https://doi.org/10.46765/2675-374X.2025v7n1e316 ORIGINAL ARTICLE

Frailty score analysis of multiple myeloma patients in the evaluation prior to autologous hematopoietic stem cell transplantation

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Section editor: Abrahão Elias Hallack Neto

Received: Nov. 24, 2025 • **Accepted:** May 5, 2026

ABSTRACT

Introduction: Multiple myeloma (MM) is a common hematological neoplasm that is more prevalent at older ages. Autologous stem cell transplantation (ASCT) remains a relevant treatment option. The International Myeloma Working Group (IMWG) developed a score to assess frailty, dividing patients into fit, intermediate-fit, and frail. This study aims to analyze the profile, using the IMWG frailty score, of MM patients evaluated for ASCT. **Methods:** Retrospective, with a prospective arm, observational, descriptive study based on the review of records of MM patients evaluated for ASCT using the IMWG score in a Brazilian hospital from 2023 to 2025. **Results:** Eighty-one patients composed the sample, with a median age of 59 years. Using the IMWG frailty score, 57% of patients were classified as fit, 34% as intermediate-fit, and 9% as frail. Scoring on the IMWG score was decisive to contraindicating transplant (statistically significant difference compared to the fit group). There were no significant differences between groups concerning the toxicities, with a trend toward an increased risk of febrile neutropenia among frail patients ($p = 0.058$). The proportion of patients aged over 60 years was similar across groups. **Conclusion:** The IMWG frailty score is a valuable tool and reinforces the necessity of considering variables beyond age. Further discussion is required to validate these findings in diverse populations.

Keywords: Multiple Myeloma; Frailty; Hematopoietic stem cell transplantation.

INTRODUCTION

Multiple myeloma (MM) is a disease characterized by the clonal expansion of plasma cells in the bone marrow, leading to a clinical presentation that includes cytopenias, osteolytic lesions, hypercalcemia, and renal dysfunction[1]. It accounts for approximately 10% of hematologic malignancies, ranking as the second most common condition within this group, with a median age at diagnosis of 65 years[2]. According to data from the Brazilian Unified Health System Database DATASUS (Departamento de Informática do Sistema Único de Saúde), 19,579 cases of MM were diagnosed in Brazil from 2020 to 2024, of which 4,295 occurred in the Northeast region and 794 in the state of Ceará during this period[3].

The use of high-dose melphalan followed by autologous stem cell transplantation (ASCT) after initial disease control with chemotherapy regimens has been established as the standard of care since studies in the

1990s demonstrated improvements in progression-free survival, disease-free survival, and overall survival. Although still considered incurable, MM treatment has seen remarkable advances in recent years, leading to prolonged patient survival through the use of immunomodulatory drugs, proteasome inhibitors, and anti-CD38 monoclonal antibodies[4].

With the advent of these new therapeutic strategies, the role of autologous transplantation has been reevaluated, raising questions about whether this procedure should be reserved for a potential second remission. However, high-dose melphalan followed by ASCT maintains its role in optimizing response rates even when used in combination with highly effective novel therapies, thus continuing to serve as the standard of care for eligible patients[2,4-6].

Given its proven benefits, at diagnosis, patients must be assessed for eligibility for autologous transplantation. This evaluation considers age, organ function, and overall physical condition, as this therapy – although generally safe – carries inherent risks such as infectious complications, mucositis, and organ dysfunction secondary to melphalan toxicity[4,7].

Within this context, the discussion surrounding frailty assessment in patients with MM has gained increasing attention in recent years. The development of frailty scoring systems aims to predict the likelihood of treatment-related adverse reactions, decreased progression-free survival, and reduced overall survival. Frailty assessment has also been incorporated into eligibility analyses for autologous transplantation, though it has not yet been routinely implemented in many centers[8,9].

Frailty is a process associated with aging that encompasses decreased organ function and sarcopenia, influenced by individual biological factors and environmental conditions. Myeloma itself contributes to this process, leading to a state of vulnerability and reduced physiological reserve in response to stressors (10,11).

Although often associated with aging, frailty does not necessarily correlate with chronological age; an older individual may be robust, while a younger patient may be frail. It represents a heterogeneous process that challenges assumptions about age and vulnerability[10,11].

Frailty assessment is essential to avoid exposing patients to excessively aggressive medical therapy. It takes into account comorbidities, cognition, functionality, and nutritional status, in addition to objective scoring systems. Among the various tools developed, the International Myeloma Working Group (IMWG) frailty score is considered the gold standard[12].

The IMWG frailty score categorizes patients into three groups – fit, intermediate-fit, and frail – based on age, the Charlson comorbidity index, the Katz Index of Activities of Daily Living, and the Lawton Instrumental Activities of Daily Living Scale. Developed in a 2015 study involving 869 patients with a median age of 74 years, this tool demonstrated significant differences in 3-year overall survival (84% in the fit group vs. 57% in the frail group) and in treatment discontinuation rates at 12 months (16% in fit vs. 31% in frail patients), with findings validated in a real-world study in 2016[11-14].

Therefore, this study aims to analyze the clinical profile of MM patients evaluated for eligibility for ASCT in a specialized center from 2023 to 2025. It seeks to correlate the degree of treatment-related toxicity with the IMWG frailty score classification and to identify the main reasons for contraindicating transplantation.

MATERIALS AND METHODS

This was a retrospective observational study with a prospective arm, conducted at a single center and based on the individual, epidemiological, and clinical characteristics of the study population. The study population consisted of patients evaluated at the stem cell transplantation outpatient clinic of our institution who had a diagnosis of MM and for whom the IMWG frailty score was applied during the eligibility assessment period from 2023 to 2025. Patients who did not have proper documentation of the frailty score in their medical records were excluded.

The institution where the study was developed is a public service that receives referred patients from public hospitals throughout the state and from some nearby states. All the patients analyzed had the score applied before the decision to proceed with ASCT, after nine to 12 cycles of induction. Besides the IMWG score, patients evaluated in this center for ASCT also have the Eastern Cooperative Oncology Group (ECOG) score, cardiopulmonary function tests, abdominal ultrasound, odontologic evaluation, and full biochemical serum tests analyzed before proceeding to ASCT.

This study evaluated data from August 2023 to May 2024 retrospectively. From that date onward, data were analyzed prospectively, applying the scores using the same methodology previously applied. The final sample comprised 81 patients with MM who underwent IMWG frailty scoring as part of their eligibility evaluation for ASCT from 2023 to 2025, up to May 2025, with outcomes followed until October 1, 2025.

The following variables were analyzed: age, sex, IMWG frailty score, eligibility for transplantation, contraindication reasons, conditioning regimen, degree of toxicity according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI-CTCAE v5.0) criteria, occurrence of febrile neutropenia, and median neutrophil and platelet engraftment times. Among the 34 patients who underwent transplantation during the study period, two had not yet completed toxicity assessment or engraftment data, with only a description of one case of febrile neutropenia. International Staging System scores were not analyzed, given data heterogeneity as patients were referred from different services with variable stratification data availability.

Data analysis was performed based on the variables listed above, using descriptive statistics for all patients. Characteristics were grouped according to the IMWG frailty score classification.

Statistical analyses were conducted using R Studio version 4.1.0. Tests were performed by dividing patients into three groups (fit, intermediate-fit, and frail) according to the IMWG frailty score, and subsequently into two groups by combining intermediate and frail patients. The chi-square test with contingency tables was used to assess the relationship between frailty score and transplantation eligibility, conditioning regimen, presence of grade ≥ 3 toxicity, and febrile neutropenia. To compare mean age and median neutrophil and platelet engraftment times between groups, analysis of variance (ANOVA) tests were applied. A $p < 0.05$ was considered statistically significant.

From an ethical standpoint, this research adhered to Resolution No. 466 of the Brazilian National Health Council (Conselho Nacional de Saúde) (December 12, 2012), which regulates clinical studies involving human subjects. Patient confidentiality was ensured by the researchers, with written informed consent obtained from all participants or their legal guardians through the signing of an informed consent form. The study was approved by the Research Ethics Committee of the Hospital Universitário Walter Cantídio, under the certificate of ethical approval number 87099725.2.0000.5045.

RESULTS

The sample consisted of 81 patients, with a slight predominance of females (53%). Ages ranged from 31 to 71 years, with a median age of 59 years at the time of evaluation. The median age and the proportion of patients over 60 years were similar across the different frailty score groups, as summarized in Table 1.

According to the IMWG frailty score, 57% of patients were classified as fit, 34% as intermediate-fit, and 9% as frail. In the eligibility evaluation for ASCT, among patients classified as intermediate or frail, there was a predominance of transplant contraindication, showing a statistically significant difference compared to the fit group, when assessed using the chi-square test, demonstrating the relevance of using the IMWG frailty score in that assessment (Table 2).

Overall, 43% of patients were deemed ineligible for transplantation. Besides frailty, other relevant factors influencing contraindication included patient comorbidities – particularly heart failure, which alone does not

Table 1. General characteristics.

	Total	Fit	Intermediate-fit	Frail
Total patients, n (%)	81 (100)	46 (57)	28 (34)	7 (9)
Females, n (%)	43 (53)	31 (67)	10 (36)	2 (29)
Males, n (%)	38 (47)	15 (33)	18 (64)	5 (71)
Median age (years)	59 (31-73)	60 (31-72)	59 (43-73)	59 (38-65)
Proportion above 60 years, % (n/n)	39.5 (32/81)	39 (18/46)	39 (11/28)	43 (3/7)
Contraindicated, n (%)	35 (43)	14 (30)	16 (57)	5 (71)
Transplanted, n (%)	34 (52)	24 (70)	8 (28)	2 (29)
Conditioning regimen	20 melphalan 200 mg/m^2 (59%) 14 reduced dose (41%)	16 melphalan 200 mg/m^2 (67%) 8 reduced dose (33%)	3 melphalan 200 mg/m^2 (37.5%) 5 reduced dose (62.5%)	1 melphalan 200 mg/m^2 (50%) 1 reduced dose (50%)
Pre-ASCT response	2 CR 23 VGPR 9 PR	2 CR 14 VGPR 8 PR	7 - VGPR 1 - PR	2 - VGPR
Neutrophil engraftment time (days)	10	10	9	10
Platelet engraftment time (days)	15.5	15	15.5	17

CR: complete response; PR: partial response; VGPR: very good partial response. Source: Elaborated by the authors.

Table 2. General stats.

Frailty score group	Variables	Variables	Statistical analyses
	Contraindicated	Indicated	
Fit	14	31	
Intermediate-fit	16	9	$X^2 = 9.1068$
Frail	5	2	p = 0.01053
	Mean age	Standard deviation	
Fit	58.1	8.620	
Intermediate-fit	58.9	7.540	ANOVA
Frail	54.3	10.000	p = 0.42700
	Melphalan 200 mg/m^2	Reduced dose	
Fit	16	8	
Intermediate-fit	3	5	$X^2 = 2.1756$
Frail	1	1	p = 0.33700
	Neutrophil engraftment day	Standard deviation	
Fit	9.67	0.482	
Intermediate-fit	9.33	0.516	ANOVA
Frail	10.00	0.000	p = 0.18100
	Platelet engraftment day	Standard deviation	
Fit	14.5	2.13	
Intermediate-fit	15.8	2.48	ANOVA
Frail	17.0	1.41	p = 0.19200
	No febrile neutropenia	Febrile neutropenia	
Fit	10	14	
Intermediate-fit	0	7	$X^2 = 5.3804$
Frail	0	2	p = 0.06787
	No febrile neutropenia	Febrile neutropenia	
Fit	10	14	$X^2 = 3.5885$
Intermediate-fit/frail	0	9	p = 0.05818
	Toxicity 0-2	Toxicity 3+	
Fit	11	13	
Intermediate-fit	1	5	$X^2 = 4.4021$
Frail	2	0	p = 0.11070

Source: Elaborated by the authors.

modify the frailty score – disease progression, and patient refusal after initial evaluation. Regarding the two frail patients who had undergone transplantation, both were young patients whose IMWG frailty scoring was determined by the impact of myeloma bone involvement sequelae on daily activities, despite preserved organic function. Twelve patients were awaiting hospital bed availability for ASCT realization.

Among those who underwent transplantation (42% of the cohort), most (59%) received the conventional conditioning regimen (melphalan 200 mg/m^2) rather than the reduced-intensity regimen. Median neutrophil engraftment occurred on day 10, and platelet engraftment on day 15.5 after infusion of hematopoietic stem cells. There were no statistically significant differences between frailty groups regarding these variables.

Regarding toxicities, including mucositis, diarrhea, hepatic toxicity, nausea, and vomiting (graded according to the NCI-CTCAE v5.0), 56% of patients exhibited at least one grade 3 or higher adverse event, with diarrhea being the most frequent (Table 3). There were no statistically significant differences between frailty groups concerning the presence of toxicities.

Table 3. Degree of toxicity according to NCI-CTCAE v5.0 criteria related to ASCT.

	All	Fit	Intermediate-fit	Frail
Grade 3 or more toxicity, n/n (%)	18/32 (56)	13/24 (54)	5/6 (83)	0 (0)
Mucositis, %	3 grade 1 (9) 24 grade 2 (75) 4 grade 3 (13) 1 grade 4 (3)	2 grade 1 (8) 21 grade 2 (88) 1 grade 3 (4)	2 grade 2 (33) 3 grade 3 (50) 1 grade 4 (17)	1 grade 1 (50) 1 grade 2 (50)
Nausea and vomiting, %	10 grade 1 (31) 18 grade 2 (56) 4 grade 3 (13)	7 grade 1 (29) 16 grade 2 (67) 1 grade 3 (4)	2 grade 1 (33) 1 grade 2 (17) 3 grade 3 (50)	1 grade 1 (50) 1 grade 2 (50)
Hepatic toxicity, %	31 grade 1 (97) 1 grade 2 (3)	23 grade 1 (96) 1 grade 2 (4)	6 grade 1 (100)	2 grade 1 (100)
Diarrhea, %	2 grade 1 (6) 13 grade 2 (41) 17 grade 3 (53)	1 grade 1 (4) 10 grade 2 (42) 13 grade 3 (54)	2 grade 2 (33) 4 grade 3 (67)	1 grade 1 (50) 1 grade 2 (50)
Febrile neutropenia, %	10 did not presented (27) 23 presented (73)	10 did not presented (42) 14 presented* (58)	7 presented (100)	2 presented (100)

Source: Elaborated by the authors. *1 with hemodynamic instability.

Specifically for febrile neutropenia, 42% of patients classified as fit did not develop this event during hospitalization, whereas all other transplanted patients experienced febrile neutropenia. Only one fit patient exhibited hemodynamic instability, suggesting a trend toward an increased risk of febrile neutropenia among frail patients, although this did not reach statistical significance ($p = 0.058$) (Table 2).

DISCUSSION

The IMWG frailty score was developed to address the need for a more accurate evaluation of elderly patients – a highly heterogeneous population – beyond chronological age, in order to determine eligibility for specific MM therapies and predict treatment-related toxicities (14). The original study that introduced the frailty score reported a higher median age of 74 years and a larger proportion of frail patients (30%) compared to the present sample, a difference likely related to the inclusion criteria, which considered only patients ineligible for ASCT[14].

In contrast, the study that validated the frailty score, which included transplant-eligible patients, showed a similar median age to that of the present study (63 years), but with a higher proportion of frail patients (48%) and fewer fit patients (18%)[13].

The study that originally established the IMWG score demonstrated that frail patients exhibited higher rates of treatment discontinuation as well as a greater proportion of grade ≥ 3 non-hematologic adverse events, both with statistical significance – findings not observed in the current study[14].

A 2018 study that evaluated the utility of the IMWG frailty score in determining autologous bone marrow transplant eligibility among 131 elderly patients newly diagnosed with MM found that frail classification was statistically correlated with transplant contraindication, consistent with the results of this work. Furthermore, it suggested that intermediate-fit patients aged over 70 years derive limited benefit from undergoing autologous transplantation. That study reported a higher median age (70 years) and a greater proportion of intermediate (60%) and frail (7%) patients than the present study, as expected given that it focused on patients aged 65 to 75 years[15].

A retrospective Chinese study involving 322 newly diagnosed MM patients with a median age of 58 years also identified the IMWG frailty score as an important factor influencing transplant eligibility. It concluded that the absence of frailty (fit or intermediate-fit IMWG classification) was the best indicator for selecting appropriate candidates for ASCT[16].

That same study reported that both non-frail (fit or intermediate) and frail groups had similar median ages – 56.7 and 59.5 years, respectively – similar to findings in the present study. However, it noted that approximately 78% of non-frail patients were younger than 65 years[16]. In contrast, in our study, the proportion of patients aged over 60 years was similar across all three frailty groups, demonstrating the variability of frailty classification in relation to chronological age and the marked heterogeneity of our patient population.

As shown, frailty assessment in MM can help in treatment intensity decisions, including autologous transplantation, and may serve as a predictor of treatment-related toxicities. Although no statistically significant differences in non-hematologic toxicities were observed among frailty groups in this study, there was a trend toward fit patients being less likely to develop febrile neutropenia.

Similarly, a Canadian study published in 2023 evaluated frailty as a risk factor for febrile neutropenia in MM patients undergoing autologous transplantation. It identified altered frailty scores (ECOG combined with the Revised Myeloma Comorbidity Index) as a significant risk factor for febrile neutropenia, though again, no differences were observed between frailty groups regarding non-hematologic toxicities[17].

In that same study, when frailty was assessed using the IMWG score, no statistically significant difference was found in the incidence of febrile neutropenia among frailty groups[17].

CONCLUSION

Despite its inherent limitations as a single-center, partly retrospective study, the present work demonstrates the importance of frailty assessment in determining eligibility for autologous bone stem cell transplantation among patients with MM. The IMWG frailty score proved to be a valuable tool, showing a significant association with transplant contraindication.

Furthermore, the findings reinforce the necessity of considering variables beyond chronological age, as evidenced by the heterogeneity in age distribution across the frailty score categories.

Although no statistically significant association was observed between the presence of non-hematologic treatment-related toxicities and frailty status, frailty evaluation remains useful for determining the appropriate treatment intensity to which a patient may be subjected and for defining the indication for ASCT. Nevertheless, further discussion is required to establish the most suitable frailty assessment tool and to validate these findings in diverse populations.

CONFLICTS OF INTEREST

Nothing to declare.

DECLARATION OF USE OF ARTIFICIAL INTELLIGENCE TOOLS

The authors declare that no artificial intelligence tools were used in the preparation, writing, data analysis, or review of this manuscript.

FUNDING

Not applicable.

DATA AVAILABILITY STATEMENT

Data will be provided upon request.

AUTHOR CONTRIBUTIONS

Conceptualization: Cunha FM, Duarte FB. **Investigation:** Cunha FM, Gurgel LA, Castelo LF, Freire NCB, Leitão JPV, Araujo BSGSP, Barroso KDN, Oliveira GM, Rocha MLFC, Vasconcelos ETMFS. **Methodology:** Cunha FM, Duarte FB. **Formal Analysis:** Cunha FM, Mota Segundo HA. **Data Curation:** Cunha FM, Gurgel LA, Castelo LF, Freire NCB, Leitão JPV, Araujo BSGSP, Barroso KDN, Oliveira GM, Rocha MLFC, Vasconcelos ETMFS. **Project Administration:** Cunha FM. **Writing:** Cunha FM. **Funding Acquisition:** Not applicable. **Supervision:** Duarte FB. **Final Approval:** Cunha FM.

ACKNOWLEDEGMENTS

Nothing to declare.

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