



## Research Letter to Editor

# Prospective comparison between geriatric assessment and clinical evaluation in 200 newly diagnosed older adults with multiple myeloma

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## 1. Introduction

Impressive therapeutic progress has been obtained in multiple myeloma (MM) due to the introduction of proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies, and, more recently, T-cell redirecting therapies such as CAR T-cells and bispecific antibodies [1]. MM is primarily a disease of the older patient with a median age of

70 years and around one third of patients older than 75 years at time of diagnosis [2]. Ageing is associated with comorbidities and frailty. Frail and older patients with MM have an increased risk for treatment-related side effects and benefit from dose-reduced or less dose-dense regimens [3].

Geriatric assessment (GA), part of comprehensive geriatric assessment (CGA) process, is the gold standard for frailty evaluation and

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includes assessment of the functional status, comorbidities, nutrition, and geriatric symptoms in addition to evaluation of the cognitive and mental status and symptoms like fatigue [4]. Since GA is time consuming and not required for all older patients, simplified geriatric screening tools like the G8 have been widely adopted [5]. G8 registers age, food intake, weight loss over the last three months, body mass index (BMI), mobility, neuropsychological conditions, number of prescription drugs, and how patients consider their health status [6].

Specific disease-oriented geriatric screening scores have also been developed. In 2014, the International Myeloma Working Group (IMWG) published a frailty scoring system based on age, comorbidities, physical and cognitive functioning that could predict mortality and the risk of treatment toxicity in older adults with MM [7]. In 2021, a simplified IMWG score was introduced that is less time consuming but also less sensitive [8] for detecting geriatric problems compared to the original IMWG score. Despite the availability of several geriatric and frailty scoring systems for MM, they are not widely adopted; many physicians still rely on their clinical assessment to judge a patient as fit or frail and to decide if treatment can be given at full or reduced dose.

## 2. Methods

In this non-interventional, single-arm, multicenter observational study, clinical assessment (CA) and geriatric screening by G8 (followed by geriatric assessment [GA] if  $G8 \leq 14$ ) were independently performed in 200 newly diagnosed older ( $\geq 70$  years) patients with MM. The study was approved by Ethics Committee Research UZ / KU Leuven and by the Ethics Committee of each participating hospital. The primary study endpoint was to compare CA with G8 (followed by GA and IMWG if  $G8 \leq 14$ ) before treatment initiation. The secondary endpoint was to describe the evolution of frailty/fitness after three months of treatment and at time of relapse if the latter occurred within one year of treatment.

CA was performed by the treating physician whereas G8, GA, and IMWG scoring were independently done by a trained nurse or other health care professional within 48 h of the CA. Results obtained by G8, GA and IMWG were communicated to the treating physician before treatment initiation. We registered if, and to what extent, the results influenced the initial therapeutic decision of the treating physician. After three months of treatment and at relapse CA and G8, GA and IMWG were repeated according to the same protocol as at time of diagnosis.

Descriptive statistics were used for patient characteristics. Group comparisons were performed by the Fisher exact test for categorical variables or Mann-Whitney *U* test or independent *t*-test for continuous or ordinal variables. All tests were performed at a two-sided 5% significance level. Calculations were done using SAS software (version 9.4 of the SAS System for Windows).

## 3. Results

Between April 2017 and October 2019 200 patients were enrolled from 20 Belgian hematological sites. No prior anti-myeloma treatment was allowed before enrollment except for local radiotherapy or a short course of maximum four days of high-dose dexamethasone. The patient data flow is described in Supplementary Fig. 1. Median age at time of enrollment was 79y (range: 70-96y) with 29% of patients aged between 75 and 79y, 28.5% between 80 and 84y, and 17% 85y or older. Patient and clinical characteristics are described in Supplementary Table 1.

At baseline, 113 (56.5%) patients were clinically assessed (CA) as fit and 87 (43.5%) as frail by their treating physicians. All patients also underwent G8 screening at baseline. The result of the G8 screening tool is a value ranging from 0 to 17. In total, 62 (31%) patients scored  $\geq 14/17$ , suggesting absence of a geriatric risk profile (G8 fit), whereas 138 (69%) patients scored  $\leq 14/17$ , indicating the presence of a geriatric risk profile (G8 frail); for those patients GA was subsequently performed. Sixty-two patients scored fit by CA, but frail by G8 (CA fit/G8 frail); 11

**Table 1**

Comparison of G8 score between patient groups CA FIT/G8 FRAIL versus CA FIT/G8 FIT.

| Variable                                        | Statistic | CA FIT/G8<br>FRAIL | CA FIT/G8<br>FIT | P-value |
|-------------------------------------------------|-----------|--------------------|------------------|---------|
|                                                 |           | (N = 62)           | (N = 51)         |         |
| Food intake                                     |           |                    |                  |         |
| Severe decrease in food intake                  | n/N (%)   | 5/62 (8.1%)        | 0/51 (0.0%)      | <0.001  |
| Moderate decrease in food intake                | n/N (%)   | 24/62 (38.7%)      | 1/51 (2.0%)      |         |
| No decrease in food intake                      | n/N (%)   | 33/62 (53.2%)      | 50 (98.0%)       |         |
| Weight loss                                     |           |                    |                  |         |
| Weight loss >3 kg                               | n/N (%)   | 19/62 (30.7%)      | 0/51 (0.0%)      | <0.001  |
| Does not know                                   | n/N (%)   | 1/62 (1.6%)        | 0/51 (0.0%)      |         |
| Weight loss between 1 and 3 kg                  | n/N (%)   | 13/62 (21.0%)      | 6/51 (11.8%)     |         |
| No weight loss                                  | n/N (%)   | 29/62 (46.8%)      | 45/51 (88.2%)    |         |
| Mobility                                        |           |                    |                  |         |
| Bed or chair bound                              | n/N (%)   | 2/62 (3.2%)        | 0/51 (0.0%)      | 0.009   |
| Able to go out of bed/chair but does not go out | n/N (%)   | 7/62 (11.3%)       | 0/51 (0.0%)      |         |
| Goes out                                        | n/N (%)   | 53/62 (85.5%)      | 51/51 (100.0%)   |         |
| Neuropsychological problems                     |           |                    |                  |         |
| Severe dementia or depression                   | n/N (%)   | 2/62 (3.2%)        | 0/51 (0.0%)      | 0.17    |
| Mild dementia or depression                     | n/N (%)   | 3/62 (4.8%)        | 0/51 (0.0%)      |         |
| No psychological problems                       | n/N (%)   | 57/62 (91.9%)      | 51/51 (100.0%)   |         |
| BMI                                             |           |                    |                  |         |
| BMI < 19                                        | n/N (%)   | 1/62 (1.6%)        | 0/51 (0.0%)      | 0.04    |
| 19 ≤ BMI < 21                                   | n/N (%)   | 7/62 (11.3%)       | 0/51 (0.0%)      |         |
| 21 ≤ BMI < 23                                   | n/N (%)   | 10/62 (16.1%)      | 10/51 (19.6%)    |         |
| BMI ≥ 23                                        | n/N (%)   | 44/62 (71.0%)      | 41/51 (80.4%)    |         |
| Drugs                                           |           |                    |                  |         |
| Yes                                             | n/N (%)   | 48/62 (77.4%)      | 20/51 (39.2%)    | <0.001  |
| No                                              | n/N (%)   | 14/62 (22.6%)      | 31/51 (60.8%)    |         |
| Health status                                   |           |                    |                  |         |
| Not as good                                     | n/N (%)   | 18/62 (29.0%)      | 1/51 (2.0%)      | <0.001  |
| Does not know                                   | n/N (%)   | 9/62 (14.5%)       | 2/51 (3.9%)      |         |
| As good                                         | n/N (%)   | 23/62 (37.1%)      | 21/51 (41.2%)    |         |
| Better                                          | n/N (%)   | 12/62 (19.4%)      | 27/51 (52.9%)    |         |
| Age                                             |           |                    |                  |         |
| >85 years                                       | n/N (%)   | 10/62 (16.1%)      | 1/51 (2.0%)      | <0.001  |
| 80–85 years                                     | n/N (%)   | 22/62 (35.5%)      | 8/51 (15.7%)     |         |
| < 80 years                                      | n/N (%)   | 30/62 (48.4%)      | 42/51 (82.4%)    |         |

BMI, body mass index; CA, clinical assessment.

**Table 2**

Clinical assessment by physician and subdomains of geriatric assessment.

| Variable                          | Statistic    | CA FIT/G8 FRAIL | CA FRAIL/G8 FRAIL | P-value |
|-----------------------------------|--------------|-----------------|-------------------|---------|
| ADL                               |              |                 |                   |         |
| Independent                       | n/N (%)      | 39/62 (62.9%)   | 23/76 (30.3%)     | <0.001  |
| Dependent                         | n/N (%)      | 23/62 (37.1%)   | 53/76 (69.7%)     |         |
| IADL                              |              |                 |                   |         |
| Independent                       | n/N (%)      | 35/62 (56.5%)   | 20/76 (26.3%)     | <0.001  |
| Dependent                         | n/N (%)      | 27/62 (43.6%)   | 56/76 (73.7%)     |         |
| Fall                              |              |                 |                   |         |
| Yes                               | n/N (%)      | 17/62 (27.4%)   | 35/76 (46.1%)     | 0.03    |
| No                                | n/N (%)      | 45/62 (72.6%)   | 41/76 (54.0%)     |         |
| Pain score (0–10)                 | N            | 61              | 75                | 0.03    |
|                                   | Mean (Std)   | 3.49 (3.02)     | 4.72 (3.20)       |         |
|                                   | Median (IQR) | 3 (0.00; 6.00)  | 5 (2.00; 8.00)    |         |
|                                   | Range        | (0.00; 9.00)    | (0.00; 10.00)     |         |
| Fatigue score (0–10)              | N            | 61              | 75                | <0.001  |
|                                   | Mean (Std)   | 4.07 (2.57)     | 5.73 (2.71)       |         |
|                                   | Median (IQR) | 5 (2.00; 6.00)  | 6 (5.00; 8.00)    |         |
|                                   | Range        | (0.00; 9.00)    | (0.00; 10.00)     |         |
| Overall quality of life (0–7)     | N            | 61              | 74                | <0.001  |
|                                   | Mean (Std)   | 4.66 (1.25)     | 3.78 (1.46)       |         |
|                                   | Median (IQR) | 5 (4.00; 5.00)  | 4 (3.00; 5.00)    |         |
|                                   | Range        | (1.00; 7.00)    | (1.00; 7.00)      |         |
| MMSE                              |              |                 |                   |         |
| Normal                            | n/N (%)      | 55/60 (91.7%)   | 52/75 (69.3%)     | 0.004   |
| Mild cognitive impairment         | n/N (%)      | 4/60 (6.7%)     | 14/75 (18.7%)     |         |
| Severe cognitive impairment       | n/N (%)      | 1/60 (1.7%)     | 9/75 (12.0%)      |         |
| GDS-15                            |              |                 |                   |         |
| No depression                     | n/N (%)      | 43/60 (71.7%)   | 31/72 (43.1%)     | 0.001   |
| Risk for depression               | n/N (%)      | 17/60 (28.3%)   | 41/72 (56.9%)     |         |
| MNA-SF                            |              |                 |                   |         |
| No risk/normal nutritional status | n/N (%)      | 23/62 (37.1%)   | 12/75 (16.0%)     | 0.006   |
| Risk of malnutrition              | n/N (%)      | 39/62 (62.9%)   | 63/75 (84.0%)     |         |
| ECOG-PS (0–5)                     | N            | 60              | 76                | <0.001  |
|                                   | Mean (Std)   | 1.05 (0.832)    | 1.93 (1.100)      |         |
|                                   | Median (IQR) | 1 (1.00; 1.00)  | 2 (1.00; 3.00)    |         |
|                                   | Range        | (0.00; 4.00)    | (0.00; 4.00)      |         |
| Polypharmacy                      |              |                 |                   |         |
| No polypharmacy                   | n/N (%)      | 18/62 (29.0%)   | 23/76 (30.3%)     | 1.000   |
| Polypharmacy                      | n/N (%)      | 44/62 (71.0%)   | 53/76 (69.7%)     |         |
| CCI                               |              |                 |                   |         |
| Score 0                           | n/N (%)      | 21/62 (33.9%)   | 25/76 (32.9%)     | 0.93    |
| Score 1                           | n/N (%)      | 12/62 (19.4%)   | 17/76 (22.4%)     |         |
| Score ≥ 2                         | n/N (%)      | 29/62 (46.8%)   | 34/76 (44.7%)     |         |
| IMWG score                        |              |                 |                   |         |
| Fit                               | n/N (%)      | 8/62 (12.9%)    | 3/76 (4.0%)       | <0.001  |
| Intermediate-fitness              | n/N (%)      | 19/62 (30.7%)   | 7/76 (9.2%)       |         |
| Frail                             | n/N (%)      | 35/62 (56.5%)   | 66/76 (86.8%)     |         |

Abbreviations: CA, clinical assessment; ADL, activities of daily living; IADL, instrumental activities of daily living; MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale; MNA-SF, Mini Nutritional Assessment – short form; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; CCI, Charlson comorbidity index; IQR, interquartile range; Std, standard deviation.

patients scored frail by CA and fit by G8 (CA frail/G8 fit); 51 patients scored fit both by CA and G8 (CA fit/G8 fit); and 76 patients scored frail both by CA and G8 (CA frail/G8 frail).

The comparative results for CA fit/G8 frail patients versus CA fit/G8 fit patients are shown in [Table 1](#). Compared with CA fit/G8 fit patients, CA fit/G8 frail patients were older ( $p < 0.001$ ), had reduced nutritional status ( $p < 0.001$ ), more recent weight loss ( $p < 0.001$ ), decreased mobility ( $p = 0.009$ ), lower BMI ( $p = 0.04$ ), received more polypharmacy ( $p < 0.001$ ), and considered their own health status as poorer ( $p < 0.001$ ). In 23% of the CA fit/G8 frail cohort, physicians chose a less

intensive treatment regimen based on the information from the G8 compared to only 8% in the fit/fit group ( $p = 0.04$ ). During the first 12 months of treatment, additional dose reductions were performed in 45% of the CA fit/G8 frail vs 33% of the CA fit-G8 fit cohort ( $p = ns$ ).

All 138 patients with a G8 score  $\leq 14$  underwent GA ([Table 2](#)). We compared the GA results in CA fit/G8 frail subgroup with patients who were scored frail by both CA and G8 (CA frail/G8 frail). CA fit/G8 frail patients were more independent on activities of daily living (ADL) (63% vs 30.3%;  $p < 0.001$ ) and instrumental activities of daily living (IADL) (56.5% vs 26.3%;  $p < 0.001$ ), had decreased risk of falling (27.4% vs

46.1%;  $p = 0.03$ ), decreased pain score (median 3 vs 5;  $p = 0.03$ ), less fatigue (median 5 vs 6;  $p < 0.001$ ), increased quality of life score (median 5 vs 4;  $p < 0.001$ ), less cognitive impairment (8.4% vs 30.7%;  $p = 0.004$ ), and a lower risk for depression (28.3% vs 56.9%;  $p = 0.001$ ) compared to the CA frail/G8 frail cohort.

IMWG frailty assessment was performed in all patients who underwent GA. According to IMWG score 12.9% were fit, 30.6% intermediate-fit, and 56.4% frail in the CA fit/G8 frail subgroup; corresponding values were 4.0%, 9.2%, and 86.8%, respectively, for the frail/frail population ( $p < 0.001$ ) (Table 2).

After three months of treatment, 157 patients underwent clinical reassessment, G8 ( $n = 150$ ) and GA ( $n = 108$ ) if G8 was  $\leq 14$ . Compared to their assessment at time of diagnosis, the vast majority of evaluable patients remained in the same category (fit or frail) by CA and by G8 (respectively 82% and 80%) and only a small proportion of frail patients were reclassified as fit by CA (5%) and by G8 (6%).

Since only 17 patients had progressed within one year, no comparative analysis was performed on this small cohort.

#### 4. Discussion

MM primarily affects older individuals who frequently require a more tailored treatment approach according to their frailty status. This study enrolled 200 ‘real-world’ older patients with MM, of whom several would not be eligible for interventional trials due to their strict inclusion and exclusion criteria. Our findings suggest that integrating G8 in routine clinical practice impacts treatment choice in a significant percentage of these patients, although this study was not designed to evaluate treatment modifications on patient outcome.

Thirty-one percent of our patient cohort was judged fit by the treating physician when the G8 score pointed towards frailty. These observations resulted in a pro-active reduction of treatment intensity in about one quarter of patients. The UK FiTNEss trial is currently evaluating this frailty-adjusted therapy approach in a randomized phase III trial [9]. Our data show the limitations of clinical assessment, even by experienced hematologists, compared to validated geriatric screening tools. Risk factors like malnutrition, weight loss, polypharmacy, and personal appreciation of a poor health status are not routinely assessed although we confirmed their role as important discriminators of geriatric risk assessment in myeloma. A recent study showed a higher risk of malnutrition, depression, and cognitive impairment in patients classified as fit by IMWG [10].

The use of geriatric screening tools like G8 can help to identify the subgroup of patients who benefit from a GA, to further tailor their myeloma treatment and to identify and manage underlying geriatric problems [11,12]. The IMWG frailty score remains a landmark for geriatric assessment in MM, but every effort to better characterize the intermediate-fit subgroup is of clinical value [13]. In that regard, 86% of patients who were scored unfit both by clinical assessment and G8 were scored frail by IMWG. Now that triplet – and even quadruplet – regimens [14] have shown unprecedented clinical efficacy in newly diagnosed older adults with MM, careful patient selection remains of utmost importance to avoid overtreatment and unnecessary toxicities. To this end, our study data further support the combined use of an initial screening by clinical assessment and a geriatric screening tool like G8 with more in-depth geriatric assessment in specific subgroups. Finally, although we failed to see any significant change in frailty status after three months of treatment, longer follow-up might be needed to truly assess if and how myeloma treatment and supportive care impact on the dynamics of frailty [15].

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#### Author contributions

**Jolien Raddoux:** Conceived and designed the analysis, Collected the data, Contributed data or analysis tools, Performed the analysis, Wrote the paper. **Cindy Kenis:** Conceived and designed the analysis, Collected the data, Contributed data or analysis tools, Performed the analysis, Other contribution. **Anneleen Vanhellemont:** Conceived and designed the analysis, Collected the data, Contributed data or analysis tools, Other contribution. **Stef Meers:** Conceived and designed the analysis, Contributed data or analysis tools. **Philippe Mineur:** Conceived and designed the analysis, Contributed data or analysis tools. **Marie-Christiane Vekemans:** Conceived and designed the analysis, Contributed data or analysis tools. **Ka Lung Wu:** Conceived and designed the analysis, Contributed data or analysis tools. **Jo Caers:** Conceived and designed the analysis, Contributed data or analysis tools. **Koen Van Eygen:** Conceived and designed the analysis, Contributed data or analysis tools. **Alain Kentos:** Conceived and designed the analysis, Contributed data or analysis tools. **Julien Depaus:** Conceived and designed the analysis, Contributed data or analysis tools. **Natalie Put:** Conceived and designed the analysis, Contributed data or analysis tools. **Ann Van De Velde:** Conceived and designed the analysis, Contributed data or analysis tools. **Géraldine Claes:** Conceived and designed the analysis, Contributed data or analysis tools. **Philip Vlummens:** Conceived and designed the analysis, Contributed data or analysis tools. **Vincent Maertens:** Conceived and designed the analysis, Contributed data or analysis tools. **Nathalie Meuleman:** Conceived and designed the analysis, Contributed data or analysis tools. **Isabelle Vande Broeck:** Conceived and designed the analysis, Contributed data or analysis tools. **Mélanie Vaes:** Conceived and designed the analysis, Contributed data or analysis tools. **Karel Fostier:** Conceived and designed the analysis, Contributed data or analysis tools. **Hilde Demuyneck:** Conceived and designed the analysis, Contributed data or analysis tools. **Michel Delforge:** Conceived and designed the analysis, Collected the data, Contributed data or analysis tools, Performed the analysis, Wrote the paper.

#### Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Prof. Dr. Michel Delforge reports financial support was provided by University Hospitals Leuven. Prof. Dr. Michel Delforge reports a relationship with University Hospitals Leuven that includes: consulting or advisory and speaking and lecture fees. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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#### Appendix A. Supplementary data

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