Association of IMWG frailty score with health-related quality of life profile of patients with relapsed refractory multiple myeloma in Italy and the UK: a GIMEMA, multicentre, cross-sectional study

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Summary

Background The clinical management of patients with relapsed or refractory multiple myeloma is challenging and there is a paucity of tools to help clinicians make more informed decisions for the most suitable treatment options. We aimed to investigate the clinical utility of the International Myeloma Working Group (IMWG) frailty score in the setting of relapsed or refractory multiple myeloma, by examining its ability to capture different patient-reported health-related quality of life profiles.

Methods We did a cross-sectional analysis of a prospective observational study of patients with relapsed or refractory multiple myeloma in Italy and the UK (30 hospitals across northern, central, and southern Italy, and one hospital in London, UK). Inclusion criteria were age 18 years or older and patients who had received at least one previous line of therapy and no more than five lines. Participants were excluded if they had a psychiatric disorder or major cognitive dysfunction, or any grade 3 or higher adverse event within 2 weeks before study entry. On study initiation, physicians had to assess frailty according to the IMWG criteria, which included the Charlson Comorbidity Index, the Katz Activity of Daily Living, and the Lawton Instrumental Activities of Daily Living. Patients were asked to complete patient-reported outcome measures, including the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core30 (EORTC QLQ-C30) and its validated multiple myeloma module (QLQ-MY20). A multivariable linear regression model was used to assess the mean differences in health-related quality of life scores between frailty groups to account for key potential confounding factors.

Findings Overall, between Nov 13, 2017, and Nov 15, 2021, 415 patients with relapsed or refractory multiple myeloma, with a median age of 69·8 years (IQR 62·8–75·2) were enrolled. The median time since diagnosis was 4·4 years (IQR 2·5–7·1) and most patients (351 [85%]) had received at least two previous lines of therapy. According to the IMWG frailty score, 200 (48%) were classified as fit, 112 (27%) were classified as intermediate-fit, and 103 (25%) patients were classified as frail. Each frailty group was associated with a distinct health-related quality of life profile, with most notable differences between fit and frail patients. The largest clinically meaningful adjusted differences between fit and frail patients by the EORTC QLQ-C30 questionnaire were observed for physical functioning (Δ=–19·0 [95% CI –25·6 to –12·5; p<0·0001), fatigue (Δ=16·7 [9·7 to 23·7]; p<0·0001), insomnia (Δ=13·4 [4·1 to 22·6]; p=0·0047), and dyspnoea (Δ=12·5 [4·6 to 20·4]; p=0·0021). The most prevalent clinically important symptom in the overall population was pain; however, its prevalence varied between IMWG frailty groups at 70·9% in frail patients, 55·9% in intermediate-fit patients, and 50·5% in fit patients.

Interpretation Our findings show the clinical utility of the IMWG frailty score in the setting of relapsed or refractory multiple myeloma, in helping to distinguish between groups of patients with distinct health-related quality of life profiles. Further research is needed to examine the value of patient-reported outcome data in improving assessment of frailty in the setting of relapsed or refractory multiple myeloma.

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See **Comment** page e579

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Introduction

Over the past few decades, research advances and the development of novel targeted therapies have contributed to markedly improved survival of patients with multiple myeloma.[1] However, the occurrence of relapse or disease progression is inevitable for most of these patients.[2] The clinical management of patients with relapsed or refractory multiple myeloma in routine practice is a

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Research in context

Evidence before this study

Although treatment decision making for patients with relapsed or refractory multiple myeloma is challenging, there is a paucity of tools to help clinicians make more informed decisions. In 2015, the International Myeloma Working Group (IMWG) developed a frailty score for patients with newly diagnosed multiple myeloma, which allows for the identification of three distinct groups of patients: fit, intermediate-fit, and frail patients. We investigated the clinical utility of the IMWG frailty score in the setting of relapsed or refractory multiple myeloma by investigating its ability to identify patients with distinct health-related quality of life profiles. We did a systematic literature search in PubMed using the following key words: "relapsed" OR "refractory" AND "myeloma" AND "frailty". The search was done on March 30, 2022. No restriction for language or article type was applied and the search yielded 30 records. However, no study assessed the health-related quality of life profile of patients with relapsed or refractory multiple myeloma by the IMWG frailty group categories.

Added value of this study

We found that the application of the IMWG frailty score in the real-life setting of relapsed or refractory multiple myeloma helps to identify groups of patients with distinct health-related quality of life and symptom profiles, with most notable differences between fit and frail patients. After adjusting for key potential confounders, clinically meaningful worse health-related quality of life scores for frail patients than fit patients were found across several domains of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core30. The largest differences between fit and frail patients were observed for physical functioning (Δ=–19·0; p<0·0001), fatigue (Δ=16·7; p<0·0001), insomnia (Δ=13·4; p=0·0047) and dyspnoea (Δ=12·5; p=0·0021). Pain was the most prevalent clinically important symptom in the overall population, but its prevalence varied across IMWG frailty groups at 71% in frail patients, 56% in intermediate-fit patients, and 51% in fit patients (p=0·0027).

Implications of all the available evidence

Although the IMWG frailty score was originally developed for patients with newly diagnosed multiple myeloma, our findings suggest its clinical utility in patients with relapsed or refractory multiple myeloma. For example, assessment of frailty by the IMWG frailty score could be important to identify the most vulnerable patients with relapsed or refractory multiple myeloma with poor health-related quality of life and high symptom burden, who can benefit most from supportive care interventions and for whom aggressive treatment options could be avoided. Future research is needed to understand the value of patient-reported outcome data in improving assessment of frailty in relapsed or refractory multiple myeloma, and to consider the development of a patient-centric frailty index.

major challenge.[3,4] A wide range of possible treatment options is available for these patients, and clinical decisions are further complicated by many host-related and disease-related factors.[5] Patients with relapsed or refractory multiple myeloma typically undergo a three-drug regimen until progression or intolerance, and are continuously exposed to therapy from the time of diagnosis, which has a negative effect on their health-related quality of life.[6]

Treatment choice for patients with multiple myeloma has traditionally focused on basic parameters such as chronological age, comorbidity, and performance status.[7] In most recent years, composite frailty indices have received increased attention for the management of patients with haematological malignancies to provide more personalised treatments.[8] However, there is a dearth of information on the ability of these indices, which typically do not include patient-reported outcomes, to reflect health-related quality of life and symptom burden as perceived by patients themselves.

In 2015, the International Myeloma Working Group (IMWG) developed a frailty score based on a large sample of patients with newly diagnosed multiple myeloma who were enrolled in three randomised controlled trials,[9] and this scoring system is currently considered the gold standard to assess frailty in the setting of newly diagnosed patients.[10] Computation of this score is based on patient age plus a geriatric assessment including three measures, the Charlson Comorbidity Index (CCI),[11] the Katz Activity of Daily Living (ADL),[12] and the Lawton Instrumental Activities of Daily Living (IADL),[13] and allows for the identification of three groups of patients (fit, intermediate-fit and frail patients) with distinct survival outcomes and risk for toxicity.[9] However, clinical tools available to assist clinicians in making more informed treatment decisions for patients with relapsed or refractory multiple myeloma are scarce. Assessment of frailty in this setting could be crucial to identify the most vulnerable patients for whom aggressive treatment options can be avoided.

The primary objective of this cross-sectional study was to assess the clinical utility of the IMWG frailty score in patients with relapsed or refractory multiple myeloma by examining its ability to capture distinct patient-reported health-related quality of life profiles. A secondary objective was to assess the prevalence of clinically important problems and symptoms by IMWG frailty groups.

Methods

Study design and participants

We did a cross-sectional analysis of baseline data of a prospective observational study done in Italy and the UK

in 30 hospitals across northern, central, and southern Italy, and in one hospital in London (UK). Eligibility criteria included a confirmed diagnosis of multiple myeloma in adult patients (age 18 years or older) that was classified as relapsed or refractory multiple myeloma according to IMWG criteria,[14] and having undergone at least one previous line of therapy. Other inclusion criteria were the availability of a patient-reported outcome assessment and of all the individual components of the geriatric assessment needed to calculate the IMWG frailty score. Exclusion criteria were having any kind of psychiatric disorder or major cognitive dysfunction, any grade 3 or higher adverse event within 2 weeks before study entry, and having received more than five lines of therapies. The research protocol was previously published[15] and amended in June, 2020, to include an additional cohort and the study is ongoing. The study was done in accordance with the Declaration of Helsinki. All patients provided written informed consent, and the protocol was approved by the Ethics Committees of each participating centre.

Procedures

The research protocol stipulated that all physicians had to perform a geriatric assessment of their patients, including the CCI,[11] the ADL,[12] and IADL,[13] before study entry. The frailty score (range, 0–5) was then computed by the coordinating Data Centre (GIMEMA) by combining the individual risk scores of these scales plus patient age, according to previously established IMWG criteria.[9] Patients were classified into three frailty groups: fit (score, 0), intermediate-fit (score, 1), and frail (score, ≥2), which were then used for the purpose of this analysis.

For patient-reported outcome assessment, all patients completed the validated European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core30 (EORTC QLQ-C30; version 3)[16] and its multiple myeloma module (QLQ-MY20)[17]. The EORTC QLQ-C30 is a generic cancer measure that includes five functional scales (physical, role, emotional, social, and cognitive), three symptoms (fatigue, nausea and vomiting, and pain), a global health status and quality of life scale, and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties). The financial difficulty item was excluded for the purpose of this analysis. The QLQ-MY20 addresses specific health-related quality of life issues relevant for patients with multiple myeloma and includes two scales on disease symptoms and side-effects of treatment, one functional scale on future perspective, and one single item on body image. The items were scaled and scored using the recommended EORTC procedures.[16,17] For both questionnaires, raw scores were transformed to a linear scale ranging from 0 to 100. A higher score represents a higher level of functioning and health status or quality of life or higher symptom severity (EORTC QLQ-C30). For the QLQ-MY20, a higher score in the body image and future perspective indicated better outcomes, while for disease symptoms and side-effects of treatment, higher scores indicated worse outcomes. These questionnaires have been frequently used in multiple myeloma research for patients with newly diagnosed multiple myeloma and patients with relapsed or refractory multiple myeloma.[6,18]

Outcomes

The primary objective of this cross-sectional study was to assess the clinical utility of the IMWG frailty score in patients with relapsed or refractory multiple myeloma by examining its ability to capture distinct patient-reported health-related quality of life profiles, as measured by the mean scores of the scales from the EORTC QLQ-C30 and QLQ-MY20 questionnaires. A secondary objective was to assess the prevalence of clinically important problems and symptoms by IMWG frailty groups, as measured by the corresponding proportions in the EORTC QLQ-C30 scales. All outcomes were assessed for patients with available data.

Statistical analysis

We classified patients with relapsed or refractory multiple myeloma into three frailty groups according to the IMWG frailty score: fit, intermediate-fit, and frail.[9] We summarised the main characteristics of patients, overall and by frailty groups, using descriptive statistics. In cases of non-normal distribution, the median (with absolute range or IQR) was used instead of the mean and standard deviation. The Shapiro-Wilk test was used to assess normality. For descriptive purposes, we computed means and SDs of scores from the EORTC QLQ-C30 and QLQ-MY20 questionnaires, which we calculated overall and by IMWG frailty groups. Comparisons among groups were made with the χ^2 test in cases of categorical variables or *t* test and Mann-Whitney test in case of continuous variables.

A multivariable linear regression model was used (for each scale) to assess the mean differences in health-related quality of life scores between frailty groups to account for key potential confounding factors. In the regression model, the linearity assumption was checked by plotting the residuals against the fitted values and the homogeneity of variance was checked by examining the spread-location plot. The multivariable model included two dummies for the frailty group (ie, frail *vs* fit and intermediate-fit *vs* fit) and the following adjustment variables: sex, education (at least university degree *vs* lower education), years since diagnosis (continuous), type of multiple myeloma at diagnosis (secretory *vs* other), total number of therapy lines received before study entry (1 *vs* >1), having received any transplant before study entry (yes *vs* no), and best response to previous therapy as defined according to IMWG response criteria[19] (coded as complete/stringent complete response *vs* worse response and very good partial response *vs* worse response). The

	Overall (n=415)	IMWG frailty group		
		Fit (n=200)	Intermediate-fit (n=112)	Frail (n=103)
Sex				
Male	232 (56%)	110 (55%)	65 (58%)	57 (55%)
Female	183 (44%)	90 (45%)	47 (42%)	46 (45%)
Age at study entry, years				
Median (IQR)	69·8 (62·8–75·2)	65·7 (59·7–71·6)	70 (65·6–75·7)	77·7 (73·4–81·8)
Time since diagnosis, years				
Median (IQR)	4·4 (2·5–7·1)	4·7 (2·9–8·0)	4·3 (2·5–6·7)	4·2 (2·1–7·7)
Living arrangements				
Living alone	66/407 (16%)	29/195 (15%)	14/110 (13%)	23/102 (23%)
Living with others	341/407 (84%)	166/195 (85%)	96/110 (87%)	79/102 (77%)
Unknown	8/415 (2%)	5/200 (3%)	2/112 (2%)	1/103 (<1%)
ECOG Performance status				
0	186/413 (45%)	116/199 (58%)	49/111 (44%)	21 (20%)
1	183/413 (44%)	70/199 (35%)	58/111 (52%)	55 (53%)
≥2	44/413 (11%)	13/199(7%)	4/111 (4%)	27 (26%)
Unknown	2/415 (<1%)	1/200 (1%)	1/112 (<1%)	0
Comorbidities at study entry				
≥1	167 (40%)	38 (19%)	66 (59%)	63 (61%)
Disease status				
Relapsed disease	236/414 (57%)	124 (62%)	62/111 (56%)	50 (49%)
Relapsed and refractory disease	132/414 (32%)	58 (29%)	35/111 (32%)	39 (38%)
Primary refractory disease	46/414 (11%)	18 (9%)	14/111 (13%)	14 (14%)
Unknown	1/415 (<1%)	0	1/112 (<1%)	0
Ongoing therapy at study entry				
Ongoing therapy	299/414 (72%)	140 (70%)	86/111 (78%)	73 (71%)
No ongoing therapy	115/414 (28%)	60 (30%)	25/111 (23%)	30 (29%)
Unknown	1/415 (<1%)	0	1/112 (<1%)	0
Anaemia*				
Yes	130/414 (31%)	48 (24%)	36/111 (32%)	46 (45%)
No	284/414 (69%)	152 (76%)	75/111 (68%)	57 (55%)
Unknown	1/415 (<1%)	0	1/112 (<1%)	0
Best response to previous therapies				
Complete response or stringent complete response	135 (33%)	66 (33%)	43 (38%)	26 (25%)
Very good partial response	145 (35%)	80 (40%)	38 (34%)	27 (26%)
Stable disease	133 (32%)	53 (27%)	31 (28%)	49 (48%)
Other	2 (<1%)	1 (<1%)	0	1 (1%)
Previous transplant				
Yes	200 (48%)	135 (68%)	46 (41%)	19 (18%)
No	215 (52%)	65 (33%)	66 (59%)	84 (82%)
Previous therapy-related adverse events of grade ≥3				
Yes	105/413 (25%)	47/199 (24%)	31 (28%)	27/102 (26%)
No	308/413 (75%)	152/199 (76%)	81 (72%)	75/102 (74%)
Unknown	2/415 (<1%)	1/200 (1%)	0	1/103 (1%)

Data are n (%) or n/N (%), unless otherwise specified. ECOG=Eastern Cooperative Oncology Group. IMWG=International Myeloma Working Group. *Defined as a haemoglobin value of >2 g/dL below the lower limit of normal, or a haemoglobin value <10 g/dL.

Table 1: **Characteristics of patients with relapsed or refractory multiple myeloma, overall and by IMWG frailty group**

	Fit (n=200)	Intermediate-fit (n=112)	Frail (n=103)
EORTC QLQ-C30			
Functional scales and global health status and quality of life			
Physical functioning	71·17 (21·33)	64·75 (26·05)	48·95 (26·95)
Role functioning	69·43 (31·01)	58·93 (35·72)	51·29 (33·31)
Emotional functioning	73·93 (22·13)	72·67 (22·56)	62·94 (25·93)
Cognitive functioning	82·75 (21·03)	79·43 (24·10)	73·62 (26·25)
Social functioning	76·50 (25·13)	71·62 (29·52)	69·42 (29·62)
Global health status and quality of life	61·17 (19·71)	58·33 (21·35)	53·56 (22·43)
Symptoms			
Fatigue	35·94 (22·85)	40·54 (25·63)	54·69 (26·80)
Nausea or vomiting	6·42 (12·80)	9·76 (19·00)	9·71 (18·75)
Pain	27·42 (26·04)	33·18 (30·19)	43·37 (31·60)
Dyspnoea	20·60 (24·27)	27·63 (29·77)	33·33 (31·47)
Insomnia	32·50 (30·23)	33·93 (33·02)	43·23 (35·76)
Appetite loss	10·33 (20·16)	18·02 (25·34)	27·18 (30·87)
Constipation	19·33 (28·23)	23·42 (27·56)	31·39 (38·44)
Diarrhoea	13·83 (22·24)	16·82 (24·97)	16·67 (28·05)
EORTC QLQ-MY20			
Future perspective	59·33 (28·17)	57·61 (29·11)	53·58 (30·77)
Body image	76·05 (30·91)	77·26 (31·26)	79·33 (30·99)
Disease symptoms	22·96 (19·83)	25·57 (22·50)	34·69 (25·91)
Side-effects of treatment	18·07 (13·57)	21·73 (15·56)	23·52 (16·29)

Data are mean (SD). EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core30. QLQ-MY20=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire multiple myeloma module. IMWG=International Myeloma Working Group.

Table 2: **Health-related quality of life profile according to the EORTC QLQ-C30 and QLQ-MY20 of patients with relapsed or refractory multiple myeloma, by IMWG frailty group**

following variables at study entry were also considered in the multivariable model: ongoing treatment (yes *vs* no), myeloma status (refractory *vs* relapsed only), anaemia (yes *vs* no), disease-associated organ dysfunction (yes *vs* no), and bone lesions (yes *vs* no), as defined by the IMWG criteria.[14]

The clinical significance of between-group differences in mean scores of health-related quality of life questionnaires was evaluated according to previously defined, scale-specific, minimal important differences for the EORTC QLQ-C30[20] and for the QLQ-MY20.[21] We also examined the prevalence of clinically important problems and symptoms at the patient level by frailty group using recently developed criteria for the use of the EORTC QLQ-C30 in routine clinical practice.[22] This prevalence reflects the number of patients indicating limitations of everyday life, worrying, or need for help or care related to a specific symptom or functional impairment. These three criteria for clinical importance have been identified in a previous mixed methods study with health professionals and cancer patients.[23]

All statistical tests were two-sided with a nominal α=0·05, and there was no adjustment for multiple testing due to the exploratory nature of the study. All analyses were done on patients with available data, with SAS software (version 4). The study is registered at ClinicalTrials.gov, NCT03190525.

Role of the funding source

The Fondazione GIMEMA Franco Mandelli Onlus was involved in all steps of the study process, from study design to the final decision to submit the Article. Amgen had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication.

Results

Between Nov 13, 2017, and Nov 15, 2021, 415 patients with relapsed or refractory multiple myeloma were consecutively enrolled from 31 centres (30 in Italy and one in the UK). According to the IMWG frailty score, 200 (48%) participants were categorised as fit, 112 (27%) were categorised as intermediate-fit, and 103 (25%) were categorised as frail.

The median age of the overall study population was 69·8 years (IQR 62·8–75·2), and 232 (56%) were male and 183 (44%) were female (table 1). The median time since diagnosis was 4·4 years (IQR 2·5–7·1), and 351 (85%) patients had received at least two previous lines of therapy. 189 (46%) patients received two previous lines of therapy, 91 (22%) patients received three lines, 47 (11%) received four lines, and 24 (6%) had already received five lines. The association between previous lines of therapy and proportion of patients classified in the three frailty group categories was also examined. We did not observe a significant difference in the proportion of patients within each frailty group who had received 1–2 versus 3–5 lines of therapy (appendix p 2).

At study entry, 183 (46%) of 400 patients had bone lesions, and only 29 (7%) of 415 patients were enrolled in investigational drug trials. Further details on patient characteristics, overall and by IMWG frailty group, are presented in table 1.

The health-related quality of life profile of patients by the EORTC QLQ-C30 differed by frailty group category (table 2). Fit patients reported higher scores on all functional scales than both intermediate-fit and frail patients. Similarly, higher mean scores across all functional scales were observed for intermediate-fit patients than for the frail group. A similar trend was observed regarding symptoms, with frail patients reporting higher symptom severity across all symptom domains of the EORTC QLQ-C30 than fit patients (table 2). Disease-specific health-related quality of life measured by the QLQ-MY20 also indicated better outcomes for patients classified as fit compared with intermediate-fit and frail patients, except for the body image subscale. Further details on observed mean scores of the EORTC QLQ-C30 and the QLQ-MY20 of patients by IMWG frailty group categories are reported in table 2.

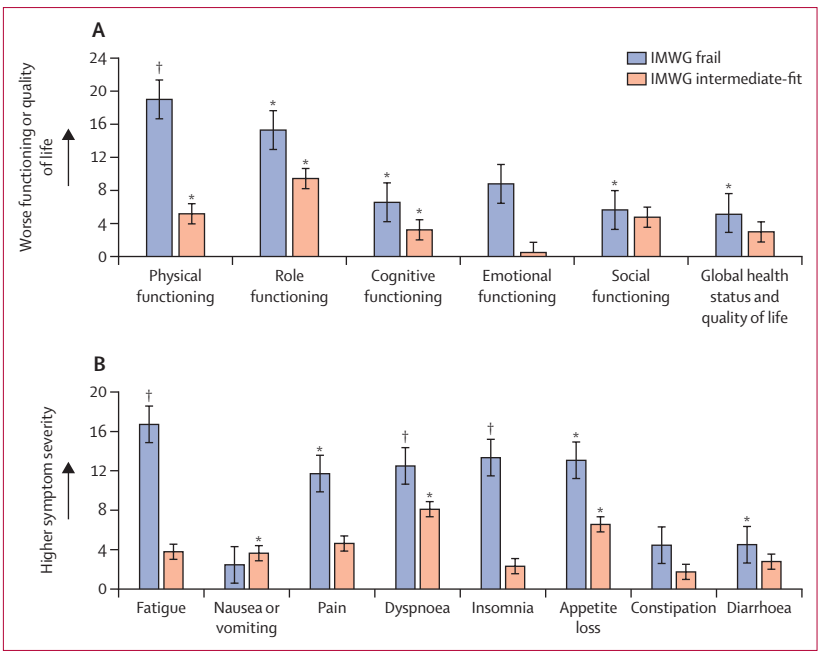

Figure 1: **Adjusted mean differences in EORTC QLQ-C30 scales of frail and intermediate-fit patients compared with fit patients with relapsed or refractory multiple myeloma, according to the IMWG frailty score**
Adjusted mean differences in functional scales and global health status and quality of life scale (A) and symptom scales (B) from the EORTC QLQ-C30 questionnaire, between frail and intermediate-fit patients and fit patients, according to the IMWG frailty score. Means were adjusted by a multivariable linear regression model including sex, education, years since diagnosis, type of multiple myeloma at diagnosis, total number of therapy lines received up to study entry, having received any transplant before study entry, best response to previous therapy defined according to IMWG response criteria, any ongoing treatment at study entry, myeloma status, anaemia, disease-associated organ dysfunction, and bone lesions at study entry, as defined by the IMWG criteria. For descriptive purposes, the scores of the functioning scales were multiplied by –1. Error bars indicate the standard error associated with the estimate. EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core30. IMWG=International Myeloma Working Group. *Small clinically relevant difference. †Medium clinically relevant difference.

See **Online** for appendix

After adjusting for key potential confounders and confirming of linear assumption and homogeneity of variance of residuals (no pattern in the residuals *vs* fitted plot and horizontal line with equally spread points was observed in the spread-location plot), clinically meaningful worse scores for frail patients than fit patients were found across 11 of 14 health-related quality of life domains investigated by the EORTC QLQ-C30. The largest clinically meaningful differences between fit and frail patients were observed for physical functioning (Δ=–19·0 [95% CI –25·6 to –12·5; p<0·0001), fatigue (Δ=16·7 [9·7 to 23·7]; p<0·0001), insomnia (Δ=13·4 [4·1 to 22·6]; p=0·0047), and dyspnoea (Δ=12·5 [4·6 to 20·4]; p=0·0021). Clinically meaningful worse scores for intermediate-fit patients than fit patients were also observed for physical functioning (Δ=–5·2 [95% CI –11·1 to 0·8]; p=0·087), role functioning (Δ=–9·4 [–17·8 to –1·1]; p=0·027), cognitive functioning (Δ=–3·2 [–9·2 to 2·7] p=0·285), nausea or vomiting (Δ=3·6

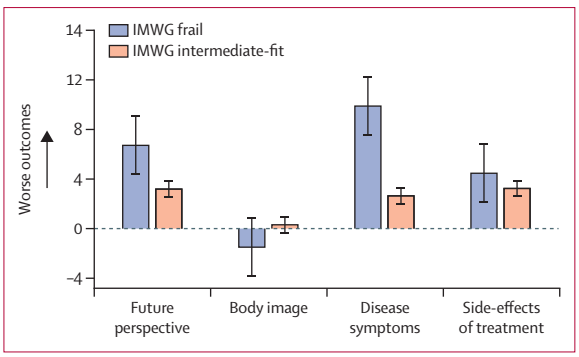

Figure 2: **Adjusted mean differences in EORTC QLQ-MY20 scales of frail and intermediate-fit patients compared with fit patients with relapsed or refractory multiple myeloma, according to the IMWG frailty score**
Differences in adjusted mean scores of the scales from the EORTC QLQ-MY20 questionnaire, between frail and intermediate-fit patients and fit patients, according to the IMWG frailty score. Means were adjusted by a multivariable linear regression model including sex, education, years since diagnosis, type of multiple myeloma at diagnosis, total number of therapy lines received up to study entry, having received any transplant before study entry, best response to previous therapy defined according to IMWG response criteria, any ongoing treatment at study entry, myeloma status, anaemia, disease-associated organ dysfunction, and bone lesions at study entry as defined by the IMWG criteria. For descriptive purposes, the scores of the scales "future perspective" and "body image" were multiplied by −1. Error bars indicate the standard error associated with the estimate. EORTC QLQ-MY20=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire multiple myeloma module. IMWG=International Myeloma Working Group.

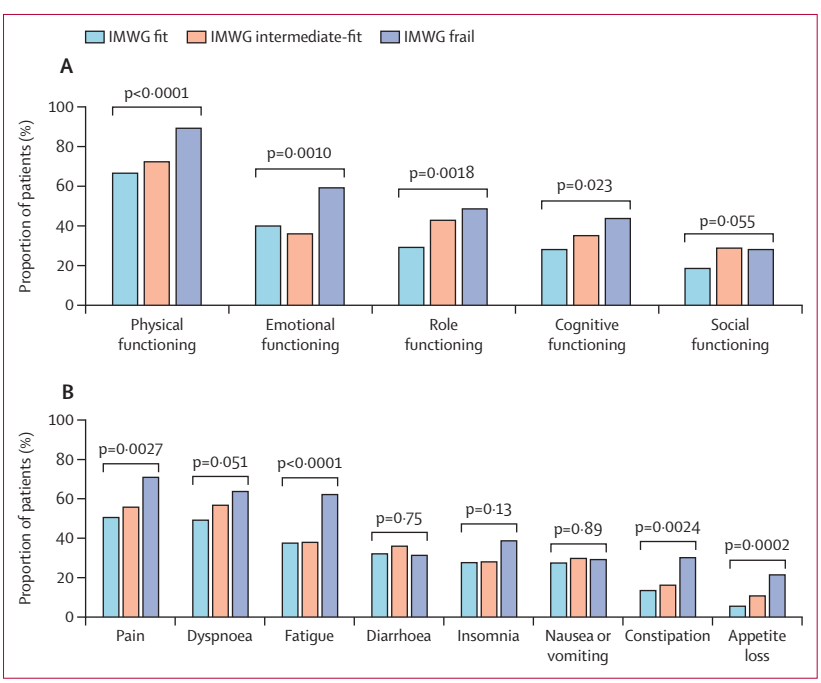

Figure 3: **Prevalence of patient-reported clinically important problems (A) and symptoms (B) from EORTC QLQ-C30 of patients with relapsed or refractory multiple myeloma, by IMWG frailty groups**
EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core30. IMWG=International Myeloma Working Group.

[−0·6 to 7·9], p=0·091), dyspnoea (Δ=8·1 [0·9 to 15·3]; p=0·027), and appetite loss (Δ=6·6 [0·2 to 12·9]; p=0·043; figure 1). No clinically meaningful differences were observed for any of the scales of the QLQ-MY20 questionnaire by frailty group (figure 2).

The prevalence of clinically important problems and symptoms varied by frailty group, with frail patients typically reporting a higher prevalence than intermediate-fit and fit patients (figure 3). Physical functioning was the most frequent clinically important problem found in the overall population (73·7% [95% CI 69·5–77·9]), with a higher prevalence in frail patients (89·3% [81·9–93·9]) than in intermediate-fit (72·3% [63·4–79·7]) and fit patients (66·5% [60·2–73·1]; p<0·0001). Pain was the most prevalent clinically important symptom in the overall population (57% [95% CI 52·3–61·8]), and its prevalence was 70·9% (62·5–79·6) in frail patients, 55·9% (47·0–65·0) in intermediate-fit patients, and 50·5% (44·1–57·8) in fit patients (p=0·0027). The three largest differences in the prevalence of symptoms between frail and fit patients were observed for fatigue (24·6 percentage points), pain (20·4 percentage points), and constipation (16·6 percentage points; figure 3). Details on prevalence by frailty group are reported in the appendix (p 3).

Discussion

We found that the application of the IMWG frailty score in the real-life setting of relapsed or refractory multiple myeloma might help to identify groups of patients with distinct health-related quality of life and symptom profiles, with most notable differences between fit and frail patients. Although this index was originally developed for patients with newly diagnosed multiple myeloma, our findings suggest its clinical utility in patients with relapsed or refractory multiple myeloma, for whom decisions regarding the type and intensity of possible treatments are challenging.

Assessment of frailty by the IMWG frailty score could be crucial—for example, to identify the most vulnerable patients with relapsed or refractory multiple myeloma with debilitating health conditions and high symptom burden, who can benefit most from supportive care interventions and for whom aggressive treatment options could be avoided. Our adjusted comparisons indicated that frail patients reported substantially worse symptomatology for fatigue, pain, dyspnoea, insomnia, appetite loss, and diarrhoea than those classified as fit. Clinically meaningful worse differences in frail patients than fit patients were also observed for key functional outcomes including physical, social, role, and cognitive functioning. Inspection of the prevalence of clinically important problems and symptoms of the three frailty groups also supported the utility of the IMWG index in detecting frequently documented problems of patients with relapsed or refractory multiple myeloma, such as pain, fatigue, and functional limitations.[6,24] For example, the percentages of patients with relapsed or refractory multiple myeloma reporting clinically important pain ranged from 50·5% in patients classified as fit to 70·9% in patients classified as frail.

Differences in patient-reported outcome scales of the EORTC QLQ-MY20 between the three IMWG frailty groups were mostly in the expected directions, but were not clinically meaningful. Although these data suggest that further research is required, we speculate that this measure might not fully capture key health-related quality of life and symptom aspects most relevant to patients with multiple myeloma treated with modern therapies. Remarkable advances have been made in the treatment of multiple myeloma since the publication of this measure in 2007[17] and research efforts are under way to update this patient-reported outcome questionnaire.[25]

Computation of the IMWG frailty score is based on age, comorbidity, and the assessment of functional status by use of the ADL and IADL scales.[9] However, it does not include patient-reported outcome measures, which can more accurately capture the unique patient's viewpoint on the impact of disease and therapy.[26] There is now convincing evidence that patients' self-reported health status information captured via patient-reported outcome measures adds unique prognostic information for survival that goes beyond traditional clinical data or physician-reported information (eg, performance status). This finding has been replicated across several cancer populations with both solid and haematological malignancies,[27,28] and patient-reported outcome data have also been successfully integrated into established disease-risk classifications to improve their accuracy in predicting survival.[29,30] Therefore, an important question to be elucidated in further analyses is whether our baseline patient-reported outcome data could provide independent prognostic information for survival outcomes. Such evidence would lay the groundwork for the development of a patient-centric relapsed or refractory multiple myeloma frailty index, by integrating (or even replacing) individual components of the IMWG frailty score algorithm with patient-reported outcome information.

Another finding of our study was the unexpectedly large prevalence of patients classified as fit according to the IMWG frailty score. Compared with the validation study of this index in patients with newly diagnosed multiple myeloma, which categorised 39% of patients in the fit group,[9] we observed that 48% of our patients with relapsed or refractory multiple myeloma could be considered fit. However, our analysis did not reveal an association between these data and the number of previous lines of therapy. Considering the paucity of studies assessing frailty in patients with relapsed or refractory multiple myeloma, putting these data into a larger perspective is challenging. However, recent data by Murugappan and colleagues[31] are of interest. The authors assessed the prevalence of frailty based on the IMWG frailty score criteria in a population of patients with relapsed or refractory multiple myeloma included in clinical trials submitted to the US Food and Drug Administration and observed that most patients (54%) could be classified in the fit group. Although several explanations might be plausible, such as survivorship bias, we speculate that this relatively high proportion of fit patients with relapsed or refractory multiple myeloma might also be partly explained by previous evidence suggesting that symptoms are typically better controlled in patients with relapsed or refractory multiple myeloma than in patients with newly diagnosed multiple myeloma.[14,32,33]

Our study has limitations. We did not record the time spent with patients by clinicians to perform the IMWG frailty assessment at study entry, and this information could have provided additional valuable data. Furthermore, our findings are only applicable to patients who have received no more than five lines of therapy. Finally, the cross-sectional design limits confirmation of the directionality of the associations among frailty, health-related quality of life, and symptom burden.

Our study also has notable strengths. As an observational study done at multiple centres, our patient population reflects patients typically seen in real-life practice and more than 90% of our patients were not enrolled in investigational drug trials. Additionally, our comparative analysis of health-related quality of life profiles by frailty group was adjusted for key observed clinically relevant confounding factors. Finally, to the best of our knowledge, this is the first study documenting the relationship between frailty groups defined by the exact IMWG criteria (ie, computed according to all the individual components of the IMWG frailty score) and the health-related quality of life profile of patients with relapsed or refractory multiple myeloma.

In conclusion, our findings suggest that the IMWG frailty score is a helpful tool in the setting of relapsed or refractory multiple myeloma to distinguish patients with different health-related quality of life profiles and symptom burdens. Further research is needed to examine the value of patient-reported outcome data in improving assessment of frailty in the setting of this condition, and to consider the development of a patient-centric frailty index.

Contributors

FE, FC, MV, and MC conceived and designed the study. GG, MTP, PN, KC, EA, AT, AL, LP, CF, DP, GMR, MO, AR, CK, NC, AG, DD, and MC provided study materials and enrolled patients to the study. FE and FC collected and assembled all the data, and verified the underlying data. All authors were involved in data analysis and interpretation, writing of the manuscript, and final approval of the manuscript. All authors had full access to all the data in the study and accept responsibility for the decision to submit for publication.

Declaration of interests

AL has received honoraria from and served on the advisory boards for Janssen-Cilag, Bristol Myers Squibb, Amgen, Takeda, Oncopeptides, GlaxoSmithKline, Sanofi, and Karyopharm, outside of the submitted work. CF reports research support from Amgen and Celgene outside of the submitted work. EA is on the advisory boards and speaking bureaus for Amgen, BMS, Takeda, Sanofi, and Janssen outside of the submitted work. FE is a consultant and adviser for Amgen, AbbVie, Janssen, and Novartis and reports research support (to institution) from AbbVie and Novartis outside of the submitted work. FE also reports research support from Amgen (to institution) during the conduct of the study. GG is on the advisory boards for AbbVie, AstraZeneca, Beigene, Incyte, Janssen, and Roche; and on the speaking bureaus for Abbvie and Janssen outside of the submitted work. GMR reports honoraria from

AbbVie, AstraZeneca, Janssen, and Gilead and research support from Gilead outside of the submitted work. MC reports honoraria from Janssen, Celgene, Amgen, Bristol-Myers Squibb, Takeda, AbbVie, Sanofi, Pfizer, GSK, and Adaptive Biotechnologies, and is on the speaking bureaus for Janssen and Celgene outside of the submitted work. MO reports honoraria from and is an adviser for Amgen, AbbVie, BMS, Celgene, GSK, Janssen, Roche, Sanofi, and Takeda outside of the submitted work. MTP reports honoraria from Janssen-Cilag, Celgene-BMS, Amgen, Sanofi, GSK, Takeda; is on the advisory boards for Janssen-Cilag, Celgene-BMS, Amgen, Sanofi, GSK, Takeda, Roche, and Karyopharm; and reports support for attending meetings or travel from Janssen-Cilag, Celgene-BMS, Amgen, Sanofi, and Takeda outside of the submitted work. MV reports honoraria from Amgen, Incyte, Novartis, Dephaforum Srl, AbbVie, and AstraZeneca and is on the advisory board for Amgen outside of the submitted work. All other authors declare no competing interests.

Data sharing

The data presented in this study are available upon reasonable request. Qualified researchers can request access to anonymised patient data. Details on sharing criteria and processes for requesting access to data can be obtained from the corresponding author.

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