine, nutrition and rehabilitation jointly develop treatment plans to ensure medical safety and maximize patient benefit (170). Regular dynamic assessments of frailty are conducted during this process to promptly adjust treatment regimens, reduce medication-related complications, improve patient compliance and reduce financial burden (170). Interventions and management strategies for frailty in elderly patients with MM remain in the exploratory phase domestically, with specific

Table IV. Timing of frailty assessment and principles of dynamic management.

Assessment timing	Purpose	Action and clinical importance	(Refs.)
At diagnosis (baseline)	Establish initial frailty status to guide first-line therapy selection	Foundation for risk-stratified treatment (fit/intermediate/frail). Use tools such as IMWG-FS, HCT- FS or cumulative deficit FI to classify patients. Frail patients may benefit from daratumumab-containing regimens; avoid overtreatment in frail or undertreatment in fit subgroups.	(33,38,60,63,78,86,89)
During therapy (every 2-3 cycles)	Monitor treatment response and toxicity; track dynamic changes in frailty	Dynamic assessment: If frailty improves (for example, increased ADL/IADL scores), consider treatment intensification (VRd dose escalated in DynaFiT study). If it worsens (reduced functional status, increased comorbidities), implement treatment de-escalation or enhance supportive care (for example, antibiotic/antiviral prophylaxis). Reassessment optimizes balance between efficacy and safety.	(33,38,63,86,89)
At disease relapse/ progression	Re-evaluate physiological reserve to guide subsequent lines of therapy	Frailty should not absolutely preclude effective novel therapies (for example, bispecific antibodies, CAR-T therapy) in RRMM, but mandates intensified supportive measures (infection prevention, symptom management). Reclassify frailty status to select regimens matching current fitness (such as lower-intensity combinations for deteriorated frailty).	(89,171-174)
Post-treatment (for example, day +100 post- auto-HCT, 12 months post-induction)	Evaluate long-term frailty recovery; assess QoL and functional outcomes	Identify persistent frailty to initiate rehabilitation (physical exercise for mobility limitations). Frail patients post-auto- HCT have poorer QoL (mobility, self-care) and higher readmission rates; targeted interventions improve functional independence. Document frailty trajectory for long-term follow-up.	(38,78,86,171)

ADL, activities of daily living; CAR-T, chimeric antigen receptor T cell; FI, frailty index; HCT-FS, hematopoietic cell transplantation frailty scale; IADL, instrumental ADL; IMWG, International Myeloma Working Group; QoL, quality of life; RRMM, relapsed/refractory MM; VRd, bortezomib/lenalidomide/dexamethasone.

operational workflows, referral protocols and follow-up procedures requiring further investigation.

12. Recommended assessment frequency during treatment

Induction therapy phase: Assessment timing and frequency. Dynamic frailty assessment during induction therapy requires frequent monitoring to capture rapid changes induced by treatment toxicity or disease response (33,38,171). The DynaFiT study (63) implemented IMWG-FS assessment at the start of each 21-day induction cycle (eight cycles total), and demonstrated that cycle-specific adjustments to treatment intensity improved outcomes. Specifically, 58% of frail patients achieved frailty category improvement, with 27% becoming fit. Complementary evidence has been provided by the HOVON 143 trial (38), which performed assessments after three and nine cycles of induction, with 78% of frail patients who improved showing changes within the first three cycles, highlighting early monitoring as critical for timely intervention. The SEER-Medicare cohort study (33) further supported that the first year post-diagnosis (encompassing induction) is a high-risk period for frailty fluctuation, with 93% of patients experiencing changes, justifying cycle-level surveillance.

Maintenance therapy phase: Assessment timing and frequency. Maintenance therapy demands sustained but pragmatic monitoring, as frailty changes are less acute but clinically impactful (86). Zhang *et al* (63) recommend frailty reassessment at maintenance initiation (post-induction) to

guide Rd maintenance dosing, with 40% of patients transitioning to maintenance showing frailty trajectory shifts that informed personalized intensity. The Hemo-IMWG GA model validation (89) supported 3-6-month intervals during maintenance, as HS and IMWG-FS integration identified late hematological toxicity risks that static assessments missed. Additionally, the GETH-TC multicenter study (86) emphasized a day +100 post-autologous HCT assessment (a key maintenance transition point) to optimize long-term care, as frailty at this timepoint strongly predicted quality of life and readmission rates.

Cross-phase core assessment nodes and implementation. A total of three non-negotiable cross-phase nodes ensure continuity: i) Baseline (pre-treatment); ii) induction-maintenance transition; and iii) disease relapse/progression. Baseline assessment using Hematopoietic Cell Transplantation Frailty Scale (86) establishes a reference for longitudinal comparison. The induction-maintenance transition assessment (63) integrates frailty changes with MRD status to avoid undertreatment/overtreatment. At relapse, reassessment via cumulative deficit FI (77) identifies frailty deterioration (observed in 30% of patients at 12 months) that guides salvage therapy adjustments. For implementation, Smits *et al* (38) noted that assessments take <10 min using electronic health record-integrated tools, and Chen *et al* (89) recommended prioritizing higher-risk groups (frail, ≥80 years) for shortened 2-month intervals during early maintenance. Recommended assessment frequency during treatment is shown in Table IV (33,38,60,63,78,86,89,171-174). Frailty in MM is a dynamic condition that fluctuates with treatment response and disease status, requiring systematic reassessment at diagnosis, during therapy, upon relapse and post-treatment to inform timely adjustments in treatment intensity (33,38,60,63,78,86,89,171-174).

13. Conclusions and future directions

MM primarily affects elderly individuals, among whom frailty is highly prevalent due to physiological decline, disease progression and medication effects. Frailty is a key predictive indicator in MM, closely associated with survival prognosis, mortality risk, transplant risk, hospitalization duration and AE incidence. During drug therapy, frail patients with MM experience increased drug toxicity, higher discontinuation rates and poorer treatment outcomes. Employing frailty as a screening tool to predict drug toxicity, and guide medication selection or dosage adjustments can optimize both efficacy and quality of life. Future research should focus on refining frailty assessment tools for MM by integrating disease-specific molecular markers, such as BCMA expression, and imaging metrics, such as muscle mass measured by CT scans. Incorporating these parameters into treatment decisions and AE evaluations may improve the accuracy of frailty identification and risk prediction.

Elderly patients with MM have not demonstrated substantial benefit from novel therapeutic agents, highlighting the need for robust risk assessment models. Frailty scores facilitate the identification of patients at a higher risk of treatment toxicity and reduced survival, thereby supporting the selection of appropriate therapeutic regimens. In certain cases, prioritizing supportive care and psychological counseling over curative therapy may still result in prolonged survival. Although various frailty assessment tools are available, there is no consensus on standardized measurement instruments. Future approaches should incorporate dynamic frailty scoring methods, such as gait speed and grip strength, to enhance treatment precision. Additionally, assessment tools specifically designed for the characteristics of the Chinese elderly population are needed.

The IMWG-FS remains the gold standard for frailty assessment in MM. However, its subjective and time-intensive nature limits widespread clinical adoption. Although alternative assessment models have been introduced, they are not yet widely implemented in practice. Frailty is inherently dynamic, yet longitudinal research remains limited. Future research should prioritize the development of time-series indicator systems to monitor frailty dynamics. Recent prospective studies are expected to provide further evidence-based guidance for the management of elderly patients with MM. In summary, frailty scoring is essential for treatment selection, prognosis assessment and safety management in elderly patients with MM. Identifying additional prognostic parameters, such as immune function and metabolic markers, will support the creation of novel prognostic models. Standardizing dynamic frailty assessment will facilitate the transition to precision medicine in geriatric MM, ultimately improving quality of life and survival outcomes.

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Authors' contributions

JLL and DYL were involved in conceptualization. JLL, DYL, CL and ZRC performed the literature search and data collection, and wrote the review. CL and ZRC reviewed and edited the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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