# Health Related Quality of Life (HRQoL) in Relapsed/Refractory Multiple Myeloma (RRMM): A Systematic Literature Review (SLR) and Meta-Analysis

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## BACKGROUND

- A range of therapeutic options for multiple myeloma (MM) are available and the landscape is rapidly evolving, particularly with the introduction of new classes of treatments such as chimeric antigen receptor (CAR) T-cell therapies and bispecific monoclonal antibodies. Nonetheless, MM remains incurable, and relapse is common.
- The symptom burden and associated health-related quality of life (HRQoL) profile for patients with MM has been characterized worse than other hematological malignancies.[2-5] Thus, characterizing patient HRQoL under the current RRMM treatment landscape, alongside traditional clinical outcomes, is important for contextualizing the patient experience and potential benefits of novel therapies in the RRMM setting.
- This systematic literature review (SLR) was conducted to quantify the pre-treatment HRQoL burden according to the European Organisation for Research and Treatment of Cancer (EORTC) 30-item Quality of Life Questionnaire (QLQ-C30) and the 20-item multiple myeloma module (QLQ-MY20) for use as a benchmark in future research.

## METHODS

### SYSTEMATIC LITERATURE REVIEW

- Systematic searches were conducted in MEDLINE, Embase, and CENTRAL (January 2012-March 13, 2024), supplemented by hand searches, for clinical trials or observational real-world evidence (RWE) which reported HRQoL outcomes of relapsed/refractory MM (RRMM) patients treated with any pharmacological intervention. The review protocol was registered with PROSPERO (CRD42023467098).
- For this study, we present observations from the evidence base that specifically reported QLQ-C30 or QLQ-MY20 outcomes.
- Study selection and data extraction were both conducted independently and in duplicate using standardized, piloted templates.

### META-ANALYSIS

- To generate benchmark values on the QLQ-C30 and the QLQ-MY20 module, inverse variance meta-analyses of baseline or pre-treatment observations were conducted to quantify HRQoL burden and facilitate comparisons across populations. When both means and medians were available, means were favored.
- The observed QLQ-C30 summary statistics were compared, according to published minimally important differences (MIDs),[6] to population normative data[7] that were age- and sex-adjusted according to global statistics available through GLOBOCAN.
- Study and patient characteristics were explored to identify trends and drivers of differences in HRQoL. For patient characteristics such as line of therapy (LOT), only within-study comparisons were synthesized to avoid conflating the impact of LOT with between-study heterogeneity.

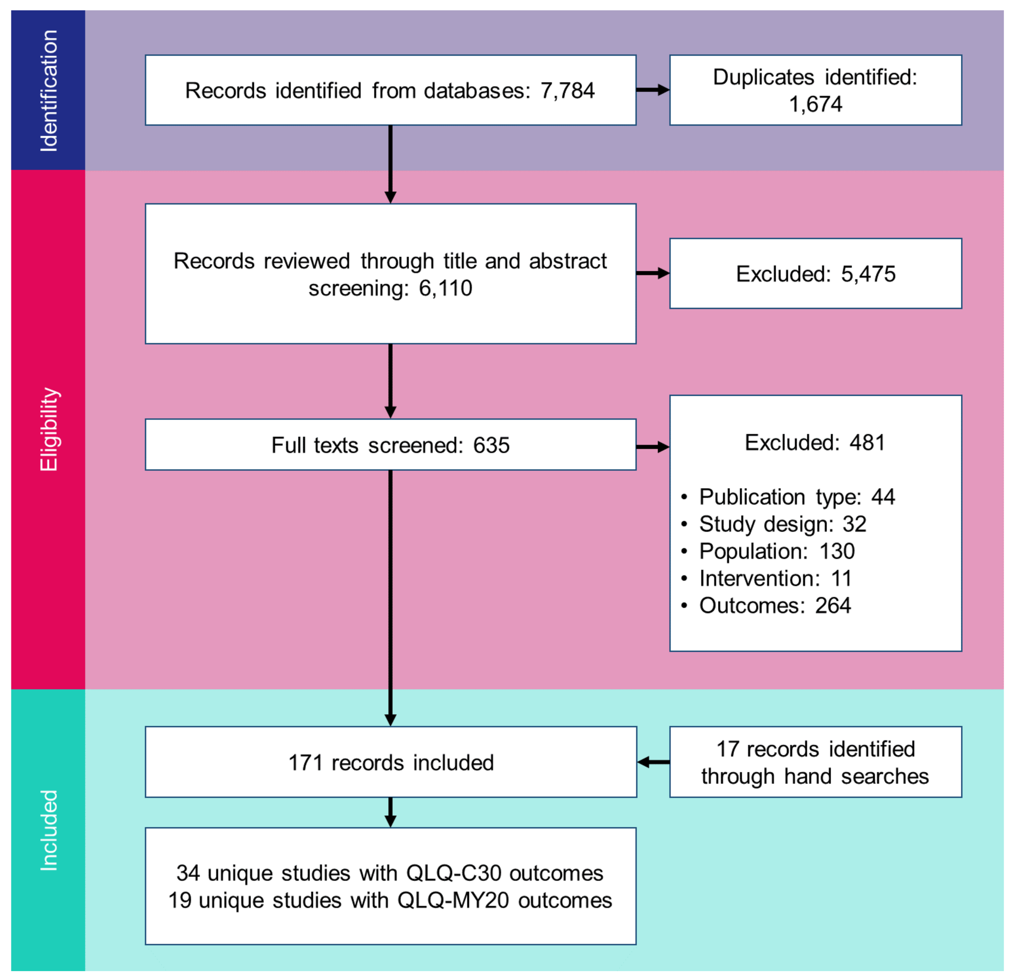
## METHODS (continued)

- Both random and fixed effects models were evaluated for fit according to the Q-test for heterogeneity. All analyses were conducted in R (r-project.org) using the *Metafor* package.[8]

## RESULTS

- An overview of the study selection process is summarized in **Figure 1**.
- Observations on the QLQ-C30 and QLQ-MY20 were available from 34 and 19 unique studies, respectively.

**Figure 1. PRISMA flow diagram for the systematic literature review**

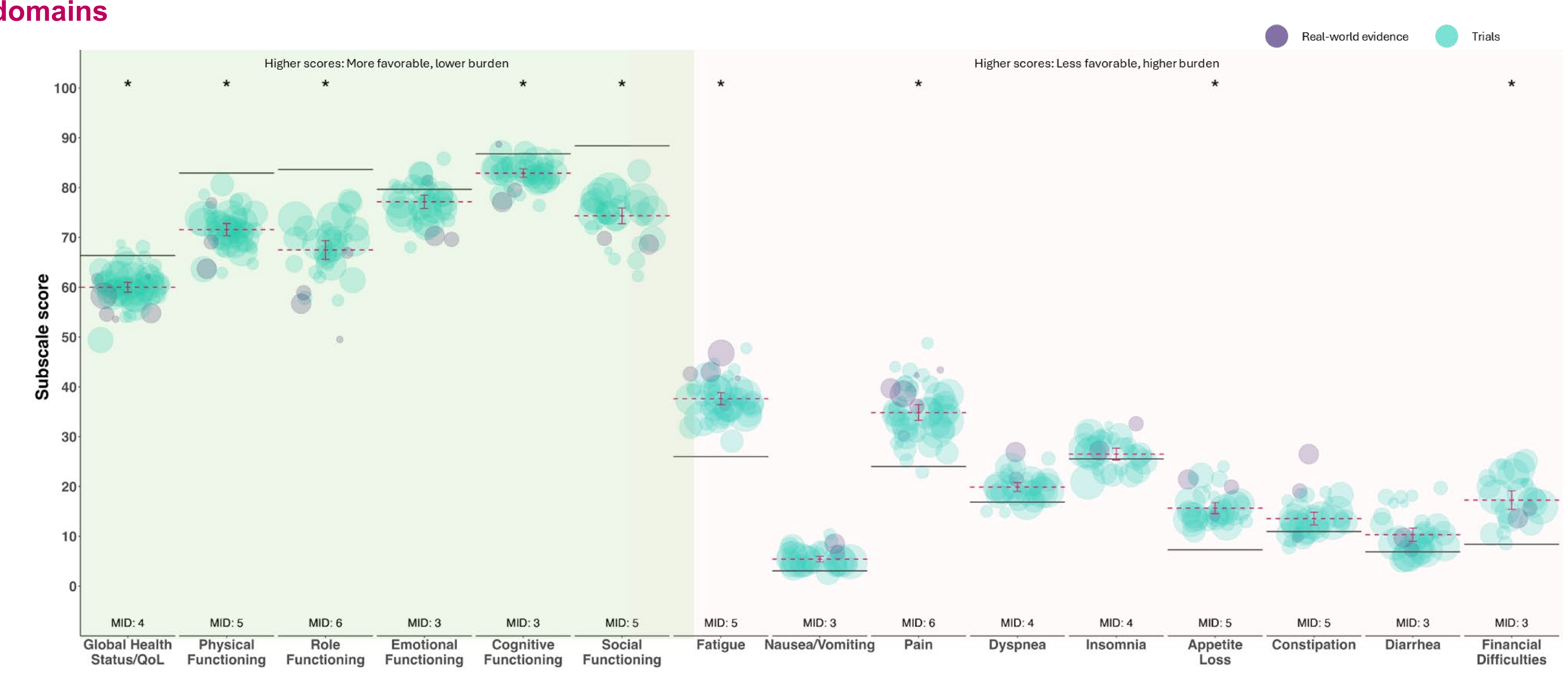



*Legend: QLQ-C30: 30-item Quality of Life Questionnaire of the European Organisation for Research and Treatment of Cancer; QLQ-MY20 : the 20-item multiple myeloma module of the European Organisation for Research and Treatment of Cancer.*

- Clinically meaningful differences between RRMM patient and general population HRQoL values were observed across nine domains and symptom items, as presented in **Figure 2**.
  - Global Health Status/QoL: 60.0 vs 66.4, MID=4.
  - Functional scales: Physical Functioning (71.6 vs 82.9, MID=5); Cognitive Functioning (82.9 vs 86.8, MID=3); Role Functioning (67.5 vs 83.6, MID=6); and Social Functioning (74.3 vs 88.4, MID=5).
  - Symptoms and single-item: Appetite Loss (15.7 vs 7.3, MID=5); Fatigue (37.6 vs 26.0, MID=5); Pain (34.8 vs 24.0, MID=6); and Financial Difficulties (17.3 vs 8.4, MID=3).
- Also presented in **Figure 2** is a table of results comparing clinical trial evidence to RWE, which revealed statistically significant differences across nine domains and symptom items. In six cases, differences between the summary estimates (both trials and RWE studies) and population norms were also clinically meaningful.

## RESULTS (continued)

**Figure 2. Observed values and summary estimates, with age- and sex-adjusted population norms for each of the QLQ-C30 domains**

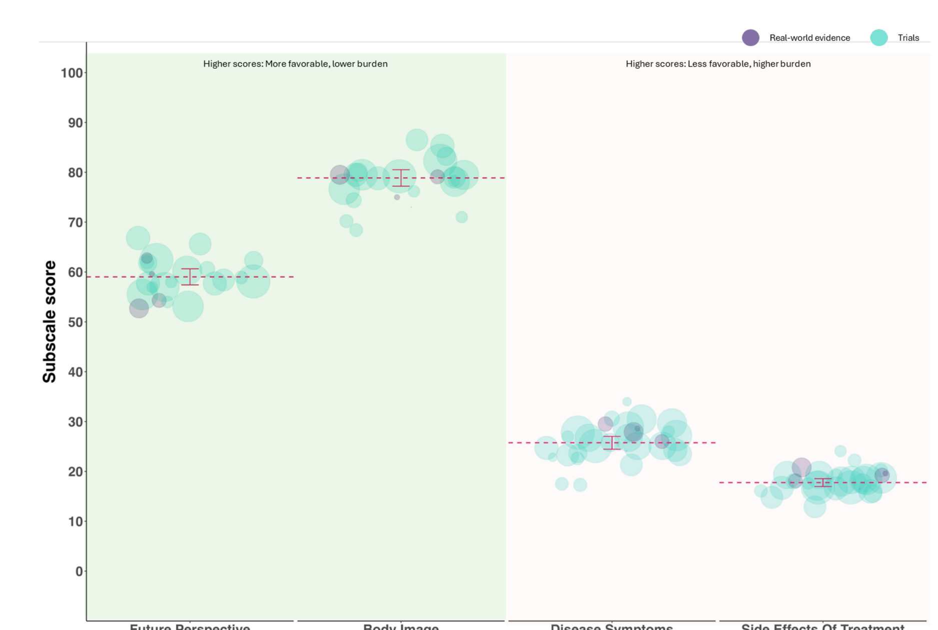



| | Global Health Status/QoL | Physical Functioning | Role Functioning | Emotional Functioning | Cognitive Functioning | Social Functioning | Fatigue | Nausea/Vomiting | Pain | Dyspnea | Insomnia | Appetite Loss | Constipation | Diarrhea | Financial Difficulties |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **N studies (N patients)** | 32 (9,042) | 25 (7,441) | 24 (6,456) | 21 (6,284) | 22 (6,362) | 21 (6,213) | 28 (7,831) | 21 (6,336) | 29 (7,935) | 19 (5,958) | 19 (5,889) | 20 (6,020) | 20 (5,949) | 19 (5,881) | 16 (5,195) |
| **Summary mean (95% CI)** | 60.0 (59.0, 61.0) | 71.6 (70.3, 72.8) | 67.5 (65.6, 69.4) | 77.2 (75.8, 78.5) | 82.9 (82.1, 83.8) | 74.3 (72.7, 75.9) | 37.6 (36.4, 38.8) | 5.4 (4.9, 6.0) | 34.8 (33.3, 36.4) | 19.9 (19.0, 20.8) | 26.5 (25.3, 27.7) | 15.7 (14.6, 16.8) | 13.6 (12.3, 14.8) | 10.3 (9.0, 11.7) | 17.3 (15.4, 19.1) |
| **Adj population norm** | 66.4 | 82.9 | 83.6 | 79.7 | 86.8 | 88.4 | 26.0 | 3.1 | 24.0 | 16.9 | 11.0 | 6.9 | 25.5 | 7.3 | 8.4 |
| **RWE vs Trial design (95% CI)** | **-2.5 (-4.5, -0.5)** | -2.3 (-5.2, 0.7) | **-9.2 (-13.1, -5.4)** | **-3.0 (-5.7, -0.4)** | **-3.7 (-6.5, -0.9)** | **-5.6 (-9.8, -1.3)** | **6.5 (4.3, 8.8)** | **2.3 (0.2, 4.5)** | 2.5 (-0.3, 5.2) | **5.1 (1.6, 8.6)** | 2.8 (-1.4, 7.0) | 3.2 (-0.0, 6.4) | **5.3 (2.2, 8.4)** | -2.0 (-4.7, 0.7) | -3.2 (-6.9, 0.4) |

***Legend:** Circle size is scaled to the relative sample size of the estimate within the evidence set. Weighted summary estimates, which include both trial and RWE, for each subscale or item are presented with a red horizonal line. Age- and sex-adjusted population normative data, based on observations of 15,386 persons across 15 countries published by the EORTC Quality of Life Group, are presented for each domain (black horizonal line). Published observations of normative data[7] were weighted by the global age- and sex-distribution of multiple myeloma. Clinically meaningful differences between summary estimates and population normative data (domains and items marked with stars) were determined based on minimally important differences (MIDs) published by Cocks et al (2011).[6] Comparisons between RWE and trials are based on pooled estimates from studies of each design. Adj: Adjusted; CI: Confidence interval; RWE: Real-world evidence. Results in bold are statistically significant*

- Emotional Functioning, Dyspnea, and Constipation were statistically different (more severe) for patients in RWE study settings than trials, with clinically meaningful differences (i.e., differences that exceeded the MID) observed between the RWE setting and the normative data for Emotional Functioning and Dyspnea.
  - The tendency for higher HRQoL burden in RWE studies suggests a more diverse and severe population in clinical practice than in clinical trials.
- Four studies informed within-study comparisons of baseline, pre-treatment HRQoL based on which LOT patients were initiating (no figure). Statistically significant slopes, which represent the change in the HRQoL domain or item when comparing one line to the next successive line, were estimated for: Global Health Status/QoL (-3.8; 95% confidence interval [CI]: -6.4, -1.1), Physical Functioning (-3.1; 95% CI: -5.9, -0.3), Fatigue (+4.5; 95% CI: 1.5, 7.6), Pain (+3.9; 95% CI: 0.4, 7.4).
- The evidence base for patient baseline observations from the MM-specific QLQ-MY20 module was similarly well-populated, with observations described across 19 unique studies as presented in **Figure 3**.
  - This evidence was primarily informed by clinical trials.
  - Notably, patients had high scores on Body Image at baseline. As there are no population norms available for this disease-specific module, limited inferences can be made on the relative weight of these observations compared to other populations.
- Observations on the Side Effects of Treatment domain were statistically significantly higher in RWE settings than in trials. As these are baseline, pre-treatment observations, this is likely due to the more controlled selection process used in recruiting patients in trials compared to RWE settings.

**Figure 3. Observed values and summary estimates for each of the QLQ-MY20 domains**




| | Future Perspective | Body Image | Disease Symptoms | Side Effects Of Treatment |
|---|---|---|---|---|
| **N studies (N patients)** | 13 (4,665) | 17 (5,558) | 15 (4,722) | 16 (5,487) |
| **Summary mean (95% CI)** | 78.9 (77.2, 80.5) | 25.8 (24.5, 27.0) | 59.0 (57.4, 60.6) | 17.8 (17.0, 18.5) |
| **RWE vs Trial design (95% CI)** | -0.3 (-4.2, 3.6) | 2.4 (-0.0, 4.9) | -3.2 (-6.5, 0.1) | 1.8 (0.2, 3.3) |

***Legend:** Circle size is scaled to the relative sample size of the estimate within the evidence set. Weighted summary estimates, which include both trial and RWE, for each subscale or item are presented with a red horizonal line. Comparisons between RWE and trials are based on pooled estimates from studies of each design. CI: Confidence interval; RWE: Real-world evidence.*

## DISCUSSION

- This SLR offers a contemporary profile of HRQoL in RRMM based on commonly used instruments as measured in the pre-treatment setting. It confirms and quantifies the high HRQoL-related burden experienced by patients with RRMM and identifies key domains of interest based on comparisons with the general population.
- The QLQ-C30, the commonly used HRQoL measure, is demonstrably reliable and valid across multicultural clinical settings. The MM-specific module, the QLQ-MY20, is used in conjunction with the C30 and is psychometrically robust to patient experiences and treatments with MM.
  - The availability of population normative data for the QLQ-C30 suggests MM patients have lower HRQoL; however, the important variability in norms across geographies must be acknowledged.
- HRQoL varied by study setting, with higher HRQoL observed pre-treatment in trials than in RWE settings for nine QLQ-C30 domains and items.
  - However, as HRQoL tended to be less well-reported in RWE settings, future research may lead us to further characterize this patient population and support a better understanding of HRQoL-related treatment impacts in clinical practice.
- Evidence suggests HRQoL-burden increases with LOT. Although this evidence was limited to observations from four studies, it does reinforce the documented increase in burden borne by patients in later-line treatments.

## CONCLUSIONS

- Unsurprisingly, patients with RRMM had clinically meaningful impairments from population norms in several pre-treatment HRQoL domains. HRQoL worsened with increasing LOT as well. The novel finding of a difference between the RWE and trial settings suggests that trials may underestimate RRMM-associated HRQoL burden. As such, HRQoL improvements in clinical trials may be amplified in RWE settings, supporting the HRQoL endpoint as a powerful tool to assess the impact of novel therapies.
- By quantifying pre-treatment HRQoL burden in both trial and RWE settings, our study provides a reference for contextualizing baseline patient burden as emerging therapies for RRMM continue to evolve.

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### DISCLOSURES

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