

Dose-response Relationships of Mesenchymal Stem Cell as Living Biotherapeutics for Treating Osteoarthritis: A Systematic Review and Meta-analysis of RCTs

Mohammad Fateh Martini

Sulaiman AIRajhi University

Syed Mohammad Habib

Sulaiman AIRajhi University

Nour Kosai Sahwan

Sulaiman AIRajhi University

Muhammad Candragupta Jihwaprani

Sidra Medical

Khawaja Husnain Haider

khhaider@gmail.com

Sulaiman AIRajhi University <https://orcid.org/0000-0002-7907-4808>

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Abstract

Background

An optimal MSC dose for safe but efficacious treatment of osteoarthritis remains elusive despite encouraging results from RCTs. Our study aimed to evaluate the dose-response relationship of MSC therapy in knee OA, with a focus on safety and patient-reported efficacy outcomes.

Methods

Following PRISMA guidelines and PROSPERO registration (CRD420251101887), four electronic databases—PubMed/MEDLINE, Scopus, Web of Science, and Clinicaltrials.gov—were searched up to June 2025. Eligible clinical trials analyzed efficacy outcomes as standardized mean differences (SMDs) for the VAS and the WOMAC. Safety outcomes, including non-serious AEs (AEs) and serious AEs (SAEs), were expressed as risk ratios (RRs). Subgroup analyses were conducted for low ($< 50 \times 10^6$ cells), medium ($50 - < 100 \times 10^6$ cells), and high ($\geq 100 \times 10^6$ cells) dose categories, comparing each subgroup with the control arm and between subgroups.

Results

Thirty clinical trials met inclusion criteria ($n = 1,731$). Only the high-dose group showed a significant risk of AEs ($RR = 1.43 [1.09 - 1.89]$, $p = 0.01$) compared with controls, with no significant difference in SAEs. Functionally, low- and high-dose MSCs improved WOMAC scores at 3-months, with sustained benefits at 6- and 12-month follow-up, particularly for medium-dose injections ($SMD = -0.96 [-1.62 - 0.30]$, $p = 0.004$). Pain reduction on the VAS was significant at 6- and 12-month follow-up in the low- and medium-dose groups, but not in the high-dose group.

Conclusion

A medium dose ($50 - 100 \times 10^6$ cells) of MSCs as living biodrugs for knee OA is efficacious, with the most consistent balance between safety and efficacy. High doses confer no additional benefits but increase mild AEs incidence.

Introduction

Osteoarthritis (OA) is the most prevalent degenerative joint disorder worldwide, affecting over 300 million individuals and representing a major contributor to pain, disability, and loss of function in older adults [1, 2]. The contemporary non-surgical management strategies (i.e., physical therapy, NSAIDs, and intra-articular (IA) corticosteroid or hyaluronic acid (HA) injections, platelet-rich plasma (PRP) therapy, bone marrow aspirate concentrate (BMAC), micro-fragmented adipose tissue (MFAT), and targeted biologic agents, such as antibodies to TNF- α , IL-1, and NGF) hold promise for symptomatic outcome without altering disease progression [3, 4]. Although total knee arthroplasty (TKA) can offer substantial pain reduction and functional improvement, it is invasive, costly, and associated with significant postoperative risks, making it less suitable for younger or medically complex patients [3, 5–6].

Mesenchymal stem cells (MSCs), as living biotherapeutics, have emerged as a promising treatment option for OA due to their chondrogenic, immunomodulatory, and anti-inflammatory properties [7, 8]. A substantial number of clinical trials and pooled meta-analyses evaluating IA injections of MSCs derived from different tissue sources have reported improvements beyond symptomatic relief, including pain and function, and, most importantly, cartilage quality [9–11]. Despite encouraging clinical outcomes, substantial variability exists among published trials, particularly in relation to dosage of injected MSCs, cell source, expansion method, and injection protocols. Emerging evidence from regenerative medicine research indicates that MSC dose may significantly influence therapeutic efficacy through dose-dependent paracrine signaling, immune modulation, and tissue repair mechanisms [12, 13]. It is essential to establish an optimal dose for any drug to achieve a safe and optimal outcome, given that dose is the primary pharmacokinetic parameter.

With the increasing clinical use of MSC therapy and the heterogeneity of dosing strategies across trials, there is a critical need to systematically evaluate a dose–response relationship for MSC interventions in OA. Establishing such a relationship is essential not only for optimizing treatment protocols, improving patient outcomes, guiding regulatory standardization, and supporting rational dose selection in future trials, but also for determining the optimal MSC dose that maximizes therapeutic benefit with minimal adverse events. This meta-analysis primarily aims to investigate the dose–response relationship of MSC therapy in OA by examining how varying MSC doses influence patient-reported outcomes across clinical trials.

Methodology

Protocol and Registration

This meta-analysis was conducted whilst strictly adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study is PROSPERO-registered (CRD420251101887).

Literature Search Strategy

The search for eligible clinical trials was conducted between March and June 2025 across four electronic databases: PubMed/MEDLINE, Scopus, Web of Science, and Clinicaltrials.gov. All eligible records were systematically retrieved and screened. The keyword combination included for the search was:

Osteoarthritis; Knee osteoarthritis; Stem cell therapy; Mesenchymal stem cell therapy; Intra-articular injection; and clinical trial, and was constructed according to the search engine of each database. SH and MM screened the eligible studies, with the third or fourth authors (MJ and/or KH) consulted when there was uncertainty about study inclusion.

Eligibility Criteria

We included studies that satisfied all of the following criteria: (1) human clinical trials published from inception to June 2025, (2) non-single-arm trials; (3) had intervention arms receiving MSCs injection; (4) reported the safety and efficacy outcomes of interest; (5) provided defined doses of injected cells. On the contrary, we excluded non-clinical trials, single-arm studies, non-English-language studies, trials without dosing details, trials of non-MSC therapies, and those that reported an undefined MSC dose.

Data Extraction

Four authors (MJ, MM, SH, and NS) independently extracted data from all RCT titles and abstracts, identified the eligible studies, and finalized their inclusion after a full-text review. Disagreements and discrepancies were discussed and resolved upon discussion with MJ and KH. Data were extracted using a standardized electronic form (prepared by MJ and SH) that included fields for first author, publication year, location, study arms, sample size, MSC source, MSC dosage, injection frequency, follow-up duration, and defined outcome measures.

Quality Assessment

Four authors (SH, MM, NS, and MJ) independently assessed the quality and risk of bias for each RCT using the Cochrane Risk of Bias 2 (RoB 2) tool. This tool evaluates seven domains, i.e., random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias [14]. For each domain, the risk was classified as low, high, or unclear. Based on these ratings, the overall quality of each trial was determined as good (all seven domains were rated as having a low risk of bias), fair (only one domain was rated as having a high risk of bias, or no more than two domains were rated as having an unclear risk of bias that was unlikely to affect the outcome), or poor (two or more domains were rated as having a high or unclear risk of bias that was likely to have a significant impact on the outcome).

Outcome Measures

This meta-analysis concerns patient-related outcomes. Changes in pain severity were assessed using the Visual Analog Scale (VAS). Functional assessment was performed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), which includes subscales for pain, stiffness, and physical function. Both constituted the efficacy outcomes. In addition, we also examined the safety by analyzing the incidence of non-serious adverse events (AEs) and serious AEs (SAEs). Those outcomes were analyzed at each follow-up interval (3, 6, and 12–18 months) to better reflect the long-term efficacy of the therapy, based on available published data.

Statistical Analysis

Continuous outcomes, including all efficacy outcomes (i.e., VAS and WOMAC), were reported as mean $\pm$ standard deviation (SD) and analyzed using standardized mean differences (SMD). Pooled safety outcomes were dichotomous data and thus reported as risk ratios (RR). A random-effects model was used when heterogeneity was high; otherwise, a fixed-effects model was used. To investigate the dose-response relationship, studies were primarily grouped by MSC injectate dose: low dose ($< 50 \times 10^6$ cells), medium dose (50×10^6 to $< 100 \times 10^6$ cells), and high dose ($\geq 100 \times 10^6$ cells). Subgroup analyses were conducted based on these dose categories in addition to control arms, i.e., those without MSCs injection, to explore potential effect modification. Heterogeneity was evaluated using the I^2 statistic, with I^2 values $< 25\%$, 25% – 75% , and $> 75\%$ considered low, moderate, and high, respectively [15]. Furthermore, publication bias was assessed visually using the funnel plot. The outcome data from the graphs were extracted using PlotDigitizer version 3.1.6 (2025; <https://plotdigitizer.com>). The conversion from median and interquartile range (IQR) to mean and standard deviation (SD) was performed using standardized methods described by Luo et al. and Wan et al. [16, 17]. In addition, mean differences $\pm$ SD for the included studies were estimated using the Meta-Analysis Accelerator [<https://ma-accelerator.com/>], which has been considered a reliable and accurate method for converting statistical data [18]. The statistical analyses were performed in Review Manager (RevMan) [Computer program]. Version 5.4. The Cochrane Collaboration, 2020.

Results

Literature search results

The summary of the literature search is shown in Figure 1. Initially, we retrieved a total of 330 records across the four included databases: PubMed/MEDLINE ($n=26$), Clinicaltrials.gov ($n=117$), Scopus ($n=130$), and Web of Science ($n=57$). Screening for duplicates excluded 63 records; an additional 219 records were excluded during title/abstract screening—a full-text screening of 48 studies excluded 18 studies. A total of 30 trials that met the eligibility criteria were included in the meta-analysis [9,10,19–46].

Characteristics of included RCTs

Table 1 summarizes the characteristics of the included trials (n=30). The study pooled data from 1,731 participants; 48.2% (n=836) received MSCs. The mean age ranged from 55.8 to 57.5 years, and the majority of participants were female (62.5%, n=1082). The trials were conducted across 14 countries, with the majority in China (n=6), South Korea (n=5), Iran (n=4), and Spain (n=3). Only 2 studies were non-randomized trials [22,43]. The source of MSCs includes adipose-derived MSCs (AD-MSCs) (n=15), bone marrow-derived MSCs (BM-MSCs) (n=9), umbilical cord MSCs (UC-MSCs) (n=4), and placenta-derived MSCs (P-MSCs) (n=2). Autologous sources of MSCs were obtained in 15 trials, while the remaining 15 trials received allogeneic MSCs (n=15). According to the dosing categories, participants were assigned to three doses: low-dose ($<50 \times 10^6$ cells; n = 434), medium-dose ($50-75 \times 10^6$; n = 137), and high-dose ($\geq 100 \times 10^6$; n = 265). The remaining 895 participants served as controls. The follow-up periods ranged from 1 to 24 months, and disease severity in 26 studies was graded using the Kellgren–Lawrence imaging scale, with most patients classified as grade 2–3 and a few as grade 1 or grade 4. About the methodological quality of the included trials, the Cochrane risk-of-bias assessment summary is shown in Figure 2, and the risk of bias for each study is summarized in Supplementary Figure S1.

Analyses of outcomes

The summary of the analyzed outcomes is pooled in Table 2.

Safety outcomes

Risks of non-serious adverse events

Regarding non-serious adverse events (AEs), a significantly higher risk was only observed in the high-dose subgroup ($>100 \times 10^6$ cells) compared with the control groups (RR [95% CI] = 1.43 [1.09–1.89], $p = 0.01$). On the other hand, despite the trends toward increased events relative to control, both the medium- and low-dose subgroups did not demonstrate a significant difference (RR [95% CI] = 1.32 [1.00–1.74], $p = 0.05$; RR [95% CI] = 1.11 [0.95–1.30], $p = 0.18$; respectively). Comparisons between different injected doses revealed no significant differences in AE risk. Overall heterogeneity was low ($I^2 = 25\%$), with subgroup analysis indicating that the high-dose vs. control comparison accounted for most of the observed variability (moderate heterogeneity, $I^2 = 37\%$). The forest plot of non-serious AEs is displayed in Figure 3.

Risks of serious adverse events

Compared with control groups, no significant differences in SAE incidence were observed across the included studies (Supplementary Figure S2). This finding was consistent across all dosing categories: low dose (RR [95% CI] = 0.90 [0.35–2.28], $p = 0.82$), medium dose (RR [95% CI] = 0.33 [0.01–7.82], $p = 0.50$), and high dose (RR [95% CI] = 0.90 [0.34–3.21], $p = 0.35$). Similarly, no significant differences in safety outcomes were noted when comparing doses directly—low vs medium (RR [95% CI] = 2.89 [0.50–16.71], $p = 0.24$), low vs high (RR [95% CI] = 0.33 [0.02–7.32], $p = 0.49$), and medium vs high (RR [95% CI] = 0.33 [0.04–2.96], $p = 0.32$). The included studies demonstrated overall homogeneity, which was consistent across all subgroup analyses ($I^2 = 0\%$).

Efficacy outcomes

Changes in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score

The change in mean WOMAC score is shown in Figure 4 and in Supplementary Figs. S3–S4. At 3 months following IA injection of MSCs, we found a significant improvement in WOMAC score among low-dose and high-dose subgroups when compared to control groups, i.e., low-dose (SMD [95% CI] = -0.34 [-0.57 – -0.11], $p=0.004$) and high-dose (SMD [95% CI] = -0.36 [-0.56 – -0.17], $p=0.0002$). By 6 months post-injection, all dose subgroups showed a significant improvement compared with control groups, with the greatest improvement observed in the low-dose subgroup (SMD [95% CI] = -0.56 [-1.09 -0.03], $p = 0.04$). Those improvements were sustained at 12 months post-injection in the subgroups, except for the low subgroup, which showed no significant difference in WOMAC score by 12 months (SMD [95% CI] = -0.83 [-1.71 – 0.04], $p=0.06$). It should be noted that the high heterogeneity among reporting studies in the low-dose vs. control subgroup ($I^2 = 91\%$). Compared with the control group, there were significant improvements at 12 months with medium-dose (SMD [95% CI] = -0.96 [-1.62 – -0.30], $p=0.004$) and high-dose (SMD [95% CI] = -0.53 [-1.05 – -0.02], $p=0.04$). In addition, there was no improvement in WOMAC scores across doses at 3–6 months, with only the medium dose showing a significant improvement in the overall WOMAC score compared with the high dose (SMD [95% CI] = -0.71 [-0.85 -0.56], $p=0.04$). However, this was reported by only two studies [21,23].

Changes in the visual analog scale (VAS) score from baseline

At 3 months following MSC injection, there was no significant difference in VAS scores relative to baseline across any subgroup (Supplementary Figure S5). However, by 6 months post-injection, significant improvements in pain scores were observed in the low- and medium-dose groups compared with the control group — low dose vs control (SMD [95% CI] = -0.52 [-0.85 – -0.19], $p = 0.002$) and medium dose vs control (SMD [95% CI] = -0.51 [-0.95 – -0.06], $p = 0.03$). No significant differences were observed between the high-dose and control groups, or among the dose subgroups, at this time point (Supplementary Figure S6). A similar pattern was noted at 12 months post-injection, with significant pain reduction compared to control observed only in the low-dose (SMD [95% CI] = -0.59 [-0.94 – -0.25], $p = 0.0008$) and medium-dose (SMD [95% CI] = -0.57 [-0.94 – -0.19], $p=0.003$) groups (Supplementary Figure S7). Again, there were no significant differences in pain reduction between the high-dose and control groups or among the different dose subgroups.

Publication bias risk assessment

A funnel plot was constructed to assess publication bias qualitatively. As observed in Figure 5, the plot showed a roughly symmetrical distribution of studies around the central vertical line, suggesting a low likelihood of significant publication bias. Most studies clustered near the top of the plot, indicating smaller standard errors and higher precision, whereas a few scattered toward the bottom, reflecting greater variability.

Discussion

This meta-analysis was conducted to elucidate the optimal dosing strategy for MSC injections in OA. It included 30 clinical trials, comprising a pooled sample of 1,731 participants, with almost half receiving MSC therapy ($n = 836$). Some of the salient features of our study include: 1. This is the largest meta-analysis to date evaluating the safety and efficacy of intra-articular injection of MSCs as living biopharmaceuticals in OA patients; 2. It primarily focuses on the Primary Pharmacokinetic parameter of cell dose as a step towards establishing a dose–response relationship, which remains elusive so far; 3. Our data indicate that the high-dose MSC subgroup ($\geq 100 \times 10^6$ cells) was the only category associated with a significantly increased incidence of non-SAE, reflecting a 43% increase compared to controls ($p = 0.01$). In contrast, no significant differences in SAE were observed across all dose groups. 4. to pain outcome – mean VAS change, significant improvements were observed in the low- ($< 50 \times 10^6$ cells) and medium-dose ($50\text{--}<100 \times 10^6$ cells) groups relative to the control group, as observed at 6 months and were sustained at 12 months post-injection; 5. Lastly, functional outcomes, i.e., mean change in WOMAC scores, demonstrated significant improvement across all dose categories at 6 months compared with control; however, sustained benefits at 12 months were limited to the medium- and high-dose subgroups. In summary, the medium-dose subgroup outperformed the high-dose subgroup at the 12-month follow-up. These data suggest that a medium dose, i.e., between 50×10^6 and less than 100×10^6 cells, may represent the optimal dosing strategy for MSC-based intra-articular injections in OA patients.

Previously published evidence suggests that local administration of IA MSCs is safe, with most AEs being mild, transient, and mostly injection-related [19, 47–49]. This was further emphasized in our analysis. However, we found that only the high-dose ($> 100 \times 10^6$ cells) IA MSCs administration was associated with a significantly increased risk of non-serious AEs compared with controls. By contrast, there was no significant risk in the low- and medium-dose groups compared with the control groups. Although these AEs were benign, local, and transient, these findings demonstrated a dose-response relationship in the administered injectables, which should be considered when selecting an appropriate dosing regimen. This pattern was also described by Cao et al., who reported higher rates of mild, self-limiting AEs in high-dose MSC arms [48]. Our study also emphasized findings from earlier studies that reported no significant increase in the risk of SAEs between MSC-treated patients and controls across all dose categories [19, 49, 50]. Furthermore, Tian et al. found no significant safety risks associated with MSC source or donor tissue type (i.e., allogeneic vs. autologous). These included the risk of arthralgia and local swelling, which were comparable to those in the control groups [49]. Taken together, our findings are consistent with the available literature on the safety of IA MSC administration in knee OA. However, the higher frequency of non-serious AEs at higher doses affects the selection of an appropriate dosing strategy.

There is a paucity of meta-analytical studies comparing different doses of MSC injectables in OA. Huang et al. reviewed 16 studies on AD-MSCs and found that high-dose AD-MSCs (i.e., $> 50 \times 10^6$ cells) performed better than lower-dose and control groups but were more frequently associated with AEs [51]. In contrast, Cao et al. suggest that a dose of $100\text{--}200 \times 10^6$ cells (considered the high-dose subgroup in the study) improved the WOMAC score at 6-month follow-up. However, at 12 months, both the high-dose and low-dose ($10\text{--}64 \times 10^6$ cells) groups showed significant improvements in the WOMAC score [48]. Meanwhile, Rahmadian et al. suggested that a dose $> 25 \times 10^6$ cells conferred no additional therapeutic benefits [52]. However, this was evident only in a meta-regression analysis that pooled data from 8 RCTs involving only 300 patients [52]. They also did not perform a subgroup analysis to compare different dose ranges. Among the aforementioned studies, both Huang et al. and Cao et al. appear to be partly consistent with our efficacy findings, in which the dose range of $50\text{--}<100 \times 10^6$ cells was effective at the 12-month follow-up period [48, 51]. In addition, there was no dose-response analysis for improvement in VAS score. A meta-analysis of three RCTs by Tian et al. on UC-MSCs, pooling 101 participants, found a significant improvement in VAS scores; however, no dose-response subgroup analysis was performed for this outcome [49].

Our finding that medium-dose MSCs yielded greater improvement in WOMAC than high-dose MSCs may reflect a ceiling effect, although this was supported by only two included studies. While clinical benefits were generally reproducible across MSC sources, as demonstrated in individual clinical trials, the magnitude and durability of improvement varied and appeared to depend on product-specific characteristics, with sustained effects reported at 12–48 months in a few studies. Additionally, key determinants such as baseline OA severity, mechanical alignment, cell source and processing methods, co-interventions, and heterogeneity in study design likely influenced treatment response. It must also be noted that key factors affecting success include patient- or disease-related factors, such as OA severity, limb alignment, cell source and processing methods, concomitant treatments, and study design heterogeneity. These factors may have contributed to the variable effect sizes observed across dosing subgroups in our analysis, but they could not be formally investigated.

Strengths, limitations, and future directions

This meta-analysis has several notable strengths. Concentrating specifically on dosing strategies enabled comparisons not only between different dose categories and the control arm but also among the dose subgroups themselves. This method has not been used in prior studies. This approach offers a more nuanced understanding of how the quantity of MSC injectate influences both safety and efficacy outcomes, including whether higher doses necessarily translate into superior therapeutic benefit. The analysis incorporated key safety outcomes, i.e., AEs and SAEs, as well as patient-reported efficacy measures directly relevant to quality of life (QoL) and functional independence. As previously noted, this study represents the largest meta-analysis to date examining MSC dosing in knee OA, encompassing 1,731 pooled participants, of whom 836 received MSCs. Furthermore, the inclusion of high-quality clinical trials with $> 90\%$ randomization of participants also indicates a high level of evidence in this field.

Nonetheless, several limitations exist. This review did not conduct subgroup analyses based on MSC donor type (autologous versus allogeneic) or tissue origin (e.g., AD-MSCs, BM-MSCs, UC-MSCs, p-MSCs, and others). These aspects fall outside the scope of the present analysis and have been addressed in

prior meta-analytical studies [48, 53]. The study was also restricted to English-language publications due to limited linguistic resources, which may affect the generalizability of the findings. Finally, despite comprehensive efforts to capture all relevant data, specific dosing subgroups, particularly the high-dose cohort, had relatively small numbers of participants in the efficacy analyses. We recommend that future studies further evaluate the proposed intra-articular dose of 50 million to < 100 million MSCs beyond 12 months to better characterize long-term outcomes. Such analyses may also clarify whether a single IA MSC injection is adequate or if scheduled repeat injections are needed to maintain therapeutic efficacy and improve long-term functional outcomes.

Future trials should assess whether the current optimal dose of $50\text{--}<100 \times 10^6$ MSC maintains its effectiveness beyond 12 months and whether repeat booster injections provide additional benefit. Additionally, upcoming trials should standardize cell characterization and dosing protocols to minimize heterogeneity and confirm reproducible dose–response effects.

Conclusion

Our meta-analysis suggests that intra-articular injection of MSCs at doses of 50×10^6 to 100×10^6 cells is safe and effective for the treatment of OA. This dose range was associated with no significant risk of AEs or SAEs. It provided sustained improvements in pain (defined as mean change in VAS score) and function (defined as mean change in WOMAC score) at 12 months post-injection, compared with control and other dosing strategies. Future studies should focus on the long-term efficacy of the defined dosing strategy.

Declarations

Authors' Contributions

Conceptualization: KH, SH, MM; methodology: MJ, SH, MM; software: MJ; validation: KH, MJ; database searching: MJ, SH, MM; reports screening: MJ, SH, and MM; quality assessment: MM, NS, and SH; data extraction and analysis: MJ, NS, MM, and SH; writing—original draft preparation: MJ, NS, MM, and SH; writing—review and editing: MJ and KH; visualization: MJ; supervision: MJ and KH. All authors have read and agreed to the final version of the manuscript.

Conflict of interest:

The authors declare they have no competing interests

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Tables

Table 1. Baseline Characteristics of Included RCTs

First author	Year	Registry	Arms		Dose (cells)	Dose category	Country	Phase	Blinding	Randomization	Sample size	
											Each arm (n)	Total (n)
Freitag, et al.	2019	ACTRN12614000814673	3	Tx1	100 x 10^6	High	Australia	NA	Single	Yes	10	30
				Tx2	100 x 10^6 (twice)	High					10	
				Con	NA	NA					10	
Kim et al.	2023	NCT03990805	2	Tx	100 x 10^6	High	Korea	3	Double	Yes	125	250
				Con	NA	NA					127	
Qiao et al.	2020	NCT02855073	3	Tx1	50 x 10^6	Medium		2a	Single	Yes	10	30
				Con	NA	NA					10	
				Con	NA	NA					10	
Holiuk, et al.	2025	NCT04453111	2	Tx	60 x 10^6	Medium	Ukraine	1	Open-label	No	15	20
				Con	NA	NA					11	
ZoghAli et al.	2025	IRCT20151017024572N19	2	Tx	30 x 10^6	Low	Iran	NA	Double	Yes	30	50
				Con	NA	NA					27	
Gupta et al.	2016	NCT01453738	6	Tx1	25 x 10^6	Low	NA	NA	Double	Yes	10	60
				Tx2	50 x 10^6	Medium					10	
				Con1	NA	NA					10	
				Tx3	75 x 10^6	Medium					10	
				Tx4	150 x 10^6	High					10	
				Con2	NA	NA					10	
Dilogo, et al.	2024	NCT03800810	4	Tx1	10 x 10^6	Low	Indonesia	NA	Double	Yes	12	50
				Tx2	10 x 10^6	Low					14	
				Con1	NA	NA					13	
				Con2	NA	NA					12	
Emadedin et al.	2018	NCT01504464	2	Tx	40 x 10^6	Low	Iran	1/2	Triple	Yes	19	40
				Con	NA	NA					24	
Lee et al.	2019	NCT02658344	2	Tx	100 x 10^6	High	South Korea	2b	Double	Yes	12	20
				Con	NA	NA					12	

First author	Year	Registry	Arms	Dose (cells)	Dose category	Country	Phase	Blinding	Randomization	Sample size		
										Each arm (n)	Total (n)	
Bastos, et al.	2020	CONEP-14878813.4.0000.5533	3	Tx1	40 x 10^6	Low		NA	Double	Yes	16	40
				Tx2	40 x 10^6						14	
				Con	NA						17	
Lee et al.	2024	NCT04240873 KC19CNSI0469	2	Tx	100 x 10^6	High	South Korea	NA	Double	Yes	12	24
				Con	NA	NA					12	
Kim et al.	2022	NCT03000712	2	Tx	100 x 10^6	High	South Korea	1/2	open-label	Yes	13	26
				Con	NA	NA					13	
Jo, et al.	2017	NCT01300598	3	Tx1	10 x 10^6	Low	South Korea	1/2	Single	Yes	3	12
				Tx2	50 x 10^6	Medium					3	
				Tx3	100 x 10^6	High					12	
Lamo-Espinosa et al.	2016	NCT02123368 EudraCT: 2009-017624-72	3	Tx1	10 x 10^6	Low	Spain	1/2	No	Yes	10	30
				Tx2	100 x 10^6	High					10	
				Con	NA	NA					10	
Pico et al.	2025	NCT04863183	2	Tx	5 ± 0.5 x 10^6	Low	Colombia	1/2	Double	Yes	15	30
				Con	NA	NA					15	
Mautner et al.	2023	NCT03818737	4	Tx	20 x 10^6	Low	United States	3	Single	Yes	118	472
				Con1	NA	NA					118	
				Con2	NA	NA					119	
				Con3	NA	NA					120	
NCT02674399	2021	NCT02674399	2	Tx	100 x 10^6	High	Unites States	2	Double	Yes	19	38
				Con	NA	NA					9	
Lamo-Espinosa et al.	2020	NCT02365142	2	Tx	100 x 10^6	High	Spain	3	Double	Yes	24	48
				Con	NA	NA					26	
Ho, et al.	2022	CUHK_CCT00469	2	Tx	60 x 10^6	Medium	China	NA	Single	Yes	10	20
				Con	NA	NA					10	
Soltani, et al.	2019	IRCT2015101823298N	2	Tx	50 - 60 x 10^6	Medium	Iran	NA	Double	Yes	10	20

First author	Year	Registry	Arms	Dose (cells)	Dose category	Country	Phase	Blinding	Randomization	Sample size	
										Each arm (n)	Total (n)
			Con	NA	NA					10	
Freitag. et al.	2024	ACTRN12617001095358 / ACTRN12621000622808	4	Tx1	10 x 10 ⁶	Australia	1/2a	Double	Yes	8	4
				Tx2	20 x 10 ⁶					8	
				Tx3	50 x 10 ⁶					8	
				Tx4	100 x 10 ⁶					8	
				Con	NA					8	
Sajadi, et al.	2025	IRCT2016021123298N3	2	Tx	50 x 10 ⁶	Iran	NA	Triple	Yes	10	2
				Con	NA					10	
Vega et al.	2015	NCT01586312	2	Tx	40 x 10 ⁶	Spain	1/2	Triple	Yes	15	3
				Con	NA					15	
Lu, et al.	2019	NCT02162693	2	Tx	50 x 10 ⁶	China	2b	Double	Yes	26	5
				Con	NA					26	
Matas, et al.	2018	NCT02580695	3	Tx1	20 x 10 ⁶	Chile	1/2	Double	Yes	9	2
				Tx2	40 x 10 ⁶					9	
				Con	NA					8	
Pers et al.	2016	NCT01585857	3	Tx1	2 x 10 ⁶	Germany & France	1	Open-Label	No	6	1
				Tx2	10 x 10 ⁶					6	
				Tx3	50 x 10 ⁶					6	
Song et al.	2017	NCT01809769	3	Tx1	10 x 10 ⁶	China	1/2a	Double	Yes	6	1
				Tx2	20 x 10 ⁶					6	
				Tx3	50 x 10 ⁶					6	
Lu, et al.	2020	IRCT2016021123298N3	3	Tx1	10 x 10 ⁶	China	1	Double	Yes	7	2
				Tx2	20 x 10 ⁶					8	
				Tx3	50 x 10 ⁶					7	
Zhao et al.	2019	NCT02641860	4	Tx1	10 x 10 ⁶	China	1/2a	Double	Yes	6	1

First author	Year	Registry	Arms	Dose (cells)	Dose category	Country	Phase	Blinding	Randomization	Sample size		
										Each arm (n)	Total (n)	
			Tx2	20 x 10^6	Low						6	
			Tx3	50 x 10^6	Medium						6	
Gupta et al.	2023	CTRI/2018/09/015785	2	Tx	25 x 10^6	Low	India	3	Double	Yes	73	1
				Con	NA	Con					73	

Abbreviations: AD-MSCs, adipose-derived mesenchymal stem cells; ADSVF, adipose-derived stromal vascular fraction; BM-MSCs, bone marrow-derived mesenchymal stem cells; Con, control arm; F, female; FU, follow-up; hP-MSCs, human placental-derived mesenchymal stem cells; hUC-MSC, human umbilical cord-derived mesenchymal stem cells; M, male; MSCs, mesenchymal stem cells; NA, not available; Tx, treatment arm.

Table 2. Summary of forest plots of safety and efficacy outcomes

Outcomes	Low vs control		Medium vs control		High vs control		Low vs Medium		Low vs High		Medium vs High	
	Mean (95% CI)	p	Mean (95% CI)	p	Mean (95% CI)	p	Mean (95% CI)	p	Mean (95% CI)	p	Mean (95% CI)	p
Safety outcomes												
AEs	1.11 (0.95–1.30)	0.18	1.32 (1.00–1.74)	0.05	1.43 (1.09–1.89)	0.01	0.97 (0.82–1.16)	0.76	0.88 (0.69–1.12)	0.3	0.93 (0.68–1.28)	0.67
SAEs	0.90 (0.35–2.28)	0.82	0.33 (0.01–7.82)	0.5	0.34 (0.04–3.21)	0.35	2.89 (0.50–16.71)	0.24	0.33 (0.02–7.32)	0.49	0.33 (0.04–2.96)	0.32
Efficacy outcomes												
WOMAC												
3 months	-0.34 (-0.57–-0.11)	0.004	-0.38 (-0.77–0.02)	0.06	-0.36 (-0.56–-0.17)	0.0002	-0.05 (-0.46–0.36)	0.8	-0.06 (-0.68–0.56)	0.85	0.12 (-0.50–0.75)	0.7
6 months	-0.56 (-1.09–-0.03)	0.04	-0.48 (0.78–-0.18)	0.002	-0.33 (-0.63–-0.03)	0.03	-0.22 (-0.62–0.17)	0.26	-0.41 (-0.98–0.16)	0.16	-0.12 (-0.67–0.44)	0.68
12 months	-0.83 (-1.71–0.04)	0.06	-0.96 (-1.62–-0.30)	0.004	-0.53 (-1.05–-0.02)	0.04	-0.10 (-0.66–0.45)	0.71	-0.42 (-1.36–0.53)	0.39	-0.68 (-1.32–-0.04)	0.04
VAS												
3 months	0.00 (-0.18–0.17)	0.99	-0.19 (-0.71–0.32)	0.46	-0.06 (-0.39–0.28)	0.74	-0.06 (-0.39–0.28)	0.71	-0.16 (-0.79–0.47)	0.62	-0.08 (-0.71–0.54)	0.8
6 months	-0.52 (-0.85–-0.19)	0.002	-0.51 (-0.95–-0.06)	0.03	-0.06 (-0.47–0.36)	0.79	-0.35 (-0.73–0.04)	0.08	0.20 (-1.21–1.61)	0.78	0.41 (-1.24–2.06)	0.62
12 months	-0.59 (-0.94–-0.25)	0.0008	-0.57 (-0.94–-0.19)	0.003	-0.29 (-0.92–0.34)	0.37	-0.23 (-0.66–0.20)	0.3	-0.23 (-1.5–1.03)	0.72	-0.11 (-1.24–1.02)	0.84

Abbreviations: AEs, non-serious adverse events; CI, confidence interval; SAEs, serious adverse events; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Figures

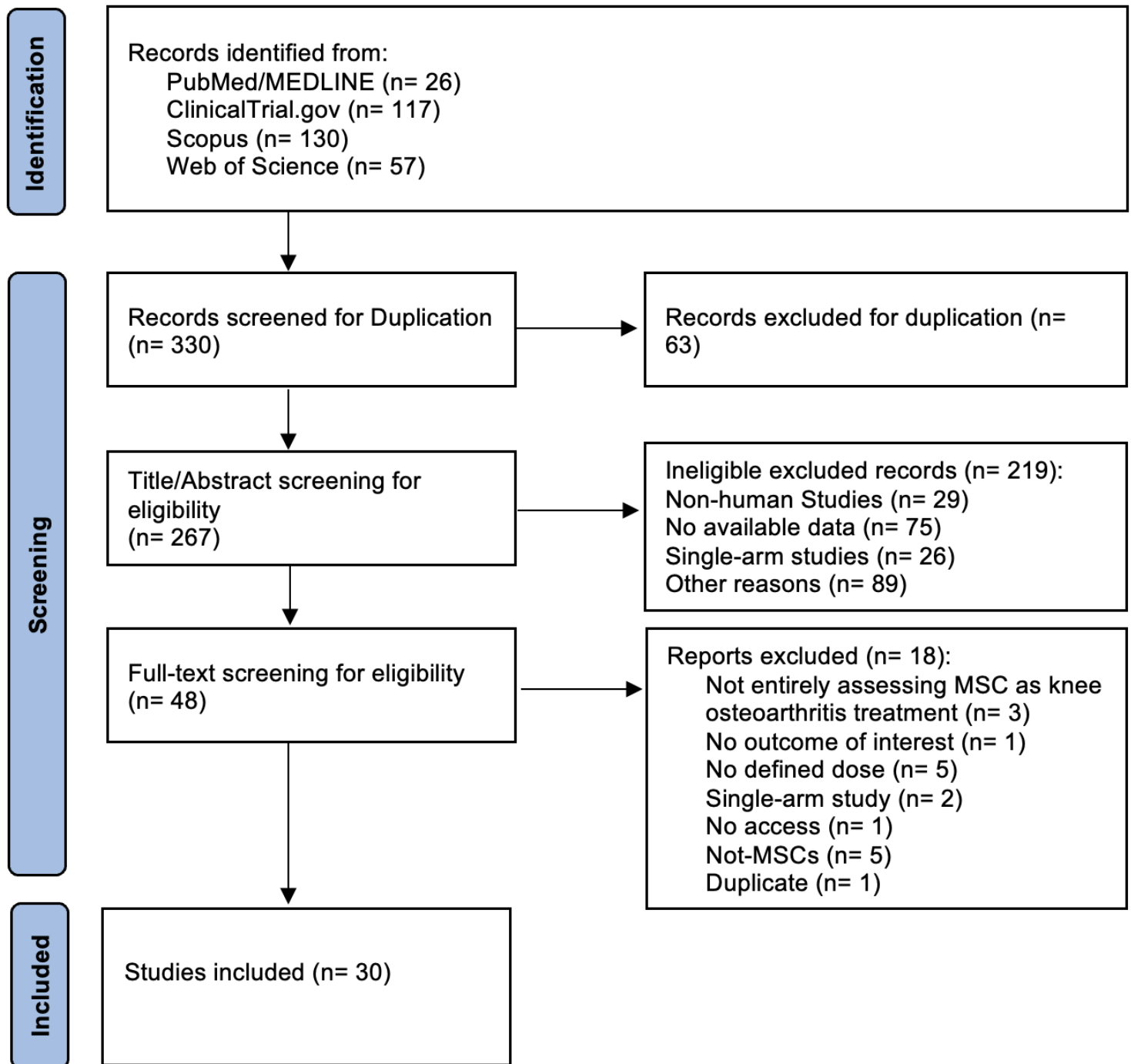


Figure 1

PRISMA flow chart.

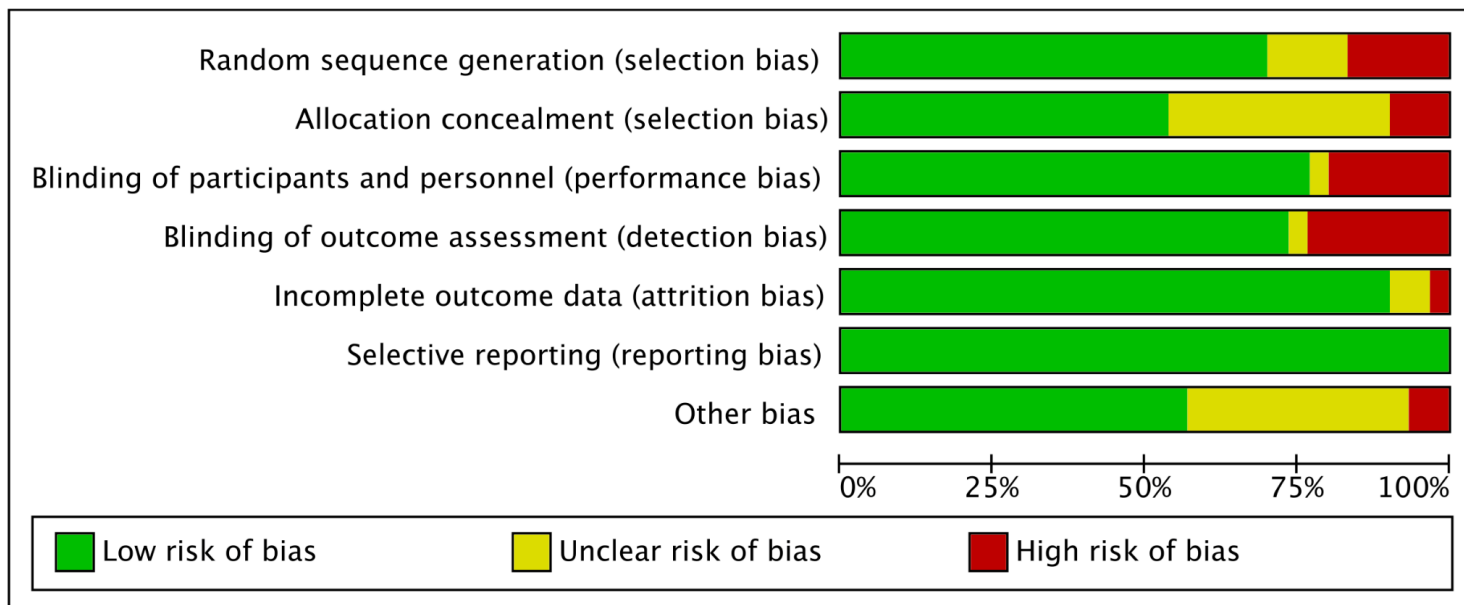


Figure 2

Cochrane Risk of Bias summary of included studies.

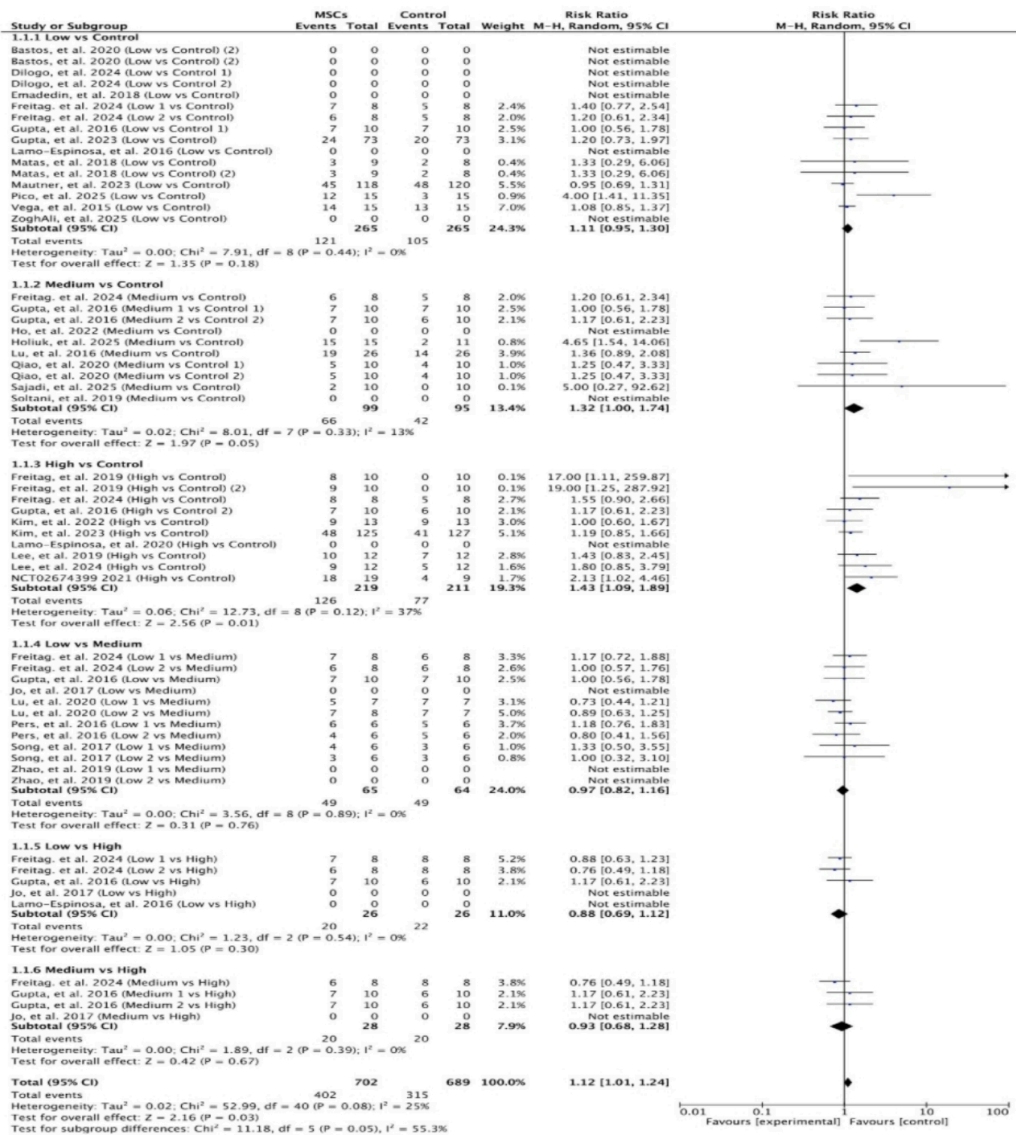


Figure 3

Forest plot of non-serious adverse events (non-ASE).

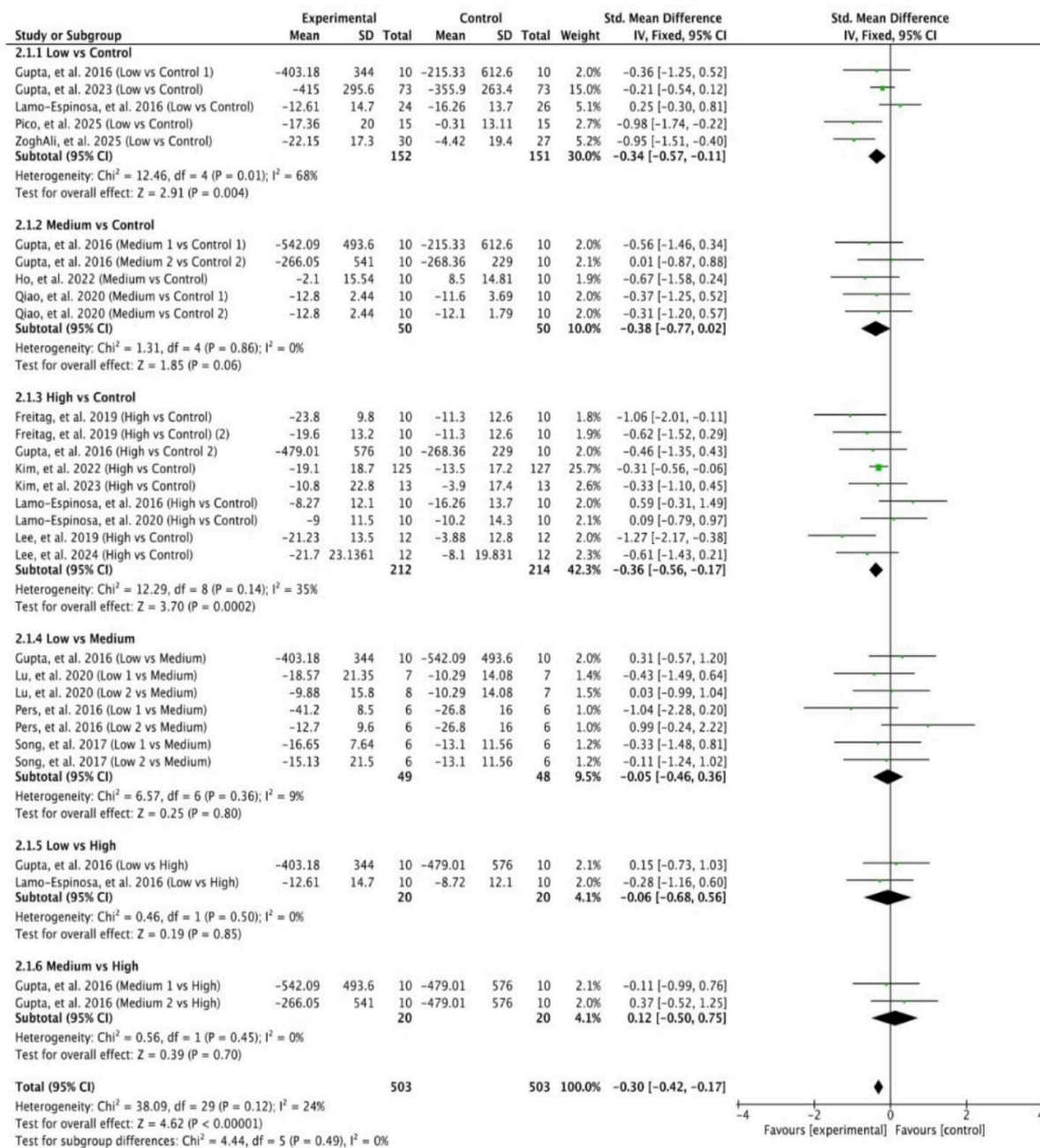


Figure 4

Forest plot of WOMAC at 3 months.

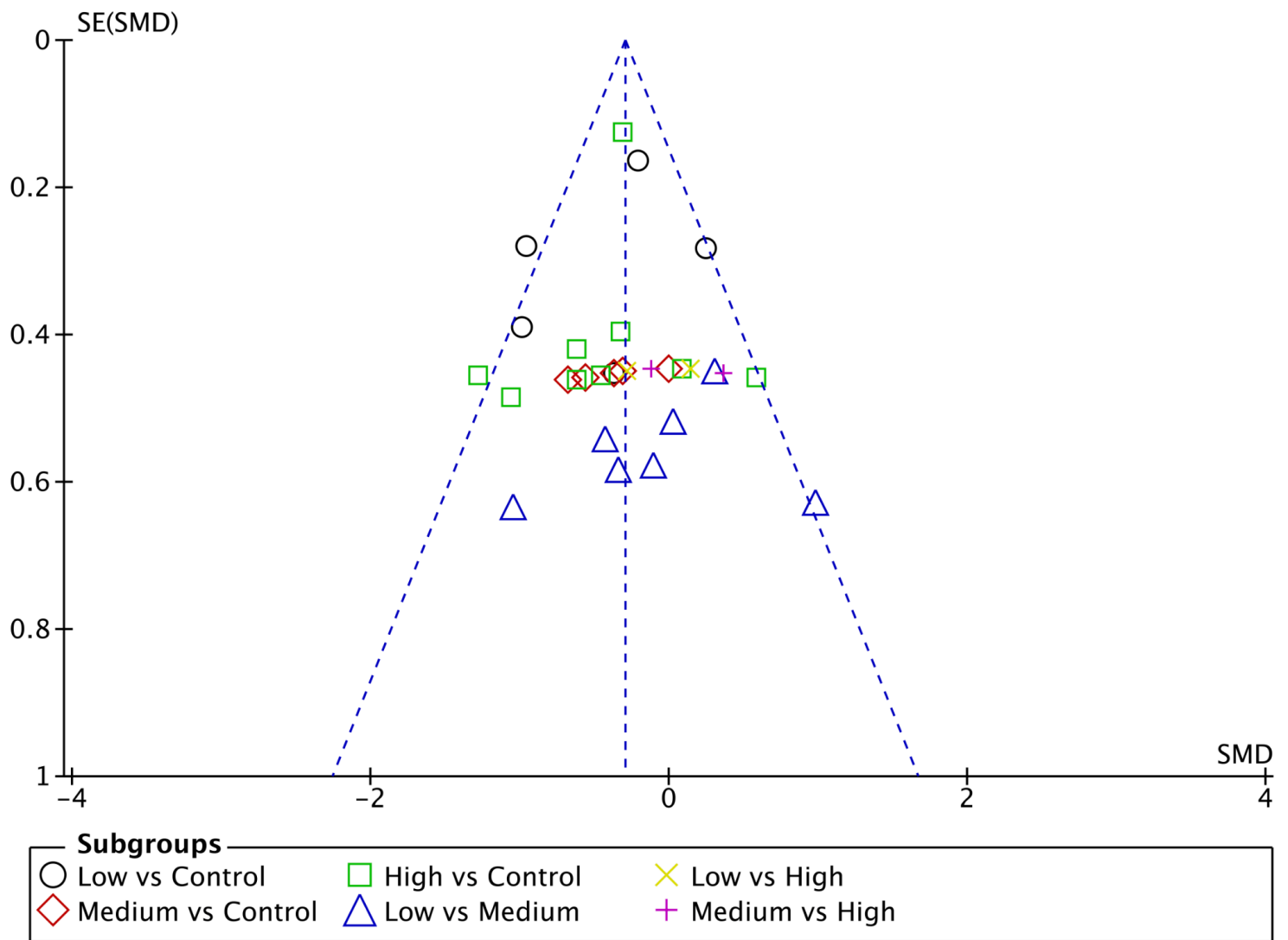


Figure 5

Funnel plot diagram showing a roughly symmetrical distribution of the analyzed studies.

Supplementary Files

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