The Prevalence and Outcomes of Frail Older Adults in Interventional Clinical Trials in Multiple Myeloma: A Systematic Review

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Main Takeaways

1. Frailty assessments are **increasingly** incorporated in MM trials
2. Prospective and longitudinal frailty assessments are needed
3. Studies focusing on frail older adults are needed

Introduction

- Multiple myeloma (MM) is an incurable blood cancer of older adults
- Several frailty tools have been developed to assess for heterogeneity in aging in MM
- Tools like the IMWG frailty score are increasingly being incorporated into clinical trials
- There remains wide variation in the incorporation, selection, and usage of these tools in MM clinical trials

Research Goal

✓ To conduct a systematic review to examine the inclusion and impact of frailty on treatment outcomes in therapeutic MM trials

Objective

1. Report on the inclusion and prevalence of frailty in therapeutic MM trials
2. Evaluate overall outcomes among frail older adults in MM clinical trials

Methodology

Search Strategy

- Databases including clinicaltrial.gov and conference abstracts till April 5th 2022 were included
- Keywords for the search criteria included: "multiple myeloma" combined with "frailty" and/or "geriatric assessment"
- The following selection criteria were used for inclusion:
  - ✓ included an interventional evaluation of a therapeutic drug for MM
  - ✓ was a clinical trial
  - ✓ reported on frailty (frailty measures as any screening or comprehensive geriatric assessment tools which assessed ≥2 aging-associated domains)

Results

Figure 1: PRISMA Diagram

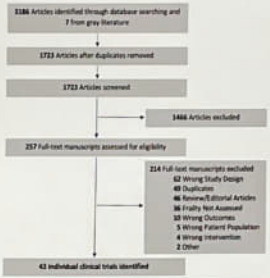


Table 1: Study Characteristics

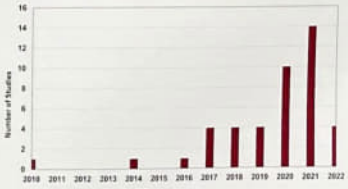
	N=43
MM Disease Phase	
Newly diagnosed	26 (60.4%)
Relapsed/Refractory	17 (39.5%)
Study Methodology	
Randomized controlled clinical trial	24 (55.8%)
Non- Randomized controlled clinical trial	19 (44.2%)
Clinical Trial Phase	
Phase I/II	20 (46.5%)
Phase III/IV	18 (41.9%)
Unknown	5 (11.6%)
Multicentre	
Yes	38 (88.3%)
No	5 (11.6%)
Geographic Region of Study	
Europe	20 (46.5%)
Global	11 (25.6%)
Asia	7 (16.3%)
United States	3 (7.0%)
Other	2 (4.6%)
Reported within last two years (2021, 2022)	18 (41.9%)
Reason for Frailty Evaluation*	
Subgroup analysis	31 (72.0%)
Study entry criteria	8 (18.6%)
Intervention based upon frailty	1 (2.3%)
Drug dosing	5 (11.6%)
Longitudinal assessment (>1 time point)	4 (9.3%)
Tools Utilized for Frailty Assessment*	
IMWG	20 (46.5%)
Simplified frailty score	16 (37.2%)
Other	12 (27.9%)
Frailty Categorization	
Three (fit-intermediate fit- Frail)	21 (48.8%)
Two (fit-frail)	9 (20.9%)
Continuous	4 (9.3%)

- Study selection criteria is shown in Figure 1
- There were 43 individual therapeutic drug trials included (Table 1)
- A total of **24 randomized controlled trials** (16 in newly-diagnosed and 8 in relapsed/refractory MM)
- A total of **19 non-randomized trials** (10 in newly-diagnosed and 9 in relapsed/refractory)
- **Increasing** number of studies reported on frailty in the last 2 years (26/41, 63%) (Figure 2)
- The **majority** of studies were conducted (20/41, 49%) in Europe
- The **most commonly** utilized tool for frailty assessment were;
  - ✓ the IMWG frailty score in (15/41, **37%**),
  - ✓ the Simplified frailty score utilized 15/41 (37%)
- **Frailty assessment** was conducted for the following reasons:
  - ✓ Study entry criteria in 8/41 (20%) studies,
  - ✓ Dose modifications in 5/41 (12%) studies
  - ✓ Subgroup analysis in 27/41 (66%) studies-
    - Included RCTs in newly-diagnosed (FIRST, MAIA and ALCYONE) as well as studies in the relapsed setting (MUK eight, BOSTON, ICARIA, ASPIRE, ENDEAVOR, ARROW, CANDOR and OPTIMISMM)
- The **UKMRA FiTNEss study** (NCT03720041), ongoing phase III RCT, was the **only study** found which is incorporating fitness assessment (adaptive drug dosing) vs standard of care (reactive drug dosing) into its primary trial design
- **Longitudinal frailty assessments** were found in a small number of studies ((UKMRA FiTNESS, HOVON 123, HOVON 143 and in the VBDD-VERRUM)
- Frailty was **categorized** differently in studies:
  - ✓ Dichotomized (frail vs non-frail) in 9/29, (31%)
  - ✓ Three categories (frail, intermediate-fit/unfit, fit) in 20/29 (69%)
- While **many** of the studies showed consistent improvements in outcomes with study interventions in frail subgroups, the magnitude of benefit was often **less** than those seen in fit patients

Conclusion

- Frailty assessments are **increasingly** being incorporated into therapeutic MM trials especially within the last 5 years with the majority of studies being conducted in Europe
- An **increasing** number of studies are currently incorporating post-hoc measure of frailty using previously collected data retrospectively
- While the most common reason for frailty incorporation remains subgroup analysis, **increasingly**, frailty assessment is being utilized for therapeutic drug dosing
- The UKMRA FiTNEss trial is the only RCT currently incorporating frailty into its primary study design

Figure 2: Study Years



Future Directions

- Further incorporation of frailty assessments prospectively and longitudinally into clinical trial will be key in personalizing treatment and improving outcomes for older adults with MM
- Future trials dedicated for treatment of older frail adults are needed to improve outcomes in this high risk patient population group

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