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Systematic Review

Treatment-related cognitive changes in multiple myeloma: A systematic review and meta-analysis

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ABSTRACT

Introduction: Multiple myeloma (MM) is an incurable blood cancer with improved survival rates due to advances in treatment, including stem cell transplantation, chemotherapy, and drug therapy. However, cognitive impact of therapies remains unclear. This study aimed to systematically review cognition in patients with MM across treatment pathways and estimate overall effects to determine whether patients experienced cognitive changes after treatment initiation.

Materials and Methods: A comprehensive search was conducted in PsycINFO, MEDLINE, Embase, and Google Scholar for full-text English articles from 2000 to 2024, aligned with the era of new treatment advances. The review included longitudinal studies and randomized controlled trials (RCTs) on cognition and quality of life in patients with MM treated via three common pathways. Measures included objective tools like the Montreal Cognitive Assessment (MoCA) and self-reported questionnaires like the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30). Two reviewers independently extracted data and assessed study bias. The meta-analyses examined cognitive changes from baseline up to six months from the start of treatment. This duration was identified due to being an intensive phase in MM therapy.

Results: Eighteen studies ($N = 5843$) were reviewed, and eight ($N = 3602$) contributed to the meta-analysis. The risk of bias analysis revealed a potential self-selection bias in participant recruitment onto studies, meaning sample populations may not be representative of the MM community. The meta-analysis revealed a significant cognitive decline from baseline across all treatment during the first six months of treatment (*standardized mean difference* $= 1.10$, $p = .02$).

Discussion: Perceived cognitive decline is prevalent in patients with MM during active treatment (<6 months), but not during the maintenance phase of MM treatment (>6 months). However, findings predominantly rely on self-reported cognitive outcomes, rather than objective assessments, which may limit reliability. More RCTs are needed to investigate domain-specific cognitive impacts using standardized objective measures. In addition, comparisons of cognitive outcomes relative to age/education-matched healthy controls should be made to evaluate cancer-related cognitive impairment.

1. Introduction

Multiple myeloma (MM) is the second most common haematological malignancy, with approximately 6000 new cases diagnosed annually in the United Kingdom (UK) alone [1]. Advances in treatment over recent decades have significantly improved prognosis, extending median survival by approximately six years [2]. Sadly, improvements have not been equitable across all patient groups with older, frailer individuals often benefitting less from therapeutic advances due to reduced treatment tolerance and exclusion from clinical trials. Among older adults, the burden of treatment-related effects is particularly pronounced. Patients with MM frequently present with comorbidities and polypharmacy, complicating disease management [3,4].

Traditionally, MM therapy consists of four to six months of treatment, but many recently approved therapies are continuous, requiring lifelong administration. Some patients now survive for 10 years or more [5]. These extended treatment durations frequently incorporate high-dose corticosteroid therapy, which has potent neurocognitive repercussions. Corticosteroids disrupt hippocampal integrity and modulate neurotransmitter systems through glucocorticoid receptor-mediated

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pathways, contributing to cognitive impairments like memory loss and executive dysfunction [6].

Chemotherapeutic regimens are central to MM treatment, but whether considering traditional chemotherapies or newer targeted approaches, greater toxicity and higher rates of discontinuation are seen in older and frailer patients [7]. Correspondingly, although survival for these groups have been improved by newer regimens, their outcomes lag younger and fitter patients [8]. Whilst quality of life has been reported to improve early in therapy as control over myeloma is established and the disease-related overlay reduces, the longer-term repercussions for treatment-related impairment are less well studied, particularly with respect to cognitive dysfunction [9].

Haematopoietic stem cell transplantation (HSCT), typically reserved for younger, fitter patients with MM, also presents significant cognitive challenges [10]. The high-dose chemotherapy required for HSCT induces neuroinflammation and oxidative stress, leading to deficits in executive functioning [11], as well as direct neurotoxicity [12], further exacerbating cancer-related cognitive impairment (CRCI).

Given the median age of MM diagnosis is 71 years, treatment-related mechanisms risk compounding the effects of age-related cognitive decline, leaving older adults particularly vulnerable. As MM therapies become increasingly continuous and long-term, the cumulative burden of neurotoxic effects on cognition in this population is of growing concern.

Accurate assessment of CRCI remains a challenge. Comprehensive neuropsychological evaluation using objective tests is considered the gold standard in neuro-oncology [12]. Tests assess cognitive domains like attention, memory, executive function, and visuospatial abilities. Full neuropsychological batteries are often not feasible in routine clinical settings due to their length, the need for trained professionals, and selection bias towards less-compromised patients. Screening tools offer a more rapid means of detecting cognitive deficits and can be clinician- or patient-administered. Widely used examples in geriatric oncology include the Montreal Cognitive Assessment (MoCA) [13] and the Mini-Mental State Examination (MMSE) [14]. These measures are validated, reliable, quick to administer, and inexpensive. Despite the availability of screening tools, most lack robust evidence for detecting CRCI [15,16]. Self-reported questionnaires, such as the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire C30 (EORTC-QLQ-30), [17] are frequently used, but do not consistently correlate with objective measures. This mismatch highlights the need for more accurate and standardized assessment approaches.

Although CRCI research has primarily focused on breast cancer [18,19] and brain tumour survivors [20], there is growing awareness of cognitive impairments across various malignancies. A systematic review by Cerulla-Torrente et al. [21] found CRCI is common in non-central nervous system cancers, though patterns and trajectories vary depending on cancer type and treatment. Within MM, research has largely focused on transplant-related toxicities in younger populations [22,23], leaving significant gaps in understanding CRCI in older populations receiving non-transplant therapies.

To address this gap, the present paper evaluates cognitive functioning in patients with MM undergoing chemotherapy, corticosteroid treatment, and HSCT. The research questions were: (i) Do patients with MM experience cognitive change after treatment onset (i.e., from baseline)? and (ii) Is perceived cognition affected more during early intensive treatment ($<$ 6 months) compared to later ($>$ 6 months) less intensive cycles? We hypothesized cognitive functioning is worse in the early phase due to intensive steroid-based therapies in MM, with later cycles resulting in less perceived impairment.

2. Methods

This review was registered with PROSPERO (CRD42024536253) and followed guidelines on Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) [24].

2.1. Search strategy

Citations were retrieved via the following databases: PsycINFO, MEDLine, Embase, and Google Scholar in November 2023 and October 2024. Retrieval time was restricted from 2000 to the search date, as congruent with the introduction of novel agents like proteasome inhibitors (PI) and immunomodulatory drugs (IMiDs) in treatment regimens. Search strategy included synonyms related to key domains of myeloma, cognition, corticosteroids, HSCT, and chemotherapy (Supplementary Information 1).

2.2. Study selection

A partial dual-review of all titles/abstracts and full-text articles was conducted according to the following inclusion criteria: (1) controlled trials (cross-sectional or longitudinal), (2) participants with confirmed MM diagnosis, (3) treatments included chemotherapy, HSCT, or drug combinations including dexamethasone and prednisolone, (4) at least one measure of cognitive function using either objective or patient-reported cognitive tests, (5) published in peer-reviewed journals, (6) studies from 2000 onwards, and (7) participants aged 18+ years. Any disagreements were resolved by consensus.

Reasons for exclusion of empirical research included: (1) research did not explicitly report cognitive effects in haematological malignancies (specifically MM), (2) research focused on neurological toxicities like chimeric antigen receptor T-cell (CAR T-cell) therapy, (3) research was only qualitative, (4) research not on humans, (5) research not reported in English, (6) studies prior to 2000, and (6) papers could not be retrieved.

2.3. Data extraction

One reviewer developed an extraction form and independently acquired data. Quality and accuracy of details was then evaluated by the second reviewer using the adapted form. Data extraction included sample size, participant characteristics, treatment type and protocol, cognitive ability assessed, cognitive task, study design, and outcome data (means and standard deviations across treatment groups and pre- and post-intervention). A Plot Digitizer Programme [26] was used to estimate means and standard deviations (SDs) when data was presented in graph form only. Where SDs were unreported, it was estimated from 95 % confidence intervals (CIs) using the eq. $SD = \sqrt{N}$ x (upper limit – lower limit)/ 3.92 as outlined in the Cochrane Handbook [27]. Exact p values were calculated where required [28].

2.4. Study quality assessment

Two independent reviewers assessed methodological quality of included studies using an adapted Risk Of Bias In Non-randomized Studies - of Exposures tool (ROBINS-E) [25]. ROBINS-E is a structured approach to assess observational epidemiological studies with signalling questions in seven domains including confounding variables, measurements of exposure, selection of participants, post-exposure interventions, missing data, measurement of outcomes, and the reporting of results. Minor adjustments to definitions of ‘exposure’ and ‘exposure window’ were made to ensure relevance to study objectives. Reviewers discussed scoring and consensus was reached for each paper.

2.5. Meta-analytic procedure

All analyses and plots were coded in R Studio (2023.12.0) using Metafor [29–32]. Weighted average effect sizes were calculated using standardized mean difference (SMD). Data were then pooled using a random-effects model. Some studies included samples not solely consisting of patients with MM. Multiple meta-analyses were conducted to assess overall cognitive effect comparing (a) cognition at baseline to 8.5–24 weeks (< 6 months) and (b) later cognition at baseline to 24+ weeks (> 6 months) post-treatment corresponding with the intensive treatment phase and maintenance phase respectively. Data input is outlined in Supplementary Information 2.

3. Results

3.1. Study selection

149 studies were identified. Following de-duplication and title and abstract screening, 39 papers were found to be potentially relevant. Five reports could not be retrieved, leaving 35 texts to be screened for eligibility. Following full-text review, papers were excluded if only conference abstracts were available, papers could not be accessed, or cognitive outcomes were not reported. A total of 18 peer-reviewed papers were included, 10 of which were identified as appropriate for inclusion in meta-analyses due to data accessibility and extrapolation. Study selection flow chart is presented in Fig. 1.

3.2. Coding procedure

Reviewed papers utilized either objective or subjective tests of cognition. Objective measures predominantly included Montreal Cognitive Assessment (MoCA), a 30-point screening test assessing various domains of executive functioning like visuospatial functions, memory, attention, language, abstraction, and orientation. MoCA is a well-validated tool with high sensitivity and specificity for identifying mild cognitive impairment [33,34]. Other batteries of neuropsychological tests included BrainCheck, a standardized, web-based cognitive testing tool assessing processing speed, visual attention, cognitive flexibility, response inhibition, and verbal declarative memory [35].

Typically, studies of subjective (patient-reported) cognition included EORTC-QLQ-C30, a 30-item self-report questionnaire including measures of functional health (physical, role, cognitive, emotional, and social), symptom scales (fatigue, pain, nausea and vomiting), global health status, and various single items assessing common symptoms like dyspnoea, appetite loss, insomnia and constipation, and perceived financial impact of disease. Other tools included Patient Reported Outcomes Measurement Information System 29 (PROMIS-29) Problem 4a [36], a validated short-form self-report measure of physical and mental health domains.

For this study we generated a mean from cognitive components of these questionnaires for our meta-analysis. EORTC-QLQ-C30 scores were calculated as averages from the appropriate cognitive functioning elements of the questionnaire (two items in total). Scores from PROMIS-29 were averages reported on a 4-item cognitive variation of the original quality-of-life measure. Both tools measured cognition as relating to attention and memory. Of the studies included in the primary meta-

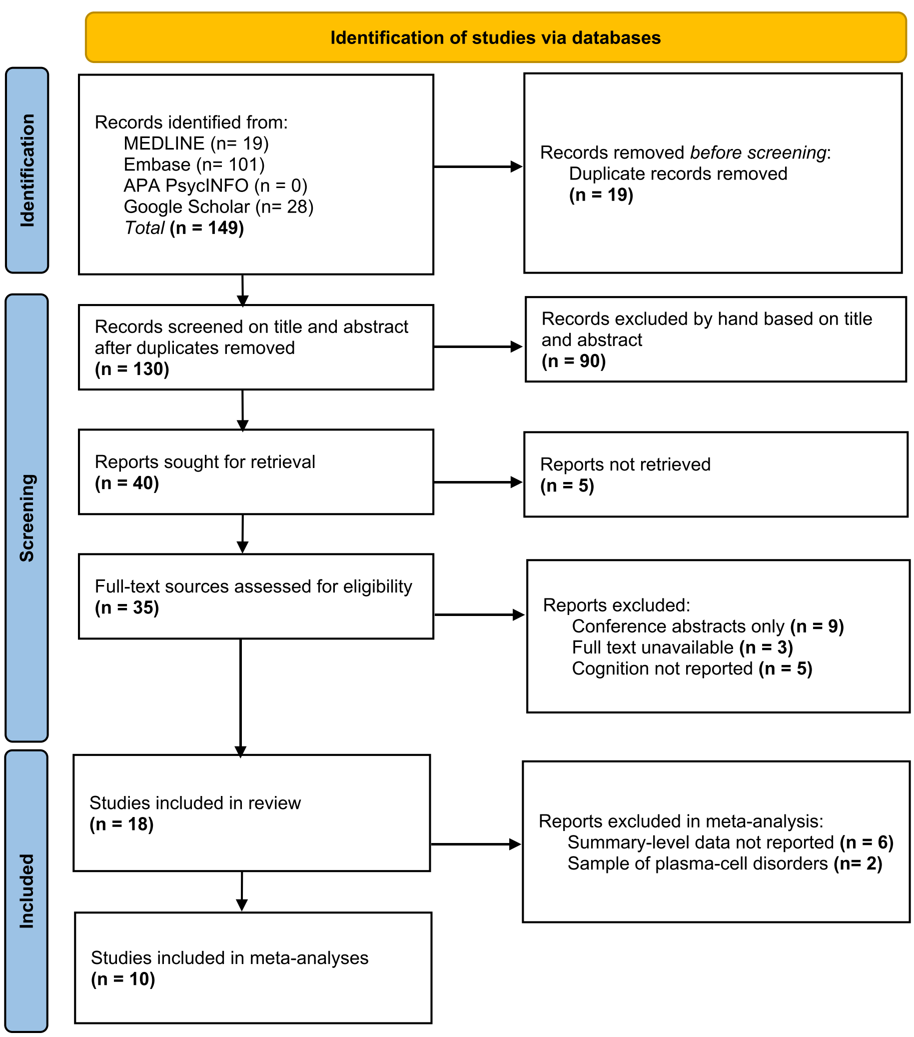

Fig. 1. Study Selection Flow Diagram (PRISMA 2020) showing records identified and screened literature for Searches performed in November 2023 and October 2024.

analysis, measures included EORTC QLQ-C30 and the cognitive variation of PROMIS-29 v2.0. MoCA was included in additional analyses (Supplementary Information 3).

All cognitive questionnaire measures used in this analysis indicated that higher scores reflected improvements in cognition. Cognitive assessments were conducted at three timepoints: baseline (T0, pre-treatment measurements as per individual study protocols), early follow-up at less than six months post-treatment initiation (T1), and later follow-up beyond six months (T2). This classification was determined in accordance with variability in assessment timepoints across studies.

3.3. Study design and sample characteristics

Of 18 selected studies ($N = 5843$), ten had been conducted in United States [37–46], two in Germany [47,48], one in Poland [49], and one in India [50]. The remaining four studies [51–54] were randomized, multi-centre drug trials spanning across Europe, the Middle East, Africa, Asia, and North and South America. The main characteristics of the study population and methodology are shown in Table 1. The sample size of studies ranged from 21 to 1085 patients. Mean ages ranged from 50 to 71.4 years. Across all 18 studies, 56.8 % of patients were male, reflective of the higher prevalence of haematological malignancies in males.

Table 1
Characteristics of studies included of association between multiple myeloma and cognition.

Authors	Year	Country	N	Mean Age (yrs)	% Male	Treatments	Cognitive Tasks	Baseline (T_0)	Timepoint 1 (T_1)	Timepoint 2 (T_2)
*Biran et al. [37]	2021	USA	42	50	35.8	AuHSCT	PROMIS-29 v2.0 Cognitive functions 4a	Pre-AuHSCT	12wks post-treatment	24wks post-treatment
*Bury-Kamińska et al. [49]	2021	Poland	21	65	43	Chemo (VCD; VTD; VD)	MoCA	Before chemo	After 4–6 cycles	
Fischer et al. [47]	2022	Germany	70	62.6	56	Chemo +/− AuHSCT	EORTC QLQ-C30	Pre-therapy	12wks post-therapy	
Franco-Rocha et al. [38]	2022	USA	11 /62 MM	56	50	Chemo + AuHSCT	BrainCheck PROMIS-29 v2.0 Cognitive functions 8a	Cross-sectional		
Jensen et al. [39]	2021	USA	89/ 121 MM	69	54	Various current therapies	EORTC QLQ-C30	Cross-sectional		
Jones et al. [40]	2013	USA	41	57.8	62.3	AuHSCT	WAIS-III HVLT-R HVLT-R Trail Making MAE	Pre-AuHSCT	4wks post-AuHSCT	12wks post-AuHSCT
Knop et al. [48]	2021	Germany	706	71.4	46.3	D-VMP VMP	EORTC QLQ-C30	Before drug therapy	Every 12wks for 1y	Every 24wks until PD
Koll et al. [41]	2020	USA	8/ 51 MM	68.3	66.7	Rd B-Rd D-Rd CAR-Rd	MoCA	NR	NR	
*Kumar et al. [50]	2024	India	31	60	58	B-Rd	EORTC-QLQ-C30	Before drug therapy	16wks	24wks
Lee et al. [42]	2008	USA	598	62	58	BORT DEX	EORTC QLQ-C30	Before drug therapy	6- and 12-wks	18-42wks
*Leleu et al. [43]	2016	USA	722	66	57	IRd P-Rd	EORTC QLQ-C30	At screening	Start of C1-C2	C4-end of treatment
*Mohanraj et al. [44]	2022	USA	21/ 70 MM	58.9	66	AuHSCT	MoCA	Within 1wk pre-AuHSCT	8.5wks after AuHSCT	
*Perrot et al. [51]	2021	Multi-continent	737	73	52	D-RD Rd	EORTC-QLQ-C30	Before drug therapy	Treatment C3	C6, C9, C12 and every 6 months until PD
*Plesner et al. [52]	2021	Multi-continent	569	Median age, 65	59	D-Rd Rd	EORTC-QLQ-C30	Before drug therapy	C2, C3, C4, C5, C6, and C7	C14, C27-, and C40
Root et al. [45]	2020	USA	55/ 260 MM	55.1	62	AuHSCT	MoCA	Pre-AuHSCT	Within 1wk post-AuHSCT,	
*Roussel et al. [53]	2020	Multi-continent	1085	58.5	58.5	D-VTd VTD	EORTC QLQ-C30	Before AuHSCT	14wks post-AuHSCT	
*Schjesvold et al. [54]	2020	Multi-continent	637	58	63	IXA P	EORTC-QLQ-C30	Screening	Start of every cycle	EOT and every 4wks until PD
*Yusuf et al. [46]	2022	USA	104	67	52	Various current therapies	EORTC QLQ-C30	Induction	12wks post-treatment	24wks post-treatment

Summary of all 18 studies from the systematic review. Acronyms were as follows: AuHSCT = autologous haematopoietic stem cell transplantation; PROMIS-29 = Patient Reported Outcomes Measurement Information System 29; Chemo = chemotherapy; VCD = bortezomib, cyclophosphamide, and dexamethasone; VTD = bortezomib, thalidomide and dexamethasone; VD = bortezomib and dexamethasone; MoCA = Montreal Cognitive Assessment; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; MM = multiple myeloma; WAIS-III = Wechsler Adult Intelligence Scale-Third Edition; HVLT-R = Hopkins Verbal Learning Test-Revised; MAE = Multilingual Aphasia Examination; D-VMP = daratumumab, bortezomib, melphalan, prednisone; VMP = bortezomib, melphalan, prednisone; PD = progressive disease; Rd = lenalidomide and dexamethasone; B-Rd = bortezomib, lenalidomide and dexamethasone; D-Rd = daratumumab, lenalidomide, and dexamethasone; CAR = carfilzomib; NR = not reported; BORT = bortezomib; DEX = dexamethasone; IXA = ixazomib; C = cycle; D-VTd = daratumumab, bortezomib, thalidomide, dexamethasone; EOT = end of treatment.

[*] Denotes studies included in meta-analysis. *Note:* Perrot et al. (2021), Plesner et al. (2021), Roussel et al. (2020) and Schjesvold et al. (2020) described statistics from two groups therefore data was included as multiple independent units in the meta-analysis.

Twelve studies included autologous haematopoietic stem cell transplantation (AuHSCT) eligible populations [37–41,44–47,49,51–53], and four included HSCT-ineligible patients [39,40,44,49]. One study [47] failed to provide sufficient information on treatment administration. Two studies are noteworthy given the widely varying regimens investigated: Jensen and colleagues [39] studied patients with 1–4 prior lines of therapy with several current therapies including transplant-eligible and transplant-ineligible pathways. Similarly, Yusuf et al. [46] included 0–4+ prior lines with some patients untreated and some on therapy on a range of transplant-eligible and transplant-ineligible pathways.

Eleven studies measured subjective cognition using EORTC-QLQ-C30 [39,42,43,46–48,50–54] while two utilized PROMIS-29 Cognitive Problems 4a and 8a [37,38]. Seven studies used objective measures of cognition [38,40,41,44,45,49] with MoCA being the most common measure. Jones et al. [40] used a series of objective measures including the Wechsler Adult Intelligence Scale Third Edition (WAIS-III) Digit Span tasks, Hopkins Verbal Learning Test-Revised (HVLT-R) recall and recognition tasks, Trail Making Test, and Multilingual Aphasia Examination (MAE) Word Association. Only Franco-Rocha et al. [38] used

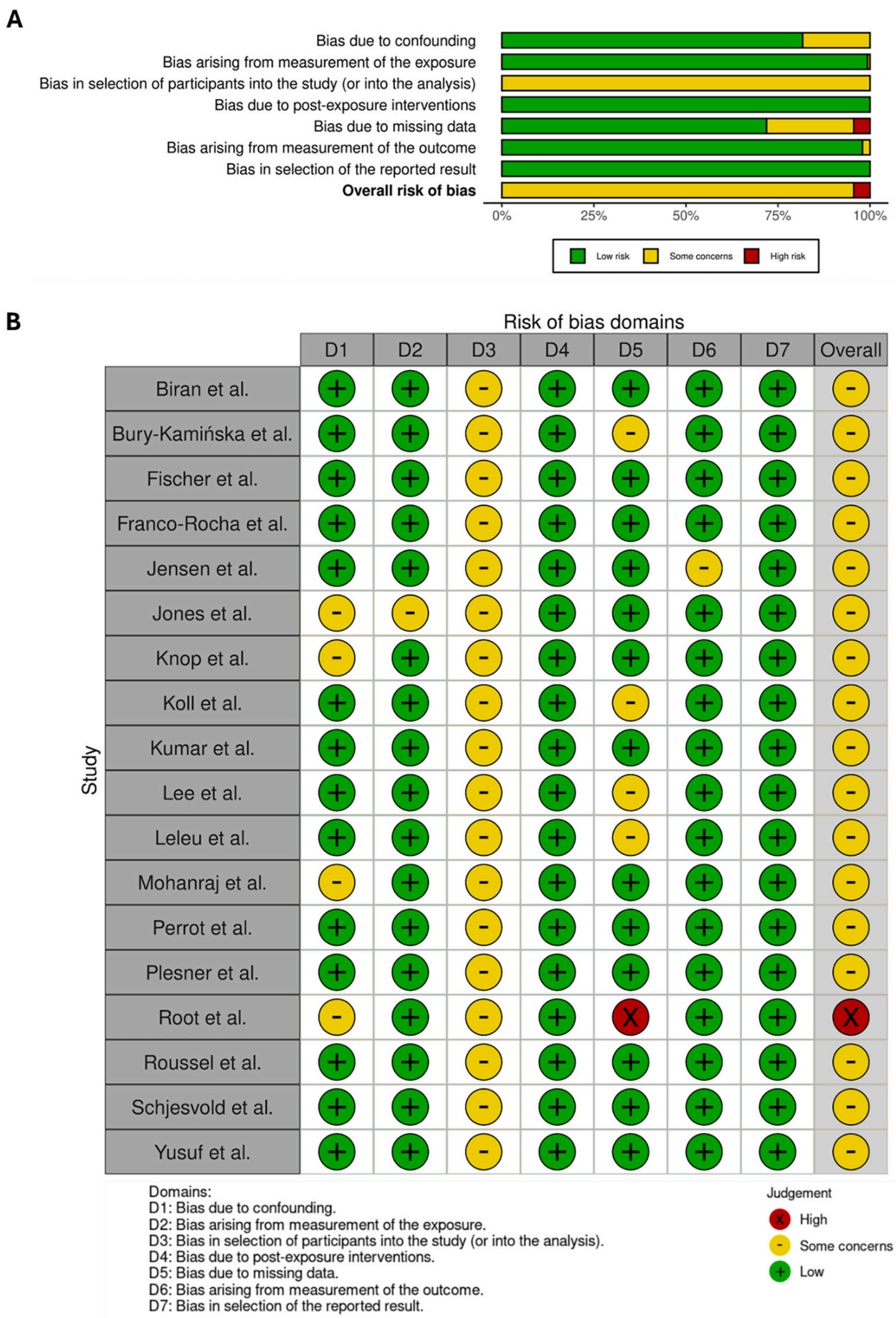

Fig. 2. Quality assessment ratings expressed as percentage (%) risk of bias across domains (A) and as individual studies (B). Only one study (Root et al. [45]) revealed a high risk of bias in their approach to missing data.

both subjective and objective measures.

3.4. Quality assessment

Results show methodological concerns were present for 18 papers, and one was considered to contain a high risk of bias (see Fig. 2). The main area of methodological concern was selection of participants into the study or analysis; four studies [37,40,44,48] did not account for all confounding factors such as co-morbidities, treatment background, and control groups; four studies showed risk of bias in the handling of missing data [37,42,43,49], one study was at risk of measurement error due to researcher awareness of patient exposure history [39]. Only one study [45] was considered at high risk of bias due to handling of missing data.

3.5. Summary of literature

Across 10 studies included in meta-analysis, there was notable heterogeneity in clinical questions addressed. Roussel et al. [53] investigated transplant-eligible patients with MM using an intensive induction regimen consolidated by autologous HSCT. Assessments were at baseline, upon completion of four chemotherapy cycles, and 100 days post-treatment (interpreted as baseline, on-treatment, and three-months post-treatment) as part of the phase 3 CASSIOPEIA trial. Schjesvold et al. [54] conducted a similar investigation, a phase 3 TOURMALINE-MM3 trial including patients newly diagnosed with MM post AuHSCT. Quality of life assessments were conducted prior to initiation, at start of every treatment cycle, at end of treatment, and then every four weeks until next line of therapy after disease progression. Likewise, Leleu et al. [43] investigated patients newly diagnosed with MM as part of the TOURMALINE-MM1 trial. In this phase 3 study, like many others [51–54], cognitive function was assessed using EORTC-QLQ-C30, with evaluations at baseline, on-treatment (at the start of cycles 1, 2, and every other cycle), and at end of treatment to determine treatment impact on patient-reported outcomes (PROs). Biran et al. [37] and Mohanraj et al. [44] also used AuHSCT-eligible patient populations with assessments at pre- and post-treatment timepoints; however, the latter used the MoCA screening tool as an objective assessment of cognition while the former used EORTC-QLQ-C30 to report subjective cognition.

Two other studies, Perrot et al. [51] and Plesner et al. [52], were health-related quality of life investigations of phase 3 studies (MAIA and POLLUX trials, respectively). Both studies involved transplant-ineligible populations on daratumumab, lenalidomide, and dexamethasone (D-Rd) and lenalidomide-dexamethasone (Rd) treatment pathways and used the EORTC-QLQ-C30. Perrot et al. evaluated patients at baseline, and at the start of cycles 3, 6, 9, and 12 followed by a routine assessment every six months until disease progression. Plesner and colleagues assessed cognition at baseline then once a month for the first six months of treatment cycles, followed up by cycles 14, 27, and 40.

Yusuf et al. [46] conducted a registry study assessing patients at baseline, with follow ups at three months and six months. Patients and treatments were highly heterogenous with variation in time from diagnosis, treatment history (between 0 and 4 lines of previous therapy), and current treatment plans (for instance, 7 % of patients were not on therapy at trial recruitment while 52 % were on dexamethasone). Kumar et al. [50] evaluated treatment-related quality of life among patients with MM undergoing drug treatment at baseline and at four and six months. However, this longitudinal prospective study exerted greater control due to the sole inclusion of patients newly diagnosed with MM and consideration of co-morbidities. Finally, Bury-Kamińska et al. [49] explored changes in patient functionality using assessments at baseline and four to six months of chemotherapy on bortezomib and dexamethasone. Like Mohanraj et al., Bury-Kamińska and colleagues used the MoCA, an objective cognitive tool, as opposed to self-reported measures.

3.6. Meta-analysis

Data from 10/18 studies were available for random-effects meta-analysis. Eight longitudinal studies reporting subjective cognitive outcomes by treatment type were included in the primary analyses. Using these data, three meta-analyses were conducted evaluating patient-reported cognitive functionality differences from baseline for (1) all data that included all PROs at all timepoints; (2) comparisons from baseline to 8.5–24 weeks (2–6 months) of initial intense treatment; and (3) comparing baseline to later timepoints (24+ weeks or 6+ months post-treatment). Summary effect sizes were generated by using SMD. A secondary meta-analysis was also conducted to include cognitive results across all studies using both objective and subjective methods (Supplementary Information 3).

In meta-analysis 1, 25 datasets ($N = 7162$ patients) from eight papers were analysed. Results showed no significant decline in mean PROs of cognition when comparing baseline to both early and maintenance treatment phases ($SMD = 1.04$, $p = .38$). Across the included studies, eight treatment arms improved cognitive function over time, as indicated by increased cognitive scores at either <6 months (T1) or > 6 months (T2) post-treatment [Kumar et al. (T1, T2), Perrot et al. D-Rd (T1, T2), Plesner et al. D-Rd/Rd (T1, T2), Leleu et al. IRd (T2), and Schjesvold et al. IXA/Placebo (T2)]. In contrast, nine treatment arms showed a decline in cognitive scores, suggesting cognitive impairment at these timepoints [Biran et al., Leleu et al. IRd/Placebo (T1), Perrot et al. Rd (T1), Roussel et al. D-VTd/VTD (T1, T2), Schjesvold et al. IXA/Placebo (T1), Yusuf et al. (T1, T2), and Leleu et al. Placebo (T2)]. These mixed findings reflect high heterogeneity in cognitive outcomes across different treatment regimens and timepoints. Large confidence intervals were shown by Kumar et al. (2024) and Biran et al. (2021), potentially due to the small sample sizes, reliance on subjective cognitive assessments, overlapping follow-up periods, treatment effects, and patient heterogeneity (see Fig. 3).

To assess the effects of cognitive change by timepoint, we performed two further meta-analyses comparing baseline to post-treatment timepoints. Meta-analysis 2 compared pre-treatment with 2–6 months post-treatment (13 datasets, $N = 3602$) showing a significant SMD of 1.10 ($p < .0001$). Meta-analysis 3 compared pre-treatment to 6–9 months post-treatment (12 datasets, $N = 3560$) resulting in a SMD of 0.98 ($p < .73$) (Figs. 4 and 5, respectively). Heterogeneity as determined by the I^2 statistic was considerably higher when comparing the latter timepoint at >6 months ($I^2 = 86.85$ %) relative to <6 months to baseline ($I^2 = 63.94$ %).

3.7. Publication bias

Bias was assessed for all 18 studies included in meta-analyses. Visual inspection of this funnel plot (Supplementary Information 4), reveals a symmetric distribution around the SMD, indicating that there is no real issue of reporting null or negative findings in this literature set. However, the lack of uniformity between studies, particularly regarding use of self-report tools, population sizes, ages of participants, and cognitive measures may indicate bias in other aspects of the data [55].

4. Discussion

This is the first systematic review and meta-analysis investigating cognitive functioning in patients with MM undergoing standard treatment pathways. Despite growing recognition of CRCI, only 18 studies were identified, 12 relying solely on two self-report questions – highlighting paucity in literature on accurate CRCI assessment in MM populations.

Our primary research aim was to assess changes in self-reported cognition following treatment onset. Only eight studies included relevant PROs, yielding a non-significant SMD of 1.04, consistent with previous CRCI literature [37,43,46,50–54]. Thirteen out of 25 datasets

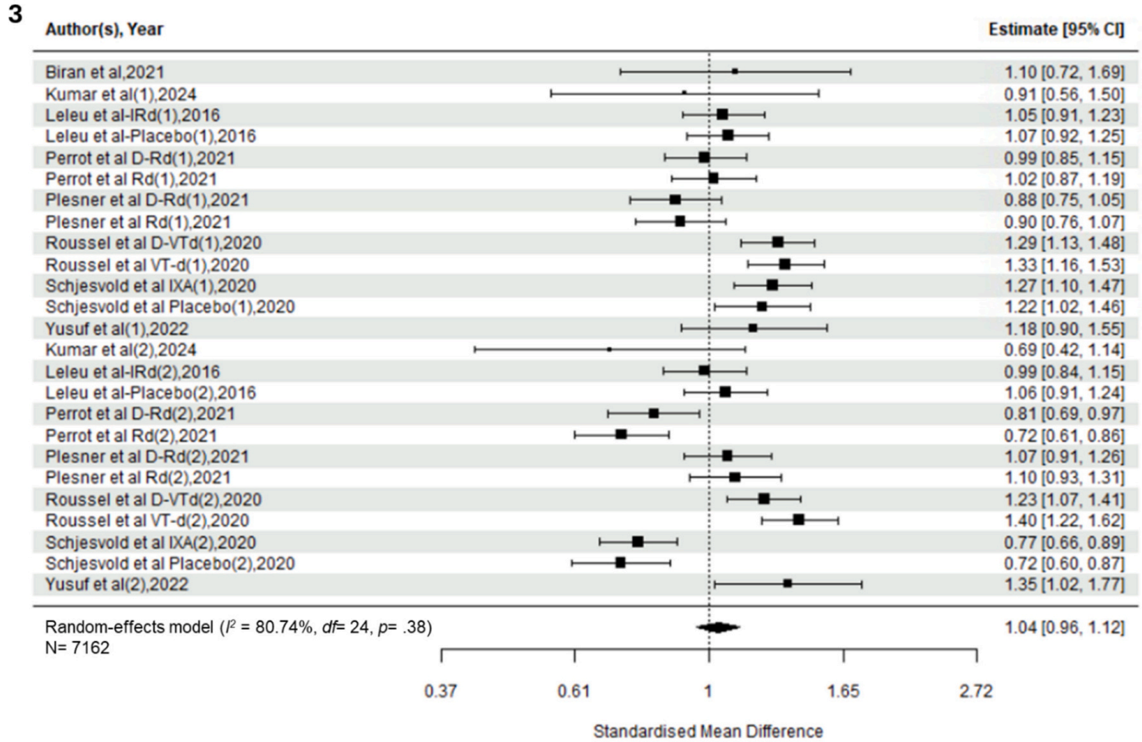

Fig. 3. Forest Plot showing individual study effects and pooled effect sizes (standardized mean differences) for cognitive function comparing changes from baseline to all post-treatment timepoints for all treatment arms. Meta-analysis 1 shows cognitive ability overall, comparing all treatment arms from baseline (T0) to both active treatment (<6 months, T1) and maintenance treatment (>6 months, T2).

Acronyms: D-VTd = daratumumab, bortezomib, thalidomide, dexamethasone; VTD = bortezomib, thalidomide, dexamethasone; D-Rd = daratumumab, lenalidomide, and dexamethasone; Rd = lenalidomide and dexamethasone; IXA = ixazomib.

Note: Treatment arms for Roussel et al. (2020), Plesner et al. (2021), and Perrot et al. (2021) are clearly outlined. Comparisons between T0 and post-treatment T1 and T2 are denoted by (1) and (2), respectively.

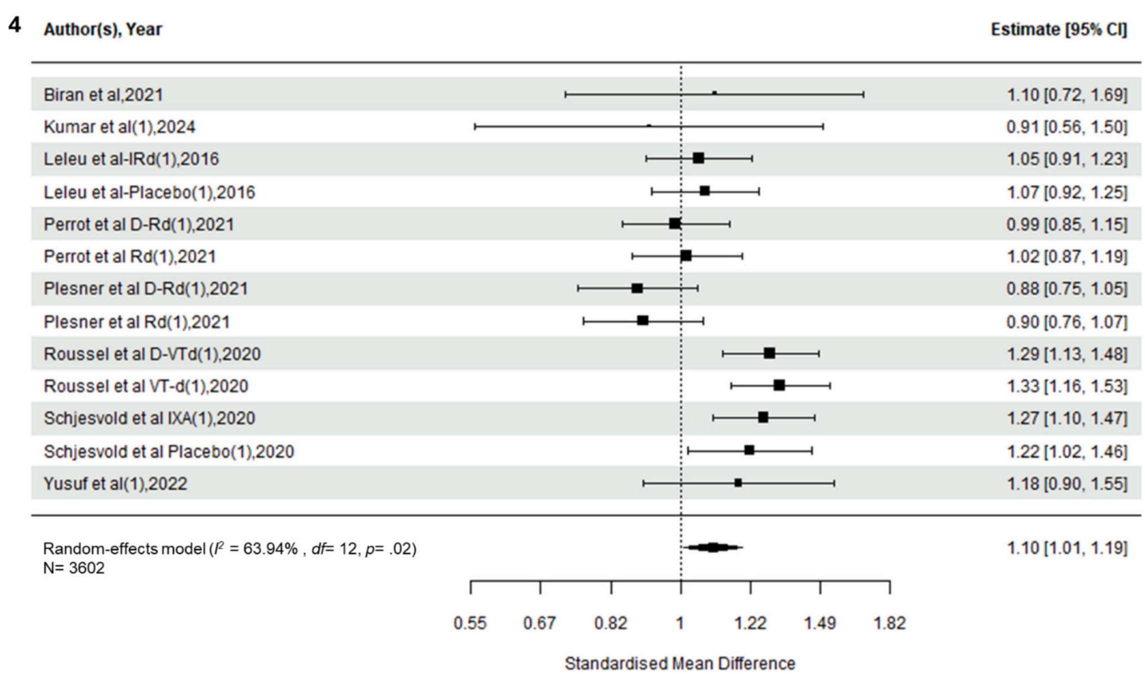

Fig. 4. Forest Plot showing meta-analysis 2, cognitive performance in patients with multiple myeloma from baseline to the early intensive 2–6 months of treatment.

showed cognitive decline, with heterogeneity accounting for 80.75 % of data (Fig. 3). Potential sources include: (i) use of only two to four self-report questions, which inadequately captures the extent of cognitive ability, potentially leading to binary effects [56]; (ii) tools like EORTC–QLQ-C30 (30 items) including only two relevant cognition-based questions, limiting CRCI assessment; (iii) varied age range

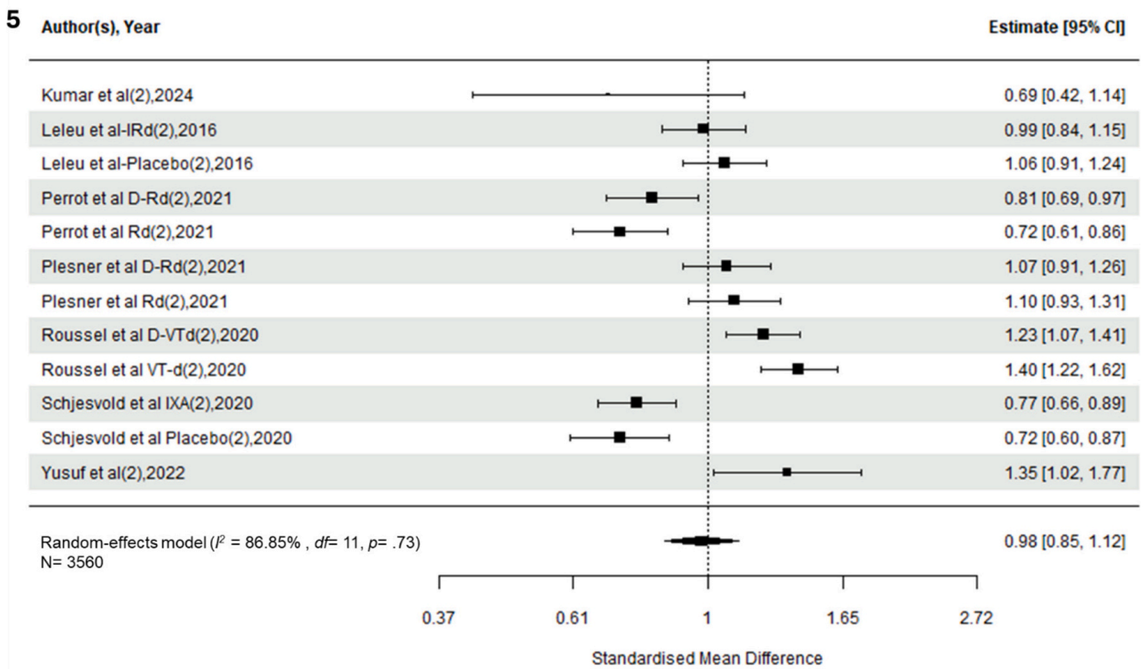

Fig. 5. Forest Plot showing meta-analysis 3, cognitive performance in patients with multiple myeloma from baseline to 6–9 months of treatment in the less intense maintenance phase.
Acronyms: D-VTd = daratumumab, bortezomib, thalidomide, dexamethasone; VTD = bortezomib, thalidomide, dexamethasone; D-Rd = daratumumab, lenalidomide, and dexamethasone; Rd = lenalidomide and dexamethasone; IXA = ixazomib.

across studies (50–78 years) affecting cognition, requiring appropriate control, [57,58]; (iv) focus on pre- versus post-treatment measures and between participant effects using PROs; and (v) methodological inconsistencies including variations in study design, treatment regimens, and assessment timepoints. For instance, studies utilizing AuHSCT (e.g., Biran et al. [37]), may show distinct cognitive trajectories compared to chemotherapy-based regimens, (e.g., Bury-Kamińska et al. [49]) and Roussel et al. [53] and Schjesvold et al. [54], assessed cognition at multiple cycles or extended follow-ups, while Yusuf et al. [46], had relatively shorter monitoring periods (e.g., 12- and 24-weeks post-treatment).

A critical shortcoming across studies was the lack of high-quality control cohorts. Where provided, comparators had other haematological malignancies or received alternative treatment. Only Franco-Rocha et al.'s [38] cross-sectional study included age-matched healthy controls. Results showed that patients with cancer had lower subjective and objective cognitive function compared to healthy controls; however, the sample included patients with a mix of MM and non-Hodgkin lymphoma, limiting specificity in assessing MM-related cognitive changes.

Many studies failed to account for age variability, comorbidities, and polypharmacy in MM populations. These factors contribute to the expected decline in frailty, mental health, and cognition, further confounding CRCI assessment. Such omissions complicate interpretations of whether cognitive impairment is due to cancer, treatment related, or instead reflects the natural course of aging and multimorbidity [59].

Our second objective was to examine the effect of treatment duration on cognition. We found significant impairment during intensive treatment (<6 months) but not in maintenance (6+ months). Early cancer treatment often induces the most pronounced cognitive changes due to heightened neuroinflammation, oxidative stress, and direct neuronal toxicity, [60] suggesting perceived deterioration was treatment-related, not solely attributable to disease progression or general age-related decline. The absence of significant self-reported effects beyond six months suggests cognitive function may stabilise following transition to maintenance therapy due to reduced treatment intensity and/or brain neuroplasticity [61]. Similar patterns have been reported in other cancer populations [62,63]. It remains unclear whether patients fully recover to pre-treatment cognitive levels or experience persistent CRCI.

Given the diversity of participant populations across papers, it is difficult to conclude the extent of cognitive deficits by treatment type. Included studies varied widely in mean age (50–71.4 years) and sex distribution (from 35.85 to 66.7 % male). Many studies attempted to collect data on education level [38–41,44,46,47,49,50], yet few reported or controlled for it [39–41,46,49]. Even fewer studies collected data on socioeconomic status [44,50], though some gathered information on income and work status [38,41,47]. Given the relationship between education, socioeconomic status, and cognitive ability is well-established in research [64,65], this lack of systemic reporting on key demographic factors can lead to misinterpretation of cognitive decline and reduced generalisability.

Greater focus on markers of disease progression and treatment pathways is required to better understand treatment impact. Cognitive outcomes vary with treatment intensity, duration, drug type, and patient-specific variables (e.g., baseline cognitive status, frailty, and neurological or psychiatric history). Identification of vulnerable subgroups, particularly older adults with multiple comorbidities, who may be disproportionately affected, is critical for developing more tailored and cognitively mindful therapeutic approaches.

Though most research relied on subjective (self-reported) measures, two studies (N = 42) [44,49] used objective measures, and when included, did not reveal significance (Supplementary Information 2). This mirrors findings in other cancer settings, e.g. Hutchinson et al. [66], where perceived cognitive impairment was more frequently reported than revealed by objective assessments. While self-report provides valuable insight into cognitive difficulties, these are susceptible to biases like mood disturbances, fatigue, and symptom awareness.

Twelve studies [38,39,42,43,46–48,50–54] used EORTC QLQ-C30 and PROMIS-29, which evaluate cognitive function by memory and attention. EORTC QLQ-C30 included only two cognitive-specific items, while variations of the PROMIS-29 incorporated between four and eight items assessing cognitive function. Both assess perceived cognitive functionality rather than actual cognitive performance and overlook deficits like inhibitory control and decision making.

Six studies [38,40,44,45,49] used objective, quantifiable measures (e.g., BrainCheck, MoCA), identifying some form of decline in cognitive functionality, e.g. language [41], memory [38,40,41,49], and executive functioning [38,40]. Impairments were often present pre-treatment; Bury-Kaminska et al. [49] found 63 % of participants showed impairment prior to AuHSCT, suggesting impairment might be related to MM or other diseases prevalent among older adults [67]. Only one study [38] incorporated both subjective and objective cognitive assessments [66]. Without objective assessments, it remains unclear whether observed cognitive impairments reflect true neurocognitive decline or are influenced by psychological and subjective factors.

Several included studies were large-scale investigations of HSCT-eligible cohorts (age range 50–71 years) [38,42,43,48,51–54], skewing results towards younger, fitter patients, despite UK MM incidence peaking at ages 85 to 89 [68]. Like many cancer trials, race or ethnicity data was often missing [69]. Nine studies focused on White, Caucasian patient groups [37–42,46,54,58], yet Black patients have a higher prevalence of MM than White and Asian patients [71]. Eight studies omitted ethnicity entirely [43,45,47,49–53]. This highlights the need for more inclusive approaches to participant recruitment and reporting practices.

Strengths of this review include stringent inclusion/exclusion criteria and quality appraisal. Despite evidence of cognitive decline during treatment, methodological concerns (limited data access, varied follow-up durations, lack of controls, overreliance on subjective reports) limit conclusions about whether impairments are within the normal range adjusted for age and comorbidity. Future research should integrate both subjective and objective cognitive assessments to enhance reliability and validity of CRCI findings. To address existing gaps, research should: (i) incorporate both neuropsychological and self-reported cognitive measures in observational and randomized treatment trials, (ii) include age- and education-matched healthy controls, and individuals with common age-related comorbidities, to improve comparability, (iii) explore cognitive outcomes by treatment regimens, (iv) ensure diversity and representation of patients with MM to enhance generalizability, and (v) adopt blinded data collection and analysis protocols to minimize bias and improve rigor.

5. Conclusion

This systematic review shows evidence of a longitudinal cognitive effect in patients with MM. Unfortunately, the paucity of literature on objective cognitive outcomes means it is difficult to clearly extrapolate the true extent of perceived detriment. There is an urgent need for robust objective cognitive measurement in patients with MM before and whilst receiving therapy. Studies should include healthy, age-matched controls, both subjective and objective measures, and reference to treatment pathways to better understand CRCI in patients with MM. It is crucial that efforts are made to measure the impact of treatment modalities and move towards personalised therapeutic choices that take account of cognition, a crucial aspect of functioning.

Author Contributions

Sumayyah Patel: Conceptualization; Methodology; Quality assessment; Data curation; Formal analysis; Validation; Investigation; Visualization; Writing – original draft; Writing – review & editing. **Melanie Burke:** Conceptualization; Supervision; Methodology; Validation; Quality assessment; Writing – review & editing. **Chris Parrish:** Conceptualisation; Supervision; Methodology; Visualization; Writing – review & editing. **Frances Seymour:** Conceptualization; Supervision; Methodology; Visualization; Writing – review & editing.

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Declaration of competing Interest

The authors 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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