Systematic Review

Clinical Response to Joint Infiltration With Bone Marrow Aspirate in Hip Osteoarthritis: A Systematic Review and Single-arm Meta-analysis

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Background: Hip osteoarthritis is a joint disease that causes worsening pain and inhibits activities of daily living. Due to poor pain control and the function of usual clinical treatment, joint infiltration with orthobiologics is a therapeutic alternative. Among these, bone marrow aspirate (BMA) represents a cellular therapy with promising clinical results.

Objective: Our study aimed to assess the clinical response of joint infiltration with BMA for hip osteoarthritis.

Study Design: We conducted a systematic review and meta-analysis of the main outcomes in hip osteoarthritis after infiltration with BMA and bone marrow concentrate (BMC).

Methods: We systematically searched PubMed, Embase, Cochrane, and Science Direct for studies evaluating patients with hip osteoarthritis who received joint infiltration with BMA or BMC. In the absence of studies with a control group, we performed a pairwise meta-analysis comparing results of a single group at follow-up vs baseline.

Results: We included 4 studies with improvement in Numeric Rating Scale pain scores associated with BMA or BMC therapy at 3 months (mean difference [MD], -3.48 points; 95% CI, -5.81 to -1.15), 6 months (MD, -3.25 points; 95% CI, -4.07 to -2.42), and 12 months (MD, -2.79 points; 95% CI, -3.83 to -1.74). There was also a significant improvement in measurable quality of life through validated questionnaires at 3 months (standardized mean difference [SMD], -0.91; 95%, CI -1.59 to -0.23), 6 months (SMD, -1.38; 95% CI, -1.79 to -0.98), and 12 months (SMD, -1.30; 95% CI, -2.44 to -0.16).

Limitations: Among our study's limitations is the lack of a randomized controlled trial in the meta-analysis. Also, since there was no comparator, we could not conduct a pairwise meta-analysis. Finally, the small sample size limits the generalization of the findings.

Conclusion: In this meta-analysis, joint infiltration with BMA or BMC was associated with an improvement in pain and quality of life in patients with hip osteoarthritis. Further randomized studies are needed to improve the quality of evidence.

Key words: Hip osteoarthritis, bone marrow aspirate, bone marrow concentrate

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Hip osteoarthritis (HOA) is a progressive joint disease that significantly affects quality of life. Characterized by chronic pain and considerable functional impairments, HOA often leads to impairment of activities of daily living (1).With population aging, the global prevalence of HOA has been estimated at 8.5%, placing a significant burden on health care systems (2).

A promising therapeutic approach is joint infiltration with orthobiologics, which aims to accelerate tissue healing and repair. Orthobiologics encompass a range of biological substances, including platelet-rich plasma, autologous conditioned serum, and stem cell therapies. Among these, bone marrow aspirate (BMA) has gained particular attention due to its potential to deliver a concentrated source of stem cells and growth factors directly to the affected joint (3,4).

Nonetheless, data on the efficacy of BMA is limited. To address this, we conducted a systematic review and single-arm meta-analysis to determine whether BMA improves outcomes relative to pain relief and overall quality of life for patients with hip osteoarthritis.

Methods

This systematic review and single-arm meta-analysis was conducted in accordance with the Cochrane Collaboration recommendations and Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (5,6). As such, its protocol was prospectively registered in PROSPERO under the protocol CRD42024566360.

Eligibility Criteria and Data Extraction

Studies meeting the following criteria were included: 1) full-text studies; 2) those assessing the efficacy of BMA or bone marrow concentrate (BMC) injection; 3) patients diagnosed with HOA. The exclusion criteria were: 1) overlapping populations; 2) patients with HOA for whom no data exist; or 4) case reports. There were no restrictions regarding the publication date or language.

Two authors (M.S. and F.V.) independently reviewed the reports to determine their eligibility through consensus. Discrepancies were resolved through consensus between the reviewers and a third author (E.M.) made the final decision in the event divergence was reached. All potentially relevant articles were reviewed by reading the full texts to identify eligible trial reports after excluding irrelevant studies. Data were manually extracted from eligible full-text articles.

Search Strategy

We systematically searched PubMed, Embase, Cochrane Library, and Science Direct databases from inception through June 2024. References of eligible papers and systematic reviews were also searched for additional studies. We included the following terms in our search strategy: "hip," "osteoarthritis," "bone marrow," and "bone marrow concentrate." The exact search strategy for each database is specified in Supplementary Table 1.

Endpoints and Subgroup Analysis

Pain was measured on the Numerical Rating Scale of pain intensity ranging from 0 (no pain) to 10 (extreme pain). For measuring quality of life, we used Western Ontario and McMaster Universities Osteoarthritis Index, Pain Disability Quality of Life Questionnaire, and Hip Disability and Osteoarthritis Outcome. Post administration of each orthobiologic, a final score of each questionnaire was calculated. As change from baseline is not commonly available across studies, the mean difference between follow-up and baseline values was used to assess improvement in those outcomes. A subgroup analysis was made for BMA and BMC for all endpoints. Finally, we also assessed the prevalence of responders to therapy at the follow-up windows of interest.

We extracted the following data from individual studies: 1) study characteristics including authors, study design, sample size, intervention, and length of follow-up; 2) patient characteristics including mean age and standard deviation, gender, and mean body mass index; 3) and the following outcomes: pain at 3 months, pain at 6 months, pain at 12 months, and the final score of questionnaires.

Quality Assessment and Quality of Evidence

We used the revised Cochrane risk-of-bias tool for assessing Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I), as per Cochrane recommendations (5). We selected pain as the outcome for assessment. Disagreements were resolved through consensus. The information was presented as a risk of bias graph and a risk of bias summary figure (Supplemental Fig. 1).

The quality of evidence was evaluated following the Grading of Recommendation, Assessment, Development, and Evaluations (GRADE) guidelines (Supplemental Fig. 2) (7). There was no quantitative assessment of small studies or publication bias, such as

a funnel plot, because the number of studies included in the meta-analysis was lower than 10 (8).

Statistical Analysis

All analyses were performed in R 4.3.0 (The R Foundation). Binary endpoints were summarized as a prevalence meta-analysis using arcsine transformation along with the inverse variance method. A restricted maximum likelihood random-effects model was applied along with a 95% CI (9). Prevalence endpoints were also assessed with a generalized linear mixed model to assess possible limitation of arcsine transformations (9). In addition, the compared postintervention values vs baseline parameters were calculated using an inverse variance random-effects model. We assessed for heterogeneity using Cochran's Q statistic and I^2 statistics. A *P* value lower than 0.05 was considered statistically significant for treatment effects. We considered high heterogeneity as $I^2 > 50\%$ (7,10).

Results

Study Selection and Characteristics

As shown in Fig. 1, the initial search produced 791 results. Following the removal of duplicate records and ineligible studies, 20 studies remained that were evaluated based on a predefined set of inclusion criteria. Of these, 4 studies were ultimately selected, comprising 81 patients. The patient characteristics and details of the studies are presented in Table 1 (11-15).

Pooled Analysis of Studies

There was a significant reduction in pain scores at the 3-month follow-up relative to baseline (mean difference [MD], -3.48 points; 95% CI, -5.81 to -1.15; $I^2 = 94\%$; $P < 0.01$; Fig. 2A). Subgroup analysis also demonstrated a significant improvement with BMC (MD, -4.50; 95% CI, -5.95 to -3.04; $I^2 = 80\%$; $P < 0.01$; Fig. 2A). Results remained consistent at the 6-month follow-up (MD, -3.25; 95% CI, -4.07 to -2.42; $I^2 = 38\%$; $P < 0.01$; Fig. 2B) and 12-month follow-up (MD, -2.79; 95% CI, -3.83 to -1,74; $I^2 = 43\%$; $P < 0.01$; Fig. 2C).

There was an improvement in quality of life at 3

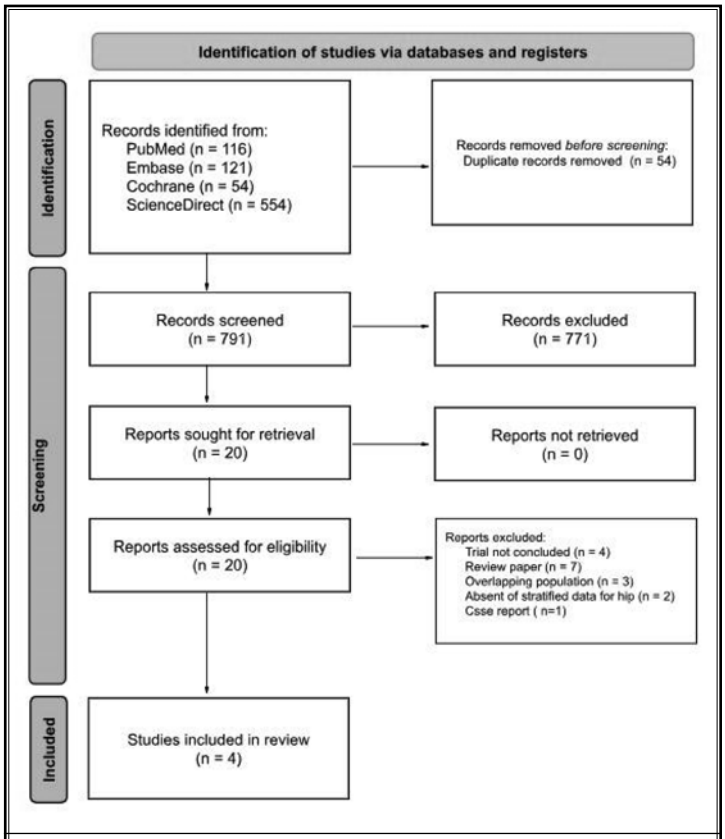

Fig 1. *Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) flow diagram of study screening and selection.*

Table 1. *Baseline characteristics.*

Author, Year	Study Design	Patients	Intervention	K-L	Age (years)	Women	BMI	Follow-up (months)
Darrow, 2018	Case Series	4	BMC	K1-K4	67.0	1 (25%)	26.2	3.0
Whitney, 2020	Case Series	16	BMC	K2-K4	57.6	9 (56.2%)	25.9	8.0
Tsitsilianos, 2022	Cohort	31	BMA	K2-K4	62.4	16 (51.6%)	NA	12.0
Burnham, 2021	Cohort	30	BMC	K1-K4	64.4	20(66.6%)	NA	12.0

Binary data is presented as n (%) and continuous data as mean unless otherwise specified; BMA: bone marrow aspirate; BMC: bone marrow concentrate; K-L: Kellgren-Lawrence Classification of Osteoarthritis; BMI: body mass index; NA: not applicable.

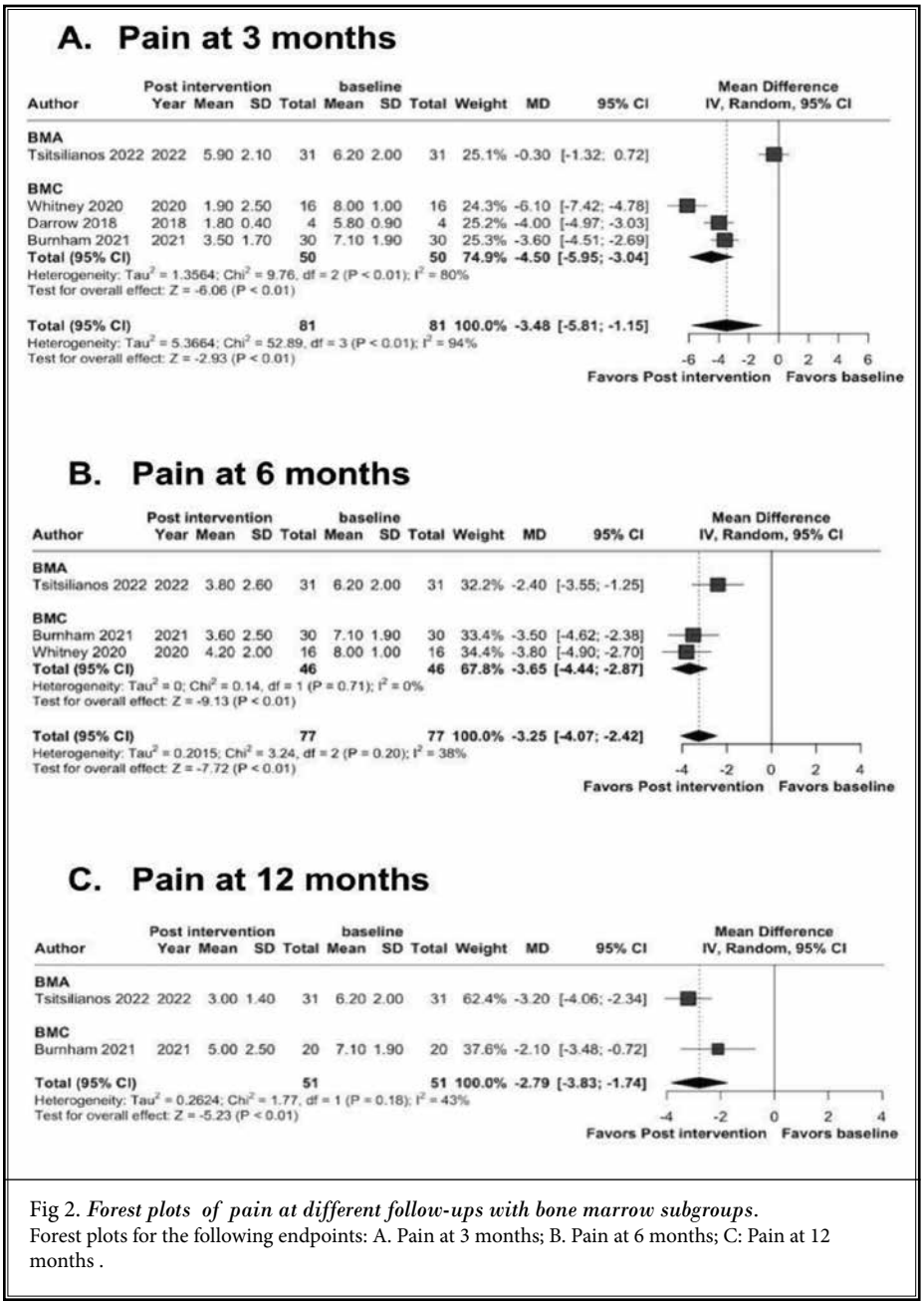

Fig 2. *Forest plots of pain at different follow-ups with bone marrow subgroups.*
Forest plots for the following endpoints: A. Pain at 3 months; B. Pain at 6 months; C: Pain at 12 months .

months relative to baseline, as indicated by a significant decrease in scores (standardized mean difference [SMD], -0.91; 95% CI, -1.59 to -0.23; I^2 = 74%; P = 0.01; Fig. 3A). A subgroup analysis for BMC also demonstrated a significant improvement (SMD, -1.13; 95% CI, -1.96 to -0.30; I^2 = 68%; P = 0.01; Fig. 3A). Results remained consistent at the 6-month follow-up (SMD, -1.38; 95% CI, -1.79 to -0.98; I^2 = 28%; P < 0.01; Fig. 3B) and 12-month follow-up (SMD -1.30; 95% CI, -2.44 to -0.16; I^2 = 88%; P = 0.03; Fig. 3C).

The prevalence of responders was 32.4% at the 3-month follow-up (95% CI, 11.9 to 63.0; I^2 = 88%; P < 0.01; Fig. 4A). At the 6-month follow-up, the prevalence increased to 50.8% (95% CI, 38.5 to 63.1; I^2 = 49%; P = 0.16; Fig. 4B). At the 12-month follow-up, the prevalence of responders was 36.5% (95% CI, 11.6 to 71.6; I^2 = 91%; P < 0.01; Fig. 4C).

Risk of Bias Assessment

As illustrated in Supplemental Fig. 1, all studies showed an overall assessment in ROBINS-I, indicating a critical or serious risk of bias. This bias primarily stemmed from issues related to confounding and the selection of patients, since randomization and blinding procedures were not feasible.

Quality Assessment

Quality assessment in GRADE demonstrated very low or low confidence due to the presence of studies with serious risk of bias, inconsistency, and imprecision issues. Hence, the actual effect might be different from the estimated effect, as illustrated in Supplemental Fig. 2 (7).

Discussion

In this meta-analysis of 4 studies with 81 patients who underwent joint infiltration with BMA or BMC for hip osteoarthritis, we found improvement in pain and quality of life in 3 post periods relative to baseline. In a subgroup analysis of BMC, there was also a satisfactory response.

Considering the prevalence of responders in this follow-up, we noted better response relative to pain reduction at the 6-month follow-up.

The increasing use of biological therapies to control pain in HOA appears as a therapeutic alternative given its incidence in older adults who wish to postpone more aggressive surgeries, such as total arthroplasty. BMA can be used in concentrate, in clot, or pure form with biological conditions and offer promising results (16). The low cost of performing this procedure makes it more accessible in clinical practice (17,18).

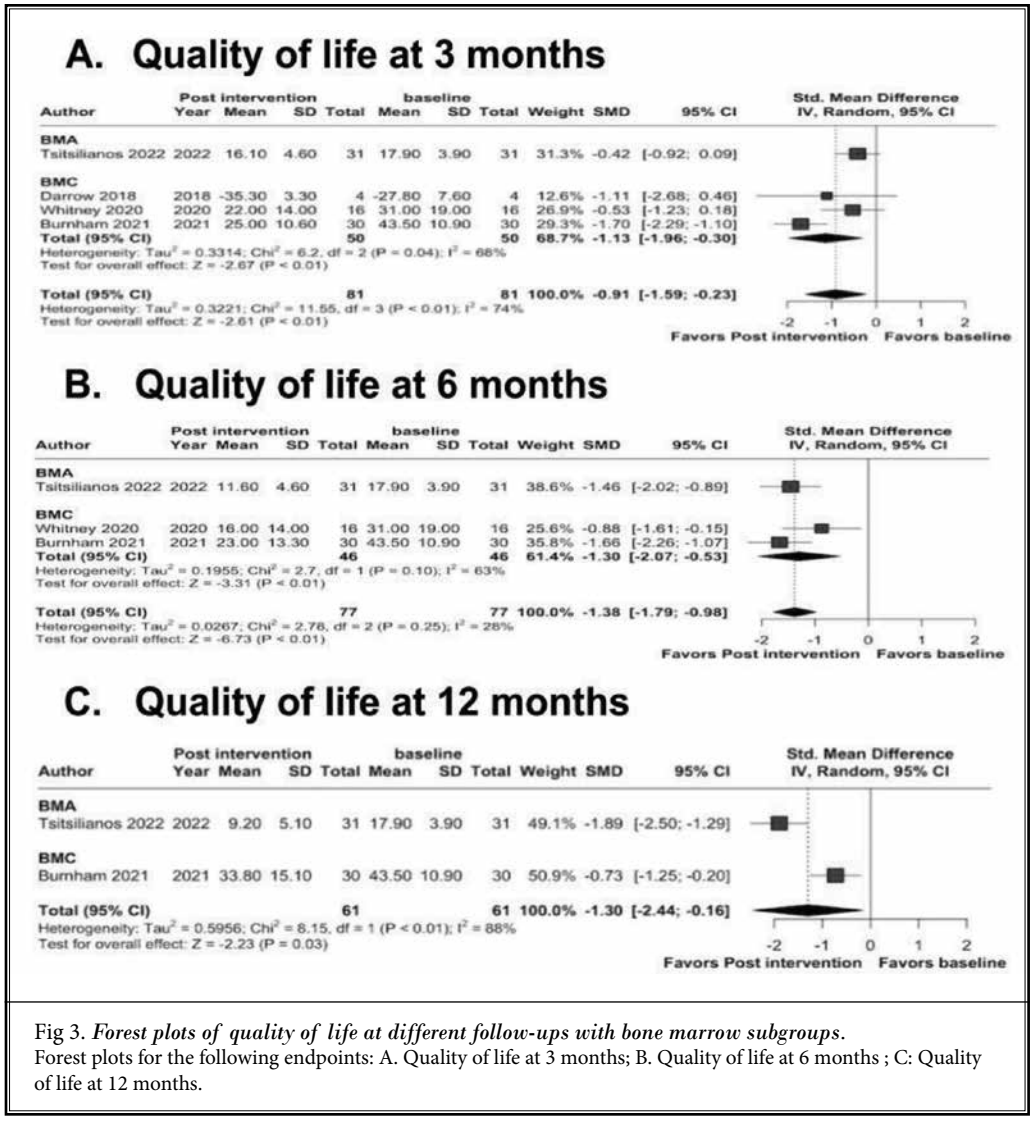

Fig 3. *Forest plots of quality of life at different follow-ups with bone marrow subgroups.*
Forest plots for the following endpoints: A. Quality of life at 3 months; B. Quality of life at 6 months ; C: Quality of life at 12 months.

Traditional treatment approaches for HOA, such as pain management and, in severe cases, joint replacement surgery, have limitations in terms of efficacy and long-term outcomes (19). In recent years, regenerative therapies have emerged, including BMC therapy; this has provided new hope for managing OA more effectively (20). BMC therapy harnesses the regenerative capabilities inherent in mesenchymal stem cells (MSCs) and growth factors found within bone marrow (21). MSCs are known for their ability to differentiate into various tissue types and to modulate the immune response, promoting tissue repair and reducing inflammation (22). The growth factors present in BMC, such as interleukin-1 receptor antagonist (IL-1Ra), IL-10, and transforming growth factor beta isoforms (TGF-β), further enhance its regenerative potential by stimulating local repair mechanisms (23).

Despite its promising therapeutic potential, BMC therapy faces regulatory challenges and practical limitations (24). Current guidelines restrict the clinical use of isolated and expanded bone marrow MSCs unless specifically approved by regulatory bodies, such as the US Food and Drug Administration (25).

Variability in the quality and quantity of MSCs obtained from BMA, influenced by donor characteristics and age, complicates standardization and widespread adoption of BMC therapy (26). However, clinical studies have demonstrated encouraging results in terms of pain relief, improved joint function, and reduced reliance on more invasive interventions like surgery (27).

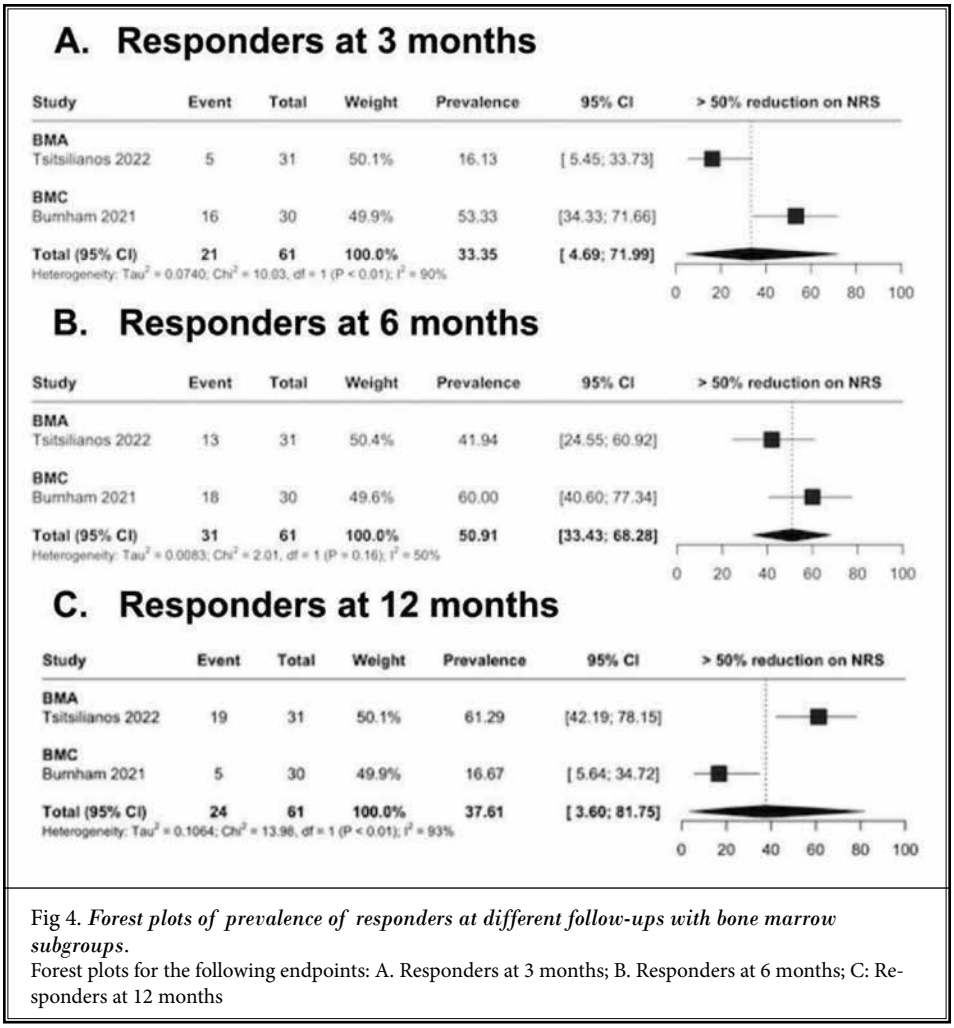

Fig 4. *Forest plots of prevalence of responders at different follow-ups with bone marrow subgroups*.
Forest plots for the following endpoints: A. Responders at 3 months; B. Responders at 6 months; C: Responders at 12 months

Studies have shown significant improvements in pain scores, functional outcomes, and patient-reported quality of life following BMC injections (28). Importantly, BMC therapy is generally well-tolerated with minimal adverse effects reported, making it a safer alternative to conventional treatments (29). Considering that few articles refer to the clinical application of BMA, it was reported that the pure form of BMA can be applied in orthopedic conditions, such as extraarticular pain in the hip trochanteric region without recurrence in one year or in severe knee osteoarthritis with good results in the first 3 months (30,31).

A previous systematic review by Zaffagnini and colleagues (32) investigated orthobiologic injections for hip osteoarthritis treatment; however, their study did not specifically focus on BMC injections and they did not conduct a statistical analysis. Therefore, to the best of our knowledge, ours is the first systematic review and meta-analysis to analyze joint infiltration with BMA for HOA, providing valuable insights on its effect on quality of life and pain relief.

Limitations

This study is not without limitations. First, the primary studies in our meta-analysis were observational in design and did not have a common comparator, which prevented conducting a pairwise meta-analysis. Nevertheless, our analyses allowed the interpretation of outcome improvement by comparing follow-up results with baseline parameters. Second, our analysis was based on a relatively small sample size of 81 patients, potentially limiting the generalizability of the findings. Third, there was a high risk of bias across the included studies, which could affect the reliability of the results. Fourth, the high heterogeneity of the pooled analysis highlights the likely effect of the different settings among the included studies due to observational design, similar but different biological products (BMA/BMC) and dose, therefore affecting the overall analysis.

These limitations highlight the importance of interpreting the outcomes cautiously. Further randomized trials are warranted to confirm the efficacy of joint infiltration with BMA for treating HOA.

Conclusion

Our findings indicate that BMC/BMA are associated with improvements in pain scores and quality of life at 3, 6, and 12 months post intervention in patients with HOA. Controlled studies, ideally randomized, are warranted to further confirm the efficacy and safety of these treatment strategies.

Authors' Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Michael Silveira Santiago and Mariana Tainá Oliveira. Quality assessment was performed by Michael Silveira Santiago and Fernanda Valeriano Zamora. The first draft of the manuscript was written by all authors. The correction of the final manuscript was done by Rosana Cipolotti. All authors read and approved the final manuscript.

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Supplementary Table 1. *Search strategies for each database.*

Database	Search strategy
PubMed	(Hip Osteoarthritis OR "Osteoarthritis, Hip"[Mesh]) AND ("Bone Marrow"[Mesh] OR bone marrow concentrate)
Embase	('Hip osteoarthritis' OR 'Hip osteoarthritis'/exp) AND ('bone marrow'/exp OR 'bone marrow concentrate')
Science direct	("Hip Osteoarthritis" AND "bone marrow")
Cochrane	('hip osteoarthritis' OR 'hip osteoarthritis'/exp) AND ('bone marrow'/exp OR 'bone marrow concentrate')

Supplementary Table 2. *Prevalence endpoints using the generalized linear mixed model method.*

Outcome	BMA (prevalence, 95%CI)	BMC (prevalence, 95%CI)	Overall (prevalence,95%CI)
Responders at 3 months	16.13 (5.45 to 33.73)	53.33 (34.33 to 71.76)	32.43 (11.91 to 63.01)
Responders at 6 months	41.94 (24.55 to 60.92)	60.00 (40.60 to 77.54)	50.82 (38.48 to 63.06)
Responders at 12 months	61.29 (42.19 to 78.15)	16.67 (5.64 to 34.72)	36.49 (11.59 to 71.57)

BMA: bone marrow aspirate; BMC: bone marrow concentrate; GLMM: generalized linear mixed model