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Efficacy and safety of single versus repeated injections of mesenchymal stem cells for the treatment of knee osteoarthritis: a systematic review and network meta-analysis of randomized controlled trials

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Abstract

Background In recent years, mesenchymal stem cells (MSCs) have been widely applied in the clinical treatment of knee osteoarthritis (KOA), demonstrating promising therapeutic efficacy. However, intervention protocols for MSCs have not yet been standardized, and evidence regarding the impact of different injection frequencies on the efficacy and safety of MSC treatment in KOA remains limited.

Objective This study aims to integrate evidence from conventional and network meta-analyses to evaluate the efficacy and safety of different intervention frequencies (single vs. repeated MSC injections) in the treatment of knee osteoarthritis (KOA).

Methods A systematic search was conducted in PubMed, Embase, the Cochrane Library, and Web of Science databases up to March 1, 2025. Traditional meta-analysis was performed to assess the efficacy and safety of MSC therapy for KOA, followed by a network meta-analysis (NMA) to evaluate the effectiveness of single versus repeated MSC injections. Outcome measures included WOMAC and VAS scores at 3, 6, and 12 months, as well as the incidence of adverse events (AEs). Traditional meta-analysis and NMA were conducted using Review Manager 5.3 and Stata SE16.0, respectively.

Results A total of 16 RCTs involving 622 patients were included. Traditional meta-analysis showed that MSC therapy significantly improved pain and knee joint function in KOA patients at different time points (3, 6, and 12 months). The results of the network meta-analysis (NMA) indicated that, compared to single MSC injections, repeated MSC

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injections provided greater improvements in pain and functional scores at 6 and 12 months, demonstrating superior efficacy. However, repeated MSC injections were also associated with a higher incidence of adverse events.

Conclusions Both single and repeated MSC injections could improve pain and knee joint function in patients with KOA. Compared to single injections, repeated MSC injections may offer superior therapeutic benefits; however, they are associated with a higher incidence of adverse events. In clinical practice, potential side effects of repeated MSC administration must be carefully considered. Future research should focus on large-scale, multicenter, and long-term randomized controlled trials to further validate the efficacy and safety of MSC therapy for KOA.

Keywords Osteoarthritis, Mesenchymal stem cells, Repeated injections, Network meta-analysis, Efficacy

Introduction

Osteoarthritis (OA) is the most prevalent chronic joint disease worldwide, with 595 million symptomatic and radiographically diagnosed cases reported globally in 2020 [1]. OA has become a major cause of disability among adults over the age of 70, and it is projected that by 2025, the number of individuals with OA-related disability will reach 11.016 million [2]. The knee joint, being the most commonly affected site in OA, exhibits significant age- and sex-related differences in prevalence [3]. Epidemiological data indicate that the prevalence of symptomatic knee OA (KOA) in individuals aged 60 and above is 10% in men and 13% in women, with over 250 million people affected worldwide [4, 5]. Characterized by pain and restricted joint mobility, KOA directly leads to diminished quality of life and impaired physical function [6]. Recent studies suggest a trend toward earlier onset of KOA, potentially associated with changes in lifestyle and the increasing prevalence of metabolic syndrome [7]. Additionally, OA-related healthcare expenditures impose a substantial economic burden, with annual costs in the United States reaching as high as $139.8 billion [8]. As the global population continues to age and obesity rates rise, the disease burden of KOA is expected to intensify [9, 10].

Current clinical interventions for KOA primarily rely on non-surgical and surgical approaches. Non-surgical treatments include lifestyle modifications (such as exercise and weight management), pharmacological pain relief (e.g., nonsteroidal anti-inflammatory drugs), and intra-articular injections (including corticosteroids and hyaluronic acid), aiming to alleviate pain and improve joint function [11, 12]. However, these measures offer only short-term symptomatic relief and fail to reverse the degenerative changes in cartilage, allowing disease progression to continue [13, 14]. For patients in the end-stage of KOA, joint replacement surgery may serve as a standard operation, yet it is limited by factors such as prosthesis longevity, the risk of postoperative complications, patient age, and surgical tolerance [15]. Existing treatment strategies fall short in terms of long-term efficacy and disease control, highlighting the urgent need for innovative therapies that can both manage symptoms and delay disease progression.

Mesenchymal stem cells (MSCs) have emerged as a focal point in regenerative medicine research for KOA due to their unique biological properties [16]. Studies have shown that MSCs modulate the joint microenvironment through multiple mechanisms, including immunoregulation, anti-inflammatory effects, and promotion of regeneration, thereby inhibiting degenerative progression and facilitating cartilage repair [6–9, 14, 17, 18]. Their secretory activity and trilineage differentiation potential (osteogenic, chondrogenic, and adipogenic) further support the capacity to repair damaged knee joint tissues [19, 20]. Compared to knee arthroplasty, intra-articular injection of MSCs offers a minimally invasive alternative [21], with multiple preclinical and clinical trials confirming its safety and effectiveness in symptom relief [22, 23].

However, there is still controversy regarding the standardized treatment protocols for MSCs, including factors such as the source of MSCs and the intervention dosage. Previous meta-analyses have primarily focused on exploring the effects of different sources and intervention doses on the efficacy for KOA patients [24, 25]. Notably, in an animal study, Mahmoud et al. [26] found that multiple MSC injections could effectively improve knee joint lesions induced by osteoarthritis and reduce inflammation, which has sparked widespread attention on the efficacy and safety of single versus multiple MSC injections. Most past studies have involved a single intra-articular MSC injection, assuming that multiple injections may offer potential benefits. Recently, Matas et al. [27] were the first to demonstrate, through a triple-blind randomized controlled trial (RCT), that repeated MSC injections show good safety over a 1-year follow-up period compared to the control group. Therefore, this study first compares the efficacy and safety of different intervention protocols in treating KOA patients through traditional meta-analysis. Given the limited number of direct comparative studies between single and repeated MSC injections, we also use network meta-analysis (NMA) to integrate both direct and indirect evidence, exploring the differences in efficacy and safety at different follow-up time points (3, 6, and 12 months) between single versus

repeated injections. This meta-analysis aims to identify the intervention protocol most likely to benefit patients, balancing efficacy and safety risks, and provide evidence-based recommendations for the optimal MSC intervention strategy for KOA.

Materials and methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for conducting a network meta-analysis [28]. The study protocol was prospectively registered in the PROSPERO database (CRD420251025791).

Search strategies

We searched all articles in online databases, including Embase, PubMed, Web of Science, and the Cochrane Library, with a search cutoff date of March 2025. We constructed the search strategy using MeSH terms and free words, mainly focusing on "mesenchymal stem cells" and "knee osteoarthritis". Detailed search strategies based on Boolean operators can be found in Supplementary Table 1. Two authors independently performed the search process, and any discrepancies in search results were discussed and resolved with a third author. To avoid missing relevant articles, we also conducted a reference search for all included studies.

Eligibility criteria

1) Population (P): Adults (≥ 18 years old) with radiographically confirmed knee osteoarthritis. Studies involving inflammatory arthritis, post-traumatic cases without degenerative changes, or studies with significant comorbidities were excluded.
2) Interventions (I) and Comparators (C): Intra-articular injection of mesenchymal stem cells (MSCs), administered as a single dose or multiple doses (≥ 2 injections). The control group represented "conventional therapy", including hyaluronic acid (HA), corticosteroids, saline, placebo, and acetaminophen. Trials combining MSC therapy with surgery or adjunctive biologics were excluded.
3) Outcomes (O): The primary outcomes were changes in the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) total score and visual analogue scale (VAS) score at 3-, 6- and 12-months post-intervention. Secondary outcomes included the Knee Injury and Osteoarthritis Outcome Score (KOOS), total adverse events (AE), and serious adverse events (SAE). Studies lacking quantifiable outcome data were excluded.
4) Study Design (S): Only full-text, peer-reviewed RCTs or controlled clinical trials were considered. Conference abstracts, reviews, meta-analyses, animal studies, and non-controlled studies were excluded.

Study selection

All retrieved records were imported into Endnote 20 (Clarivate Analytics) for automatic removal of duplicates. The remaining records underwent a two-stage screening process: (1) First stage: Two independent authors screened titles and abstracts based on predefined eligibility criteria to exclude clearly irrelevant studies. (2) Full texts of potentially eligible studies were reviewed for further assessment according to the same criteria. Any discrepancies during this stage were resolved through discussion with a third author. The study selection process was illustrated using a PRISMA flow diagram, detailing the number of exclusions and reasons at each stage.

Data extraction

A standard Excel template was created for data extraction, and the entire extraction process was conducted independently by two authors. The following variables were extracted: (1) Study characteristics: First author, publication year, country, study type, sample size per group, patient age, height, weight, BMI, randomization method, and follow-up duration. (2) MSC intervention details: MSC source, injection frequency, dose, and injection site. (3) Baseline data, WOMAC total score and VAS score at 3, 6 and 12 months, KOOS score, and safety outcomes (AE and SAE). For graphical data, the mean ± standard deviation (mean ± SD) was extracted using Origin 2021. Any discrepancies in data extraction were resolved through joint review and discussion with a third author. In cases of unclear outcome measurement data, attempts were made to contact the corresponding author.

Risk of bias assessment

The methodological quality of the included RCTs was assessed using the Cochrane risk of bias tool. Two independent researchers evaluated five domains: selection bias, performance bias, detection bias, attrition bias, and reporting bias. Each domain was rated as "low risk of bias", "unclear risk of bias", or "high risk of bias". In cases where the evaluation results were not consistent, a third researcher participated in discussions to reach a consensus.

Assessment of evidence certainty

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework was used to assess the quality of evidence for the NMA results [29–31]. The evidence quality levels are classified into four categories: high, moderate, low, and very low. For direct

comparisons (which in this study are primarily based on RCTs, with an initial quality level of high), potential downgrading was considered based on factors such as risk of bias, inconsistency, indirectness, imprecision, and publication bias. For indirect comparisons, the starting quality is determined by the lower quality of direct evidence from the primary contributing first-order loops, and further assessment was made to determine whether intransitivity exists, which may lead to downgrading. The quality of the evidence for the NMA results is then determined by combining both direct and indirect evidence, as well as their relative contribution (information size) to the network estimate. Furthermore, when determining the final grade of the NMA results, careful consideration was given to local inconsistencies within the network and the precision of the combined effect size in the NMA [32].

Statistical analysis

A conventional meta-analysis was performed using Review Manager 5.3 to calculate effect sizes from direct evidence. For categorical data, including AE and SAE, the odds ratio (OR) with a 95% confidence interval (CI) was used. For continuous data, including WOMAC, VAS, and KOOS scores, the standardized mean difference (SMD) and its corresponding 95% CI were calculated. Since the conventional therapy group included various different control groups, the outcomes prior to injection were used as the control group for traditional meta-analysis. Statistical heterogeneity was assessed using the I^2 statistic, with I^2 >50% indicating substantial heterogeneity. The choice between fixed-effects and random-effects models was based on clinical and methodological considerations, including the anticipated heterogeneity in study designs, populations, and MSC intervention protocols. A random-effects model was prioritized given the expected clinical variability across studies. To enhance the reliability of the analysis, only studies with ≥3 direct comparison pieces of evidence were included in the pooled analysis. To assess the potential impact of publication bias on the results, subgroup analyses were conducted to investigate whether studies with differing methodological quality yielded inconsistent findings. The trim-and-fill method [33] was used to assess the impact of publication bias on the results and the stability of the findings. A P-value < 0.05 was considered statistically significant.

NMA was conducted using the "mvmeta" and "network" packages in Stata/SE 16.0. The evidence network was visualized using a network plot, where nodes represented interventions, with node size reflecting sample size, and the thickness (or numbers) of connecting lines indicating the number of direct comparisons. A global inconsistency test was performed, and a consistency model was adopted when the P-value of the Z-test was >0.05 [34]. Additionally, the surface under the cumulative ranking (SUCRA) was used to rank the interventions based on outcome measures, providing a direct interpretation of the probability that each intervention was the most effective [35]. Publication bias for each outcome was assessed using funnel plots. Sensitivity analysis was used to assess the robustness of the results.

Results

Search results

A total of 527 potential records were initially retrieved from the databases. After automatically removing 182 duplicates using Endnote 20,345 records remained. Subsequently, 304 studies were excluded based on title and abstract screening by two authors. The full texts of the remaining 41 articles were reviewed, and 16 studies [27, 36–50] met the eligibility criteria and were included in both the conventional and network meta-analyses. The detailed study selection process is illustrated in Fig. 1.

Study characteristics

The 16 studies included were all RCTs published in English, with a time span of within the past 10 years. The studies covered multiple regions globally, including Europe (Spain, Portugal, Latvia), Asia (China, South Korea, India, Iran), the Americas (United States, Mexico, Chile), and Oceania (Australia), reflecting broad regional participation.

A total of 622 patients were involved in the clinical trials. The experimental group included 323 patients, with 261 receiving a single injection of MSCs, and the remaining 62 patients receiving repeated injections of MSCs. Sixteen studies (23 datasets) involved 547 patients. Fourteen studies (18 datasets) described single MSC injections, while four studies (5 datasets) investigated repeated MSC injections. Notably, two studies included both single and repeated MSC injections. Some studies compared the efficacy of multiple MSC dosage cohorts with conventional treatments, and each cohort was labeled as (1), (2), or (3). Furthermore, the sources of MSCs included BMSC (N = 9), AD-MSC (N = 6), and UC-MSC (N = 1). The injection doses ranged from 1×10^7 to 1×10^8 cells. The control group treatments included hyaluronic acid (N = 9), saline (N = 3), placebo (N = 1), acetaminophen (N = 1), and corticosteroids (N = 1). The main characteristics of the included studies are shown in Tables 1 and 2.

Risk of bias assessment

The risk of bias for the included RCTs was assessed using the Cochrane Collaboration tool [51]. Most studies were consistent in registration and reporting, with selective reporting deemed to have a low risk of bias. One study employed a single-blind design and was rated as high

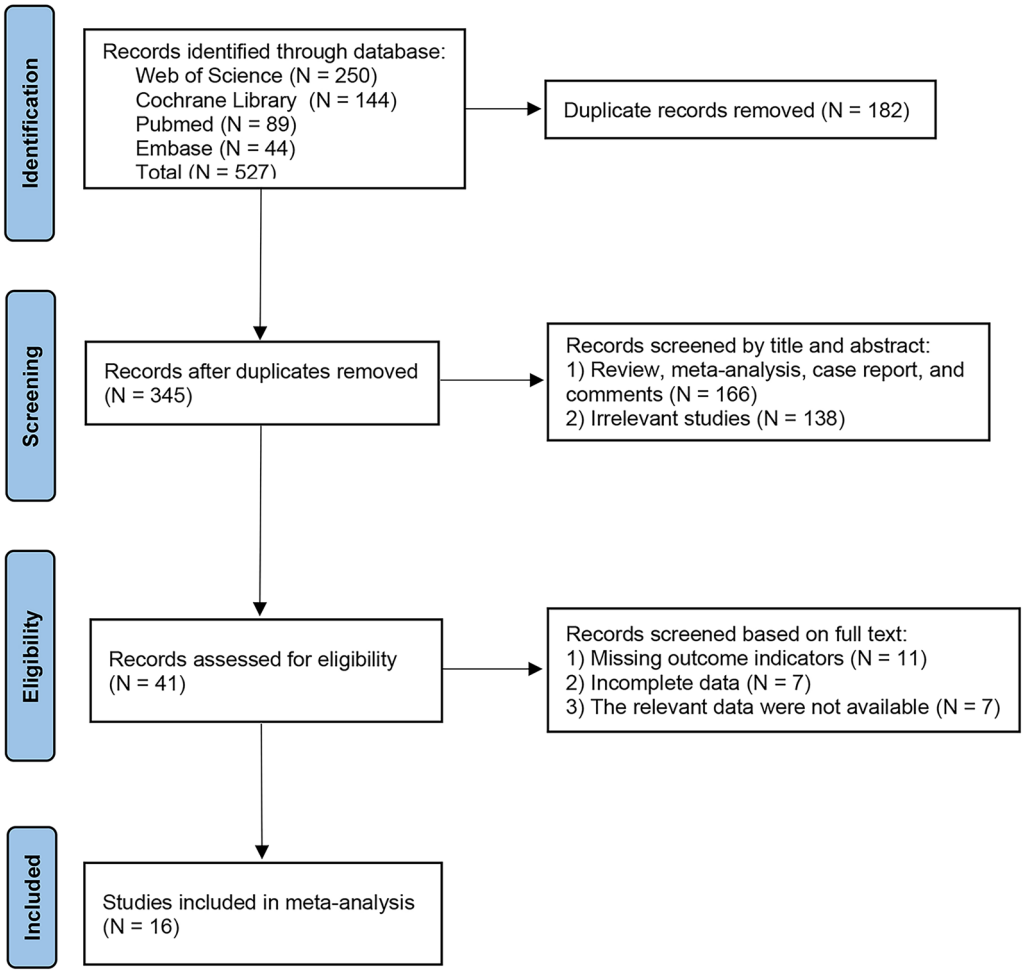


Fig. 1 PRISMA flow diagram of the study selection process

risk for performance and detection bias. Two studies were considered to have a high risk of performance bias. Missing data in two studies were not included in the intention-to-treat (ITT) analysis, resulting in a high risk of attrition bias. The majority of studies were assessed as having a low risk of bias in random sequence generation, blinding, incomplete outcome data, and selective reporting. Additionally, if the study received funding from the manufacturer of the experimental group preparation, it was considered to have an unclear risk of bias in other areas. Overall, the methodological quality of the included RCTs was deemed acceptable. The results of risk of bias assessment are shown in Fig. 2A and B.

Results of conventional meta-analysis

WOMAC total score

The WOMAC total score is primarily used to assess knee pain, functional limitations, and stiffness [52]. We conducted a conventional meta-analysis to evaluate the improvement in WOMAC total score at different time points across subgroups (single and repeated MSC injections) compared to baseline.

WOMAC total score at 3 months. The single-injection group included 7 studies (11 datasets), involving 136 patients with knee osteoarthritis; the repeated-injection group included 1 study with 10 patients. Pooled analysis showed a significant improvement in WOMAC total score at 3 months after a single MSC injection compared to baseline (SMD = −1.11, 95% CI −1.56 to −0.66, $P < 0.00001$), with substantial heterogeneity (I^2 = 64%) (Fig. 3A). Due to the availability of only one dataset in the repeated-injection group, further evaluation was not feasible. Moreover, the pooled results indicated no significant difference in the improvement effect on WOMAC score between single and repeated injections ($P = 0.13$).

WOMAC total score at 6 months. The single-injection group included 12 studies (16 datasets) involving 217 patients with knee osteoarthritis, while the repeated-injection group included 3 studies with a total of 46 patients. Pooled analysis showed that at 6 months after MSC injection, both single and repeated injections led

Table 1 Main characteristics of all articles included in the meta-analysis

Author	Year	Country	Study design	Age (MSC vs. Traditional treatment, Years ± SD, range)	Number of female/male (MSC vs. Traditional treatment)	Height (cm)	Weight (kg)	BMI (kg/m2) (MSC vs. Traditional treatment)	Kellgren-lawrence grade (MSC vs. Traditional treatment)			
									I	II	III	IV
Bastos et al. [36]	2020	Portugal	RCT	55.7 ± 7.8 vs. 55.9 ± 13.4	6/10 vs. 8/9	NA	NA	30.6 ± 4.5 vs. 31.0 ± 4.7	1 vs. 1	7 VS 4	5 VS 7	3 VS 5
Chen et al. (1) [37]	2021	China	RCT	67.7 ± 6.84 vs. 70.5 ± 8.37	14/3 vs. 5/3	NA	66.0 ± 6.80 vs. 60.5 ± 10.80	27.65 ± 3.03 vs. 25.47 ± 3.49	0 vs. 0	10 vs. 5	7 vs. 3	0 vs. 0
Chen et al. (2) [37]	2021	China	RCT	68.6 ± 6.45 vs. 70.5 ± 8.37	15/2 vs. 5/3	NA	64.2 ± 10.97 vs. 60.5 ± 10.80	26.72 ± 4.19 vs. 25.47 ± 3.49	0 vs. 0	10 vs. 5	7 vs. 3	0 vs. 0
Chen et al. (3) [37]	2021	China	RCT	64.9 ± 4.91 vs. 70.5 ± 8.37	12/3 vs. 5/3	NA	62.9 ± 10.47 vs. 60.5 ± 10.80	25.66 ± 3.78 vs. 25.47 ± 3.49	0 vs. 0	12 vs. 5	3 vs. 3	0 vs. 0
Emadedin et al. [38]	2018	Iran	RCT	51.7 ± 9.2 vs. 54.7 ± 5.3	7/12 vs. 9/15	NA	NA	30.2 ± 4.4 vs. 31.5 ± 5.4	NA	2 vs. 1	13 vs. 20	4 vs. 3
Freitag et al. (1) [39]	2019	Australia	RCT	54.6 ± 6.3 vs. 51.5 ± 6.1	5/5 vs. 3/7	1.75 ± 0.1 vs. 1.73 ± 0.1	97.1 ± 20.2 vs. 76 ± 14.5	31.6 ± 5.9 vs. 25.2 ± 3.4	NA	NA	NA	NA
Freitag et al. (2) [39]	2019	Australia	RCT	54.7 vs. 51.5 ± 6.1	6/4 vs. 3/7	1.7 ± 0.1 vs. 1.73 ± 0.1	88.7 ± 23.5 vs. 76 ± 14.5	30.4 ± 5.6 vs. 25.2 ± 3.4	NA	NA	NA	NA
Garay-Mendoza et al. [40]	2017	Mexico	RCT	55.67 ± 12.02 vs. 59.32 ± 10.85	23/7 vs. 22/9	1.63 ± 0.07 vs. 1.59 ± 0.86	78.23 ± 13.00 vs. 80.41 ± 17.52	29.48 ± 5.22 vs. 31.61 ± 7.38	NA	NA	NA	NA
Garza et al. [41]	2020	USA	RCT	59.5 ± 11.7 vs. 57.1 ± 9.1	6/7 vs. 7/6	NA	NA	28.8 ± 4.3 vs. 27.1 ± 2.7	NA	4 vs. 4	9 vs. 9	NA
Goncars et al. [42]	2017	Latvia	RCT	53.44 ± 15 vs. 58.55 ± 13	13/15 vs. 21/10	NA	NA	NA	7 sv 9	21/19	NA	NA
Gupta et al. [43]	2016	India	RCT	58.10 ± 8.23 vs. 54.90 ± 8.27	7/3 vs. 10/0	156.85 ± 9.64 vs. 152.25 ± 9.72	73.10 ± 15.86 vs. 66.10 ± 7.67	29.73 ± 6.09 vs. 28.84 ± 4.91	NA	4 vs. 3	6 vs. 7	NA
Kuah et al. (1) [44]	2018	Australia	RCT	50.8 ± 7.29 vs. 55.0 ± 10.42	2/6 vs. 3/1	172.6 ± 10.99 vs. 165.0 ± 7.87	82.9 ± 12.44 vs. 69.8 ± 11.55	27.7 ± 2.05 vs. 25.5 ± 2.84	0 vs. 1	2 vs. 0	6 vs. 3	NA
Kuah et al. (2) [44]	2018	Australia	RCT	55.0 ± 5.15 vs. 55.0 ± 10.42	3/5 vs. 3/1	174.4 ± 11.99 vs. 165.0 ± 7.87	81.9 ± 14.23 vs. 69.8 ± 11.55	26.8 ± 2.98 vs. 25.5 ± 2.84	1 vs. 1	1 vs. 0	6 vs. 3	NA
Lamo-Espinosa et al. (1) [45]	2016	Spain	RCT	65.54 ± 3.58 vs. 59.36 ± 1.90	4/6 vs. 3/7	NA	NA	27.39 ± 2.19 vs. 28.45 ± 1.68	0 vs. 0	1 vs. 4	2 vs. 2	7 vs. 4
Lamo-Espinosa et al. (2) [45]	2016	Spain	RCT	57.84 ± 1.87 vs. 59.36 ± 1.90	2/8 vs. 3/7	NA	NA	29.14 ± 1.48 vs. 28.45 ± 1.68	0 vs. 0	3 vs. 4	3 vs. 2	4 vs. 4
Lamo-Espinosa et al. (1) [46]	2018	Spain	RCT	64.40 ± 10.0 vs. 60.33 ± 0.73	4/4 vs. 2/7	NA	NA	27.49 ± 7.50 vs. vs 29.00 ± 1.53	NA	1 vs. 4	2 vs. 2	5 vs. 3
Lamo-Espinosa et al. (2) [46]	2018	Spain	RCT	58.21 ± 2.99 vs. 60.33 ± 0.73	2/6 vs. 2/7	NA	NA	28.48 ± 2.40 vs. 29.00 ± 1.53	NA	2 vs. 4	3 vs. 2	4 vs. 3
Lee et al. [47]	2019	South Korea	RCT	62.2 ± 6.5 vs. 63.2 ± 4.2	9/3 vs. 9/3	159.4 ± 7.2 vs. 159.8 ± 7.0	66.5 ± 11.1 vs. 65.7 ± 12.4	25.3 ± 4.9 vs. 25.4 ± 3.0	NA	6 vs. 5	6 vs. 6	0 vs. 1
Lee et al. [48]	2025	Korea	RCT	71.2 ± 5.7 vs. 63.8 ± 8.6	8/4 vs. 12/0	NA	NA	25.8 ± 3.2 vs. 24.1 ± 3.0	0 vs. 0	4 vs. 5	6 vs. 6	2 vs. 1
Lu et al. [49]	2019	China	RCT	55.03 ± 9.19 vs. 59.64 ± 5.97	23/3 vs. 23/3	161.35 ± 6.43 vs. 162.46 ± 5.66	63.46 ± 10.69 vs. 62.81 ± 9.44	24.27 ± 3.04 vs. 24.26 ± 2.59	2 vs. 4	18 vs. 16	32 vs. 32	0 vs. 0
Matas et al. (1) [27]	2019	Chile	RCT	56.1 ± 6.8 vs. 54.8 ± 4.5	6/4 vs. 5/4	NA	NA	27.6 ± 2.6 vs. 27.9 ± 3.4	NA	5 vs. 7	5 vs. 2	NA

Table 1 (continued)

Author	Year	Country	Study design	Age (MSC vs. Traditional treatment, Years ± SD, range)	Number of female/male (MSC vs. Traditional treatment)	Height (cm)	Weight (kg)	BMI (kg/m2) (MSC vs. Traditional treatment)	Kellgren-lawrence grade (MSC vs. Traditional treatment)			
									I	II	III	IV
Matas et al. (2) [27]	2019	Chile	RCT	56.7 ± 4.1 vs. 54.8 ± 4.5	5/5 vs. 5/4	NA	NA	27.4 ± 2.6 vs. 27.9 ± 3.4	NA	6 vs. 7	4 vs. 2	NA
Vega et al. [50]	2016	Spain	RCT	56.6 ± 9.24 vs. 57.3 ± 9.09	9/6 vs. 10/5	NA	NA	NA	NA	6 vs. 7	6 vs. 5	3 vs. 3

BMI: Body mass index, *MSC* Mesenchymal stem cell, *NA* Not applicable, *SD* Standard deviation, *vs.* Versus

to significant improvements in WOMAC total score compared to baseline (SMD = − 1.51, 95% CI − 2.01 to − 1.00, $P < 0.00001$), with considerable heterogeneity (I^2 = 84%) (Fig. 3B). Additionally, the pooled results indicated no significant difference in the improvement effect on WOMAC score between single and repeated injections ($P = 0.97$).

WOMAC total score at 12 months. The single-injection group included 9 studies (13 datasets) involving 156 patients, while the repeated-injection group included 3 studies involving 46 patients. Pooled analysis showed that at 12 months after MSC injection, both single and repeated injections resulted in significant improvements in WOMAC total score compared to baseline (SMD = −1.93, 95% CI − 2.46 to − 1.39, $P < 0.00001$), with substantial heterogeneity (I^2 = 78%) (Fig. 3C). Additionally, the pooled results indicated no significant difference in improvement between single and repeated injections ($P = 0.67$). The results across different time points suggested that both single and repeated MSC injections may provide sustained improvement in WOMAC total scores compared to pre-injection levels. Notably, in the single-injection group, there was a trend toward reduced improvement at 12 months compared to 6 months, which may reflect a relatively short duration of effect. In contrast, the repeated-injection group showed potential for more durable benefits. However, further confirmation through network meta-analysis is needed.

WOMAC score of function

WOMAC score (Function) at 3 months. The single-injection group included 4 studies (7 datasets) involving 92 patients, while the repeated-injection group included 1 study (2 datasets) involving 16 patients. Although the pooled results showed no significant heterogeneity (I^2 = 0%), a random-effects model was adopted for the analysis due to variations in MSC sources, intervention details, and baseline characteristics of the patients. Pooled analysis showed that at 3 months after MSC injection, both single and repeated injections resulted in significant improvement in WOMAC Function score compared to baseline (SMD = − 0.94, 95% CI − 1.23 to − 0.66, $P < 0.00001$) (Fig. 4A). Moreover, the pooled results indicated no significant difference in functional improvement between single and repeated injections ($P = 0.99$).

WOMAC score (Function) at 6 months. The single-injection group included 5 studies (8 datasets) involving 102 patients, while the repeated-injection group included 2 studies (3 datasets) involving 26 patients. Pooled analysis showed that at 6 months after MSC injection, both single and repeated injections resulted in significant improvement in WOMAC Function score compared to baseline (SMD = − 1.12, 95% CI − 1.41 to − 0.83, $P < 0.00001$) (I^2 = 12%) (Fig. 4B). Furthermore, the pooled

Table 2 Preparation and intervention characteristics of MSC

Author	Year	MSC (MSC vs. control)				Control	Injection	Number of injections
		Harvest location	MSCs type	MSCs source	MSCs No.			
Bastos et al. [36]	2020	Posterior iliac crests	BM-MSC	Auto	40×10^6	Corticosteroid	Joint cavity injection	1
chen et al. (1) [37]	2021	Ultrasonic-assisted liposuction	AD-MSC	Auto	16×10^6	HA	Joint cavity injection	1
chen et al. (2) [37]	2021	Ultrasonic-assisted liposuction	AD-MSC	Auto	32×10^6	HA	Joint cavity injection	1
chen et al. (3) [37]	2021	Ultrasonic-assisted liposuction	AD-MSC	Auto	64×10^6	HA	Joint cavity injection	1
Emadedin et al. [38]	2018	Iliac crests	BM-MSC	Auto	40×10^6	Saline	Joint cavity injection	1
Freitag et al. (1) [39]	2019	Abdomen	AD-MSC	Allo	100×10^6	HA	Joint cavity injection	1
Freitag et al. (2) [39]	2019	Abdomen	AD-MSC	Allo	100×10^6	HA	Joint cavity injection	2
Garay-Mendoza et al. [40]	2017	Iliac crests	BM-MSC	Auto	10mL	Oral acetaminophen 500 mg	Joint cavity injection	1
Garza et al. [41]	2020	NA	AD-MSC	Allo	3.0×10^7	Placebo	Joint cavity injection	1
Goncars et al. [42]	2017	Iliac crest	BM-MSC	Auto	5–10 mL	HA	Joint cavity injection	1
Gupta et al. [43]	2016	NA	BM-MSC	Allo	25×10^6	HA	Joint cavity injection	1
Kuah et al. (1) [44]	2018	NA	AD-MSC	Allo	3.9×106	Placebo	Joint cavity injection	4
Kuah et al. (2) [44]	2018	NA	AD-MSC	Allo	6.7×10^6	Placebo	Joint cavity injection	4
Lamo-Espinosa et al. (1) [45]	2016	Iliac crest	BM-MSC	Auto	10×106	HA	Joint cavity injection	1
Lamo-Espinosa et al. (2) [45]	2016	Iliac crest	BM-MSC	Auto	100×10^6	HA	Joint cavity injection	1
Lamo-Espinosa et al. (1) [46]	2018	Iliac crest	BM-MSC	Auto	10×10^6	HA	Joint cavity injection	1
Lamo-Espinosa et al. (2) [46]	2018	Iliac crest	BM-MSC	Auto	100×10^6	HA	Joint cavity injection	1
Lee et al. [47]	2019	Abdomen	AD-MSC	Auto	1×10^8	Saline	Joint cavity injection	1
Lee et al. [48]	2025	Iliac crest	BM-MSC	Auto	1×10^8	Saline	Joint cavity injection	1
Lu et al. [49]	2019	Abdomen	AD-MSC	Auto	5×10^7	HA	Joint cavity injection	4
Matas et al. (1) [27]	2019	Umbilical cords	UC-MSC	Allo	20×10^6	HA	Joint cavity injection	1
Matas et al. (2) [27]	2019	Umbilical cords	UC-MSC	Allo	20×10^6	HA	Joint cavity injection	2
Vega et al. [50]	2016	Posterior iliac crests	BM-MSC	Allo	40×10^6	HA	Joint cavity injection	1

AD-MSC Adipose-derived mesenchymal stem cell, *Allo* Allogeneic, *Auto* Autologous, *BM-MSC* Bone marrow-derived mesenchymal stem cell, *HA* Hyaluronic acid, *MSC* Mesenchymal stem cell, *NA* Not applicable, *UC-MSC* Umbilical cord-derived mesenchymal stem cell

results revealed no significant difference in the improvement of WOMAC Function score between single and repeated injections ($P=0.38$).

WOMAC score (Function) at 12 months. The WOMAC score (Function) at 12 months. The single injection group included 5 studies (8 datasets) with 102 patients, while the repeated injection group included 2 studies (3 datasets) with 26 patients. The pooled analysis based on a random-effects model showed that, compared to pre-treatment levels, the WOMAC score (Function) at 12 months significantly improved after either single or repeated MSC injections (SMD = – 1.19, 95% CI – 1.51 to – 0.86, $P<0.00001$) (I^2 = 0%) (Fig. 4C). Furthermore, the pooled results also indicated no significant difference between the effects of single and multiple injections on the improvement of the WOMAC score (Function) ($P=0.59$). These results suggest that both single and repeated MSC injections could significantly improve knee joint function scores at all time points. The single injection group showed an increasing improvement trend as follow-up time extended. However, no statistically significant differences were observed between the two injection protocols.

WOMAC score of pain

WOMAC score (Pain) at 3 months. The WOMAC score (Pain) at 3 months. The single injection group included 5 studies (8 datasets) with 107 patients, while the repeated injection group included 1 study (2 datasets) with 16 patients. Due to the presence of substantial heterogeneity (I^2 = 59%) and differences in MSC characteristics and patient baseline features, a random-effects model was employed. The pooled analysis showed that, compared to pre-treatment levels, the WOMAC score (Pain) at 3 months significantly improved after both single and repeated MSC injections (SMD = – 1.40, 95% CI – 1.86 to – 0.94, $P<0.00001$) (Fig. 5A). Furthermore, the pooled results also indicated no significant difference between the effects of single and multiple injections on the improvement of the WOMAC score (Pain) ($P=0.22$).

WOMAC score (Pain) at 6 months. The single injection group included 6 studies (9 datasets) with 117 patients, while the repeated injection group included 2 studies (3

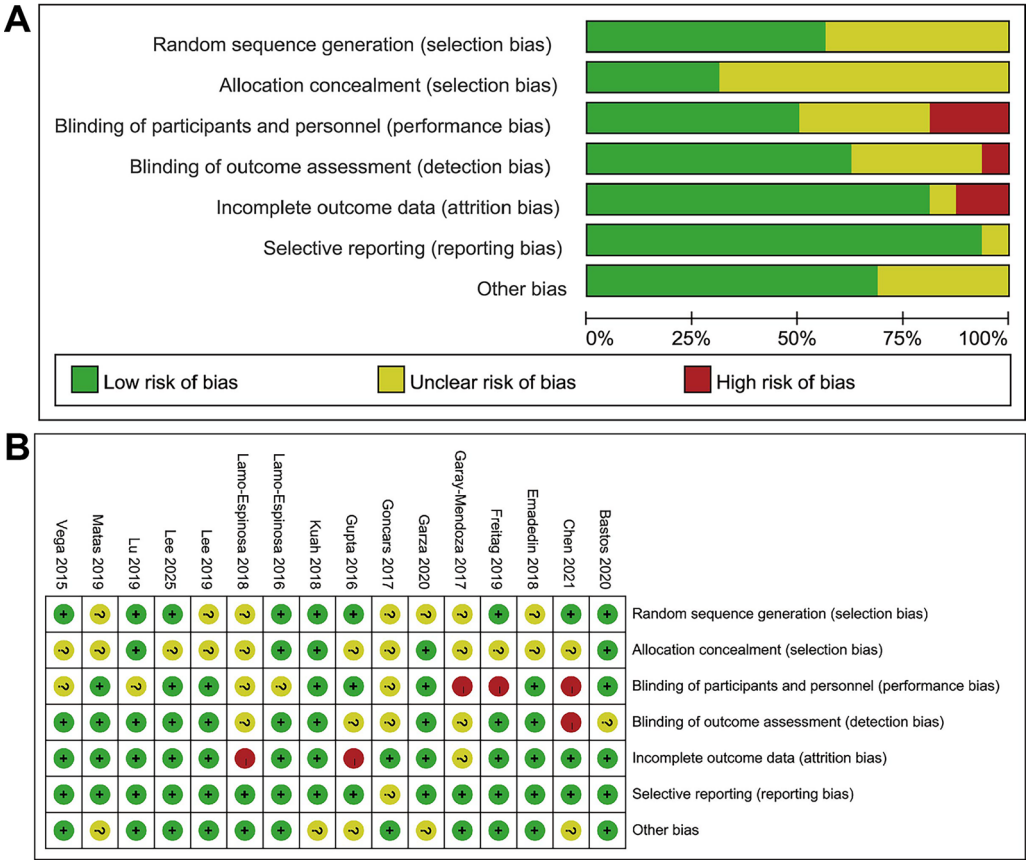


Fig. 2 The risk of bias graph of included studies. **A** Risk of bias graph; **B** Risk of bias summary

datasets) with 26 patients. The pooled analysis showed that, compared to pre-treatment levels, the WOMAC score (Pain) at 6 months significantly improved after both single and repeated MSC injections (SMD = − 1.33, 95% CI − 1.78 to − 0.87, $P < 0.00001$) (I^2 = 65%) (Fig. 5B). Furthermore, the pooled results also indicated no significant difference between the effects of single and multiple injections on the improvement of the WOMAC score (Pain) ($P = 0.18$).

WOMAC score (Pain) at 12 months. The single injection group included 6 studies (9 datasets) with 117 patients, while the repeated injection group included 2 studies (3 datasets) with 26 patients. In view of the differences in MSC characteristics and patient baseline features among the included studies, a random-effects model was applied. The pooled analysis showed that, compared to pre-treatment levels, the WOMAC score (Pain) at 12 months significantly improved after both single and repeated MSC injections (SMD = − 1.22, 95% CI − 1.54 to − 0.89, $P < 0.00001$) (I^2 = 34%) (Fig. 5C). Furthermore, the pooled results also indicated no significant difference between the effects of single and multiple injections on the improvement of the WOMAC score (Pain) ($P = 0.60$). These results suggest that both single and repeated MSC injections could significantly reduce the WOMAC pain score at all follow-up time points. However, no statistical differences were observed between the single and repeated injection groups. Given the limited number of studies and small sample sizes, these results should be interpreted with caution.

WOMAC score of stiffness

WOMAC score (Stiffness) at 3 months. The single injection group included 4 studies (6 datasets) with 92 patients, while the repeated injection group included 1 study (2 datasets) with 16 patients. Given the heterogeneity in MSC characteristics and patient baseline features among the included studies, a random-effects model was utilized. The pooled analysis showed that, compared to pre-treatment levels, the WOMAC score (Stiffness) at 3 months significantly improved after both single and repeated MSC injections (SMD = − 0.80, 95% CI − 1.08 to − 0.52, $P < 0.00001$) (I^2 = 0%) (Fig. 6A). Furthermore, the pooled results also indicated no significant difference between the effects of single and multiple injections on the improvement of the WOMAC score (Stiffness) ($P = 0.97$).

WOMAC score (Stiffness) at 6 months. The single injection group included 5 studies (8 datasets) with 102 patients, while the repeated injection group included 2

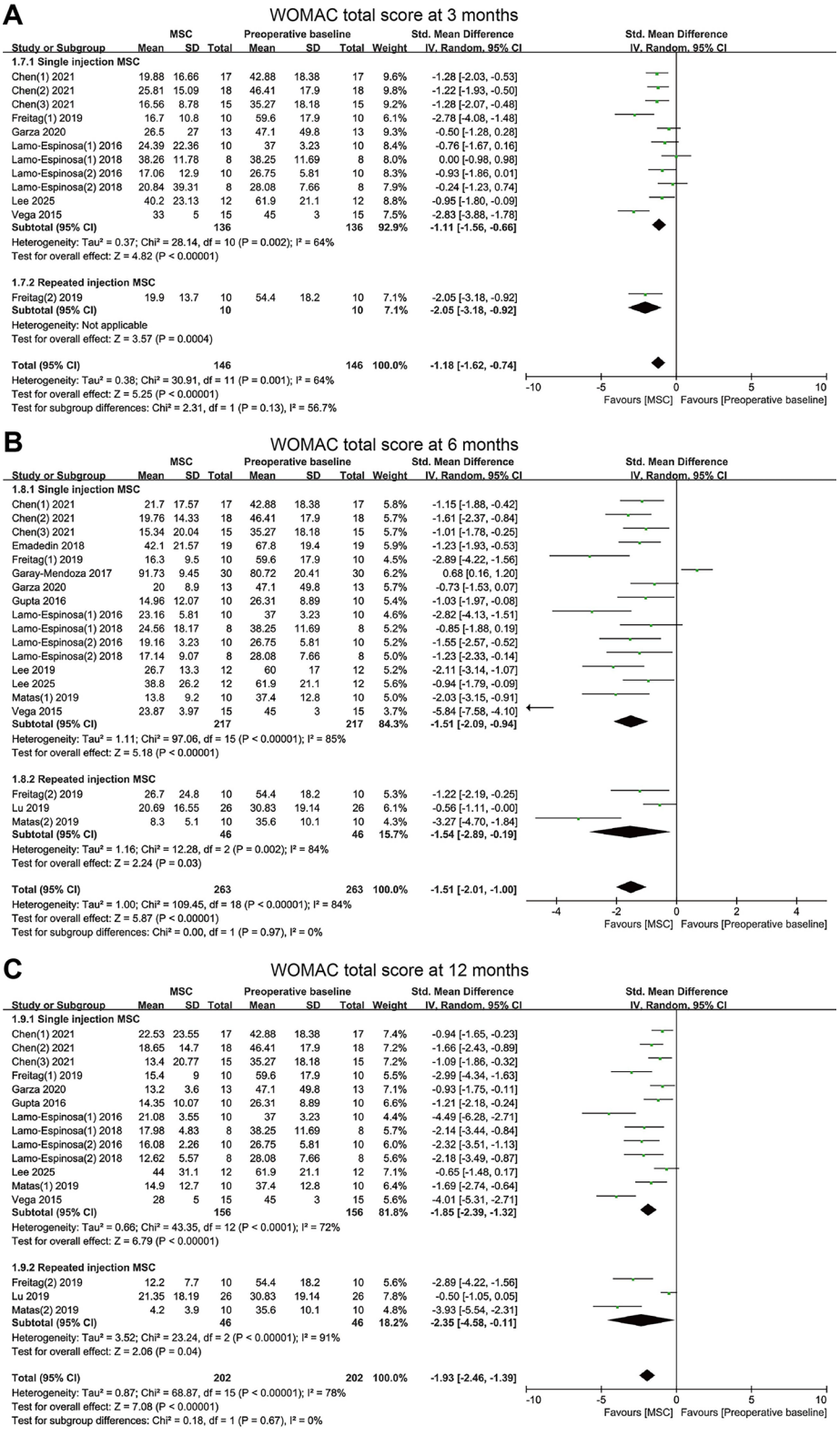


Fig. 3 Forest plots illustrating the effect of single and repeated MSC injections on WOMAC total score at different time points. **A** WOMAC total score at 3 months. **B** WOMAC total score at 6 months. **C** WOMAC total score at 12 months

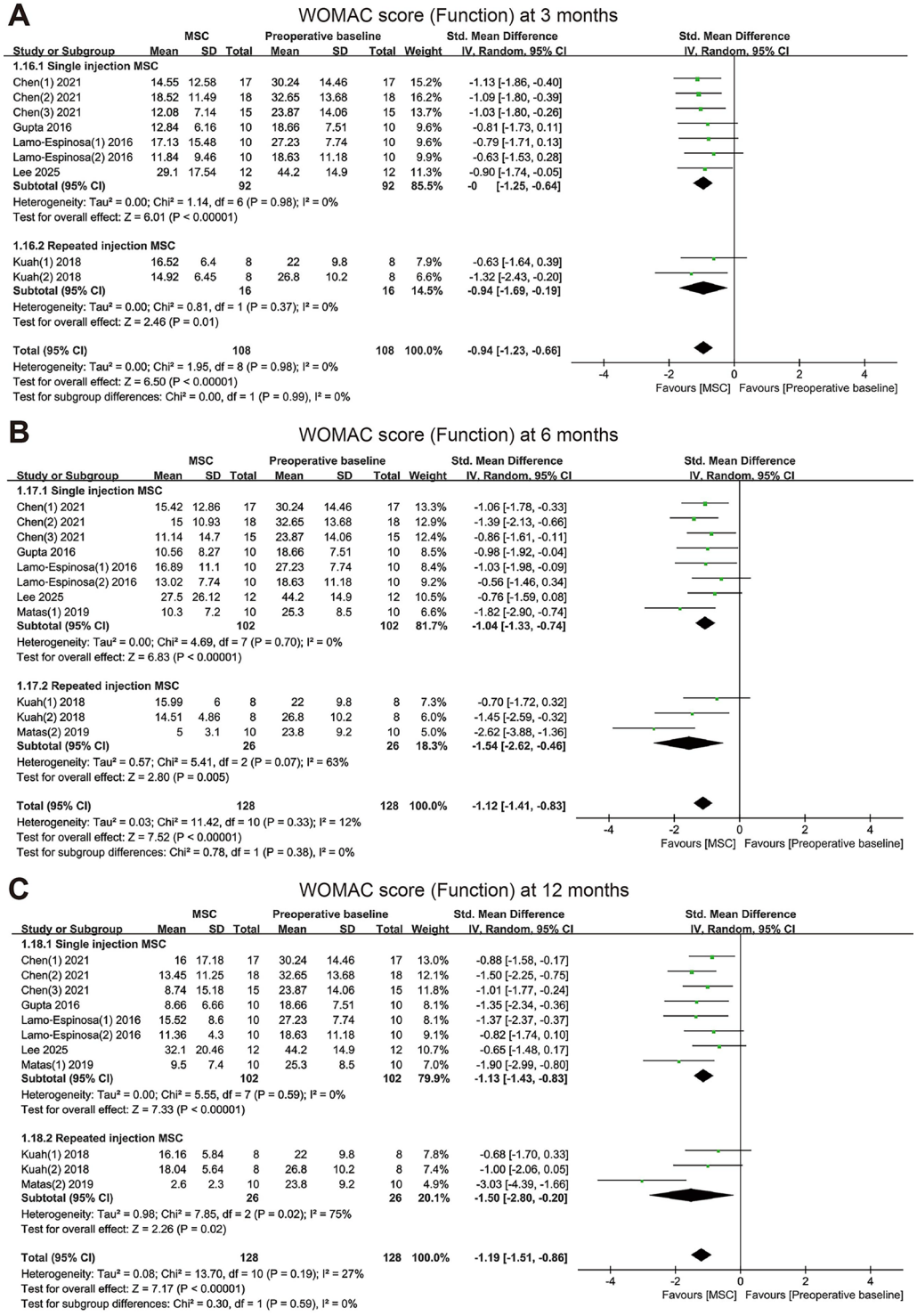


Fig. 4 Forest plots showing the effect of single and repeated MSC injections on WOMAC score (Function) at different time points. **A** WOMAC score (Function) at 3 months. **B** WOMAC score (Function) at 6 months. **C** WOMAC score (Function) at 12 months

studies (3 datasets) with 26 patients. The pooled analysis showed that, compared to pre-treatment levels, the WOMAC score (Stiffness) at 6 months significantly improved after both single and repeated MSC injections (SMD = − 0.92, 95% CI − 1.18 to − 0.66, $P < 0.00001$) (I^2 = 0%) (Fig. 6B). Furthermore, the pooled results also indicated no significant difference between the effects of single and multiple injections on the improvement of the WOMAC score (Stiffness) ($P = 0.23$).

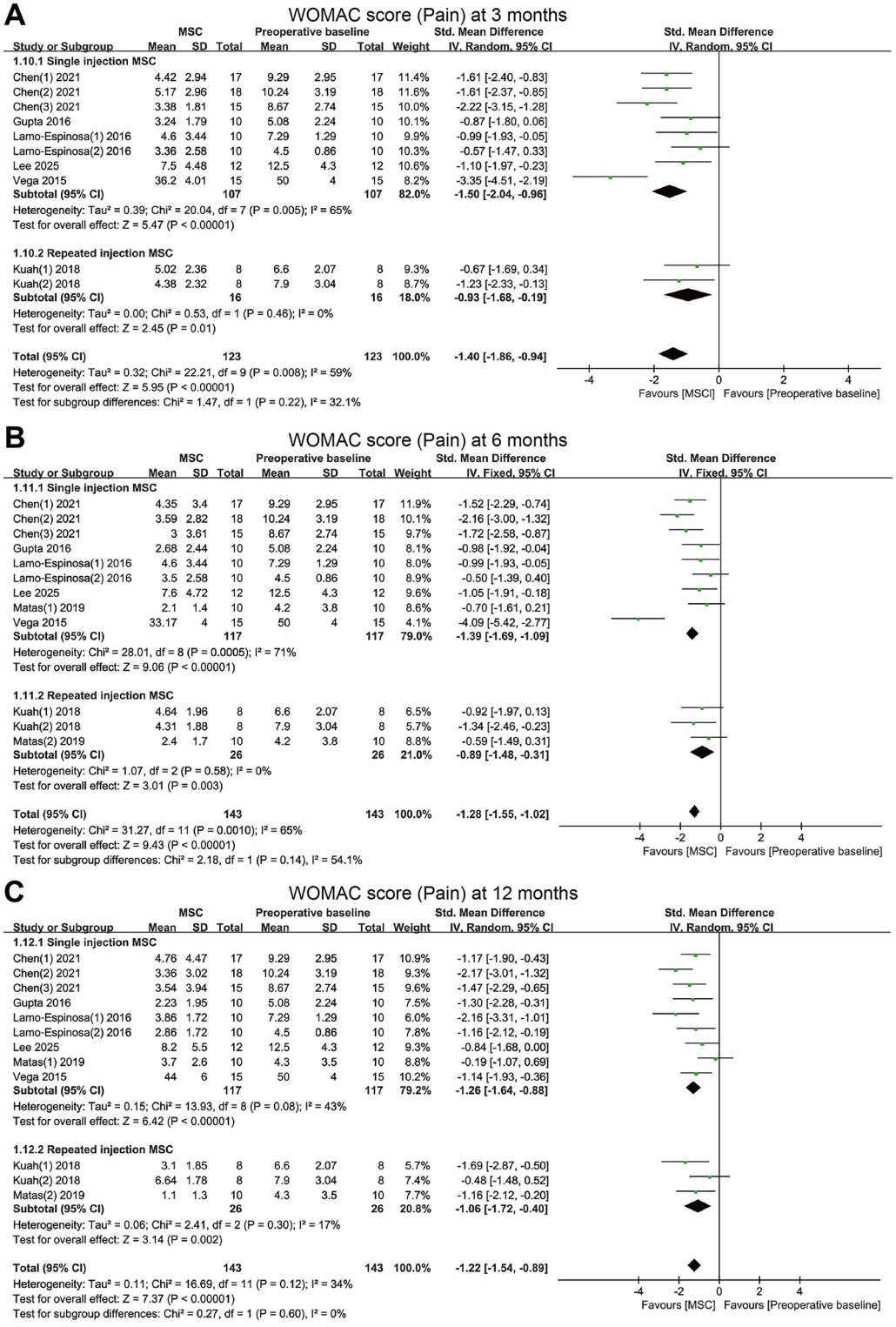


Fig. 5 Forest plots illustrating the effect of single and repeated MSC injections on WOMAC score (Pain) at different time points. **A** WOMAC score (Pain) at 3 months. **B** WOMAC score (Pain) at 6 months. **C** WOMAC score (Pain) at 12 months

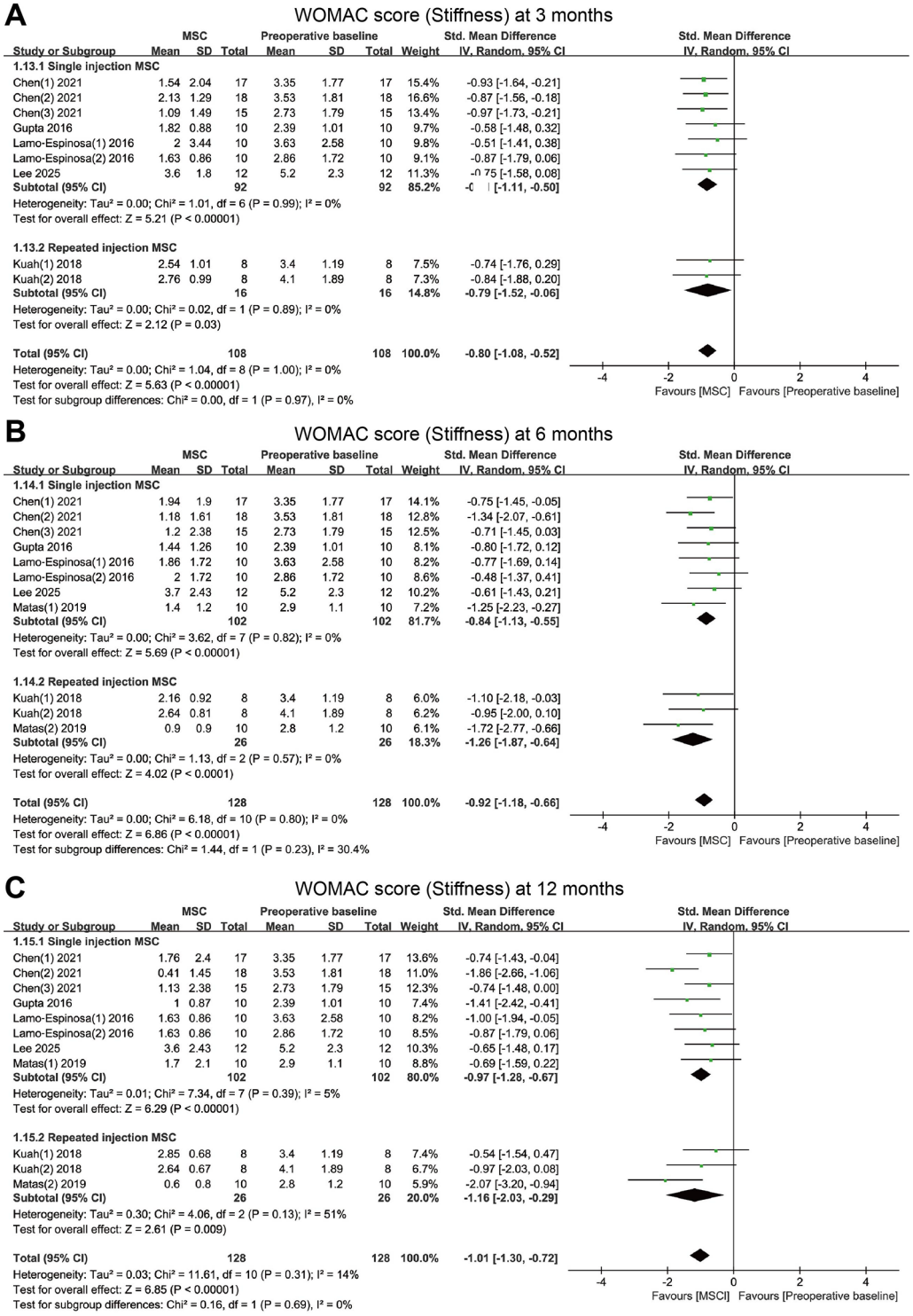


Fig. 6 Forest plots showing the effect of single and repeated MSC injections on WOMAC score (Stiffness) at different time points. **A** WOMAC score (Stiffness) at 3 months. **B** WOMAC score (Stiffness) at 6 months. **C** WOMAC score (Stiffness) at 12 months

WOMAC score (Stiffness) at 12 months. The single injection group includes 5 studies (8 datasets) with 102 patients, while the repeated injection group includes 2 studies (3 datasets) with 26 patients. The pooled analysis showed that, compared to pre-treatment levels, the WOMAC score (Stiffness) at 12 months significantly improved after both single and repeated MSC injections (SMD = − 1.01, 95% CI − 1.30 to − 0.72, $P < 0.00001$)

(Fig. 6C). Furthermore, the pooled results also indicated no significant difference between the effects of single and multiple injections on the improvement of the WOMAC score (Stiffness) (I^2 = 14%) (P = 0.69). In conclusion, compared to pre-injection levels, both single and repeated injections could improve knee joint function, stiffness, and pain at various follow-up time points. There were no significant differences in the effectiveness between the two injection protocols. However, due to study heterogeneity and small sample sizes, the results should be interpreted with caution.

VAS score

VAS score at 3 months. The single injection group includes 6 studies (10 datasets) with 123 patients, while the repeated injection group includes 1 study (2 datasets) with 16 patients. Given the heterogeneity in MSC characteristics and patient baseline features among the included studies, a random-effects model was utilized. The pooled analysis showed that, compared to pre-treatment levels, the VAS score at 3 months significantly improved after both single and repeated MSC injections (SMD = − 1.22, 95% CI − 1.60 to − 0.84, P < 0.00001) (I^2 = 50%) (Fig. 7A). Furthermore, the pooled results also indicated no significant difference between the effects of single and multiple injections on the improvement of the VAS score (P = 0.98).

VAS score at 6 months. The single injection group included 10 studies (14 datasets) with 194 patients, while the repeated injection group included 3 studies (4 datasets) with 52 patients. The pooled analysis showed that, compared to pre-treatment levels, the VAS score at 6 months significantly improved after both single and repeated MSC injections (SMD = − 1.46, 95% CI − 1.82 to − 1.10, P < 0.00001) (I^2 = 65%) (Fig. 7B). Furthermore, the pooled results also indicated no significant difference between the effects of single and multiple injections on the improvement of the VAS score (P = 0.91).

VAS score at 12 months. The single injection group included 7 studies (11 datasets) with 133 patients, while the repeated injection group included 3 studies (4 datasets) with 52 patients. The pooled analysis showed that, compared to pre-treatment levels, the VAS score at 12 months significantly improved after both single and repeated MSC injections (SMD = − 1.57, 95% CI − 1.96 to − 1.18, P < 0.00001) (I^2 = 60%) (Fig. 7C). Furthermore, the pooled results also indicated no significant difference between the effects of single and multiple injections on the improvement of the VAS score (P = 0.41). Through the pooled analysis of the VAS score, we found that both single and repeated MSC injections may improve patient pain at different time points compared to pre-treatment. However, there were no significant differences in efficacy between the two injection protocols.

KOOS score

The KOOS score is a tool used to evaluate knee joint damage based on the subjective feelings of patient, including five aspects: daily activities, pain, quality of life, sports, and symptom improvement [53]. We conducted a traditional meta-analysis using data from the 12-month follow-up time point to explore the effects of different injection protocols before and after injection on the KOOS score.

KOOS score (activities of daily living) at 12 months. The single injection group included 3 studies, involving 38 patients, while the repeated injection group included 1 study, involving 10 patients. The pooled analysis of the single injection group showed that, compared to pre-treatment levels, the KOOS score (activities of daily living) at 12 months significantly improved (SMD = 1.35, 95% CI 0.77 to 1.93, P < 0.00001; I^2 = 0%) (Fig. 8A).

KOOS score (pain) at 12 months. The single injection group includes 4 studies, involving 66 patients, while the repeated injection group includes 1 study, involving 10 patients. The pooled analysis of the single injection group showed that, compared to pre-treatment levels, the KOOS score (pain) at 12 months significantly improved (SMD = 1.35, 95% CI 0.99 to 1.71, P < 0.00001; I^2 = 0%) (Fig. 8B).

KOOS score (quality of life) at 12 months. The single injection group includes 3 studies, involving 38 patients, while the repeated injection group includes 1 study, involving 10 patients. The pooled analysis of the single injection group showed that, compared to pre-treatment levels, the KOOS score (quality of life) at 12 months significantly improved (SMD = 1.37, 95% CI 0.76 to 1.99, P < 0.0001; I^2 = 43%) (Fig. 8C).

KOOS score (sport) at 12 months. The single injection group includes 3 studies, involving 38 patients, while the repeated injection group includes 1 study, involving 10 patients. The pooled analysis of the single injection group showed that, compared to pre-treatment levels, the KOOS score (sport) at 12 months significantly improved (SMD = 1.43, 95% CI 0.62 to 2.24, P = 0.0005; I^2 = 65%) (Fig. 8D).

KOOS score (symptom improvement) at 12 months. The single injection group includes 3 studies, involving 38 patients, while the repeated injection group includes 1 study, involving 10 patients. The pooled analysis of the single injection group showed that, compared to pre-treatment levels, the KOOS score (symptom improvement) at 12 months significantly improved (SMD = 1.04, 95% CI 0.61 to 1.47, P < 0.00001; I^2 = 0%) (Fig. 8E). These results suggested that, compared to the control group, single MSC injection may have a positive impact on daily activities, pain, quality of life, sports, and symptom improvement in patients with knee osteoarthritis. However, due to the limited number of studies in the repeated

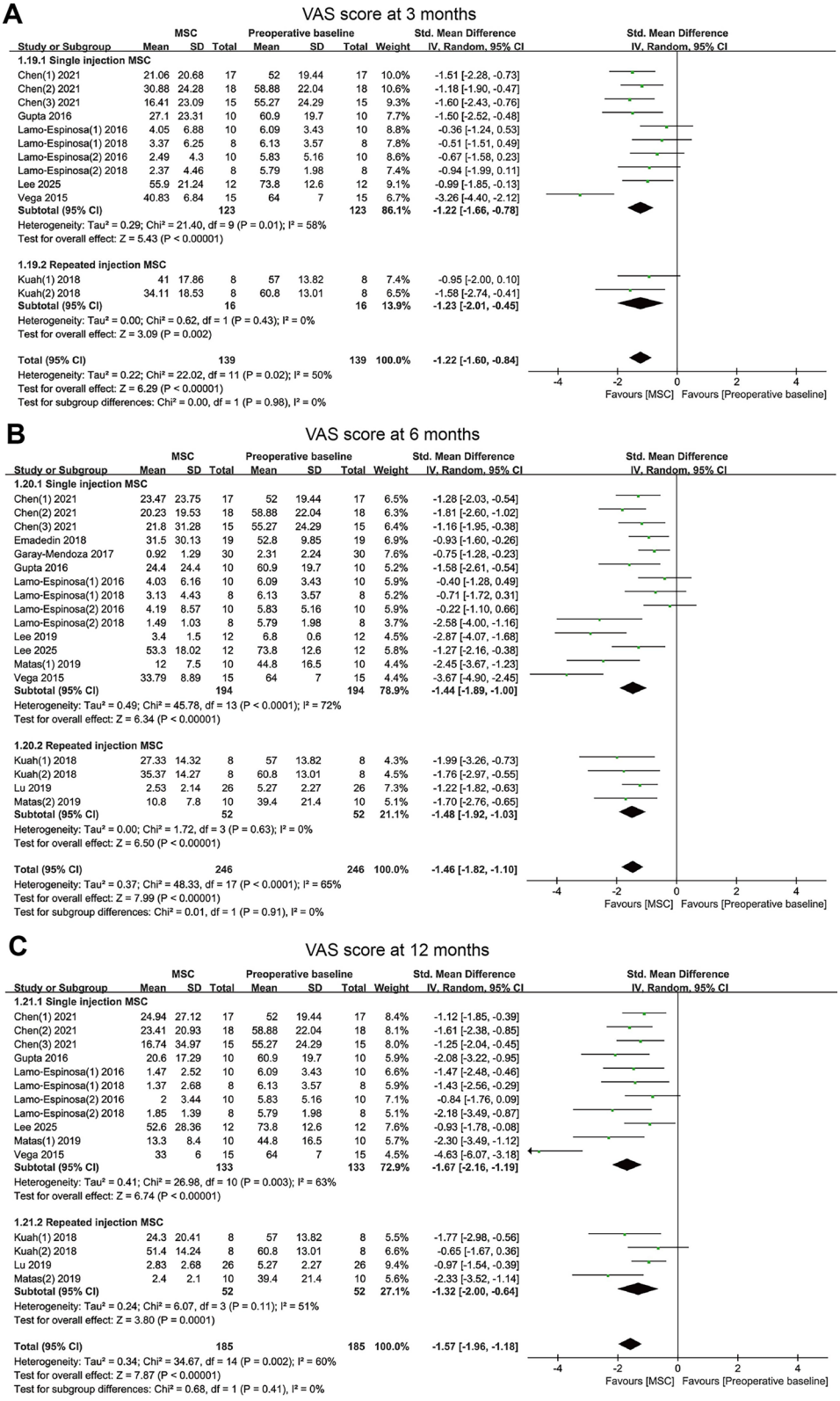


Fig. 7 Forest plots showing the effect of single and repeated MSC injections on VAS score at different time points. **A** VAS score at 3 months. **B** VAS score at 6 months. **C** VAS score at 12 months

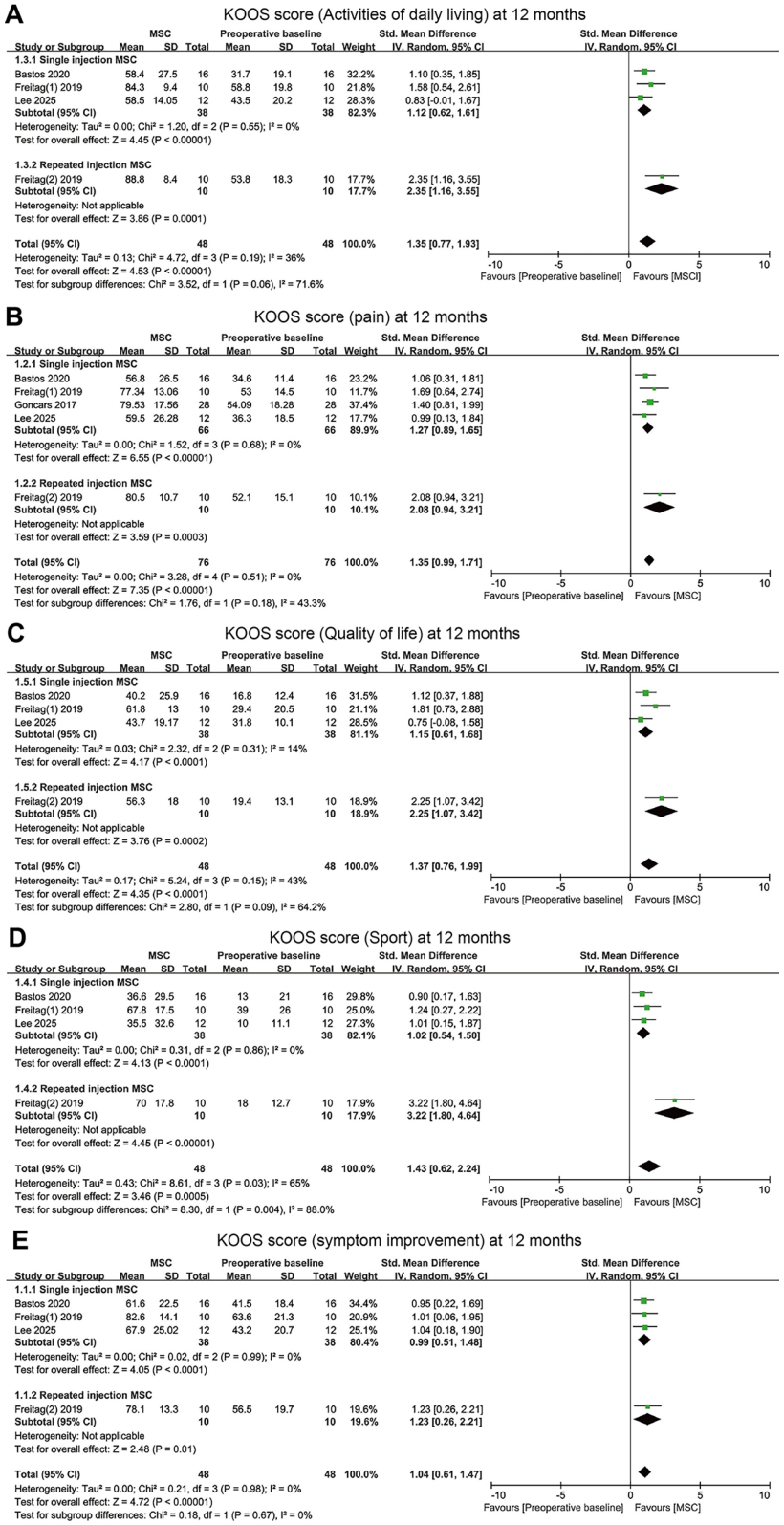


Fig. 8 Forest plots illustrating the effect of single and repeated MSC injections on KOOS score at 12 months. **A** KOOS score (Activities of daily living) at 12 months. **B** KOOS score (pain) at 12 months. **C** KOOS score (Quality of life) at 12 months. **D** KOOS score (Sport) at 12 months. **E** KOOS score (symptom improvement) at 12 months

MSC injection group, caution should be exercised when interpreting these results further.

WORMS score (articular cartilage)

The WORMS score is a rating of cartilage damage in the knee joint based on MRI imaging [54]. We conducted a pooled analysis of the scores from several studies. The single injection group includes 4 studies (7 datasets) with 90 patients, while the repeated injection group includes 1 study with 10 patients. The results showed that, compared to pre-treatment levels, the WORMS score (articular cartilage) did not significantly improve after a single MSC injection (SMD = 0.11, 95% CI − 0.16 to 0.39, $P = 0.42$; I^2 = 0%) (Fig. 9). Due to the limited number of studies and sample sizes, caution should be exercised when interpreting these results further.

Results of network meta-analysis

WOMAC total score

WOMAC total score at 6 months. In the network meta-analysis, a total of 17 datasets were included, involving 487 patients. The network evidence plot for the three intervention protocols is shown in Fig. 10A. The network forest plot illustrates the results of three pairwise comparisons, showing no statistical difference in treatment effects between the single and repeated MSC injection groups (Fig. 10B). Based on SCURA ranking results, the repeated MSC injection group was ranked as the best treatment for reducing the WOMAC total score with a probability of $P = 73.8$ (Fig. 10C). This was followed by the single MSC injection ($P = 48.1$) and conventional therapy ($P = 28.2$).

WOMAC total score at 12 months. In the network meta-analysis, a total of 14 datasets were included, involving 358 patients. The network evidence plot for the three intervention protocols is shown in Fig. 10D. The network forest plot showed that, compared to single MSC injection, repeated MSC injection may effectively reduce the WOMAC total score at 12 months (SMD = −1.47, 95% CI − 2.86 to − 0.07; very low certainty) (Fig. 10E). Based on SCURA ranking results, the repeated MSC injection group was ranked as the best treatment for reducing the WOMAC total score with a probability of $P = 98.8$ (Fig. 10F). Single MSC injection ranked second with a probability of $P = 48.1$. These results suggested that repeated MSC injection may be the best option for improving the WOMAC total score at 12 months.

WOMAC score of function

WOMAC score (Function) at 6 months. A total of 10 datasets involving 246 patients were included. The main evidence for all pairwise comparison protocols regarding WOMAC score (Function) is shown in Fig. 11A. Among these, repeated MSC injection significantly reduced the WOMAC score (Function) at 6 months compared to single MSC injection (SMD = − 1.24, 95% CI − 2.33 to − 0.15; low certainty) (Fig. 11B). Based on SCURA ranking results, the repeated MSC injection group was ranked as the best treatment for reducing the WOMAC score (Function) with a probability of $P = 99.7$ (Fig. 11C). This was followed by single MSC injection ($P = 36.0$) and conventional therapy ($P = 14.9$). These results suggest that repeated MSC injection may be the best option for improving the WOMAC score (Function) at 6 months.

WOMAC score (Function) at 12 months. The data is consistent with that at 6 months, including a total of 10 datasets involving 246 patients. The network evidence plot for the three intervention protocols is shown in Fig. 11D. The network forest plot showed that, compared to the conventional therapy group, repeated MSC injection may effectively reduce the WOMAC score (Function) at 12 months (SMD = − 0.30, 95% CI − 0.59

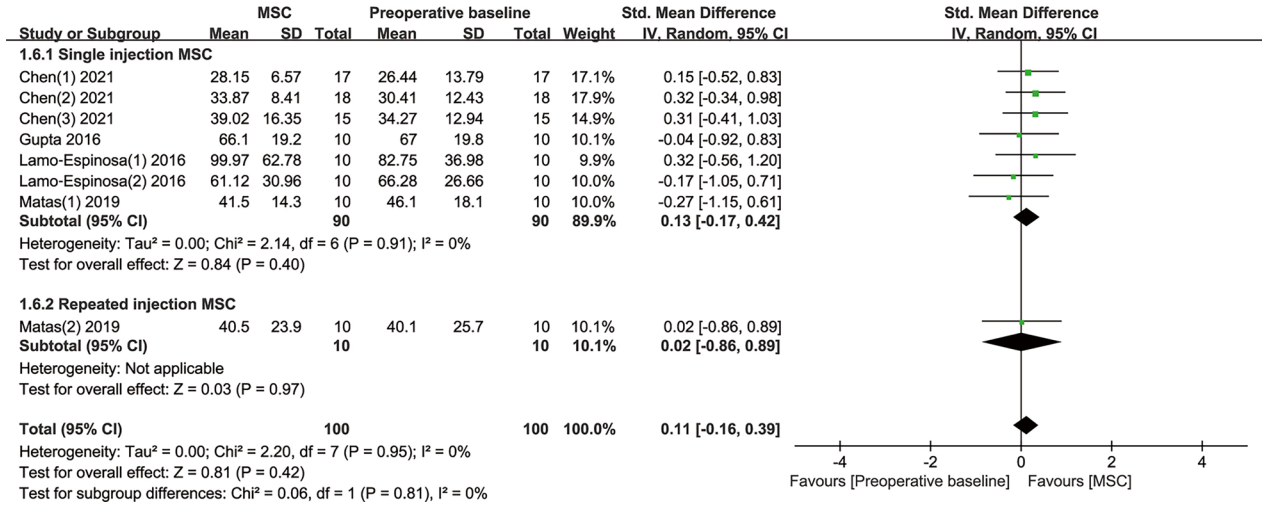
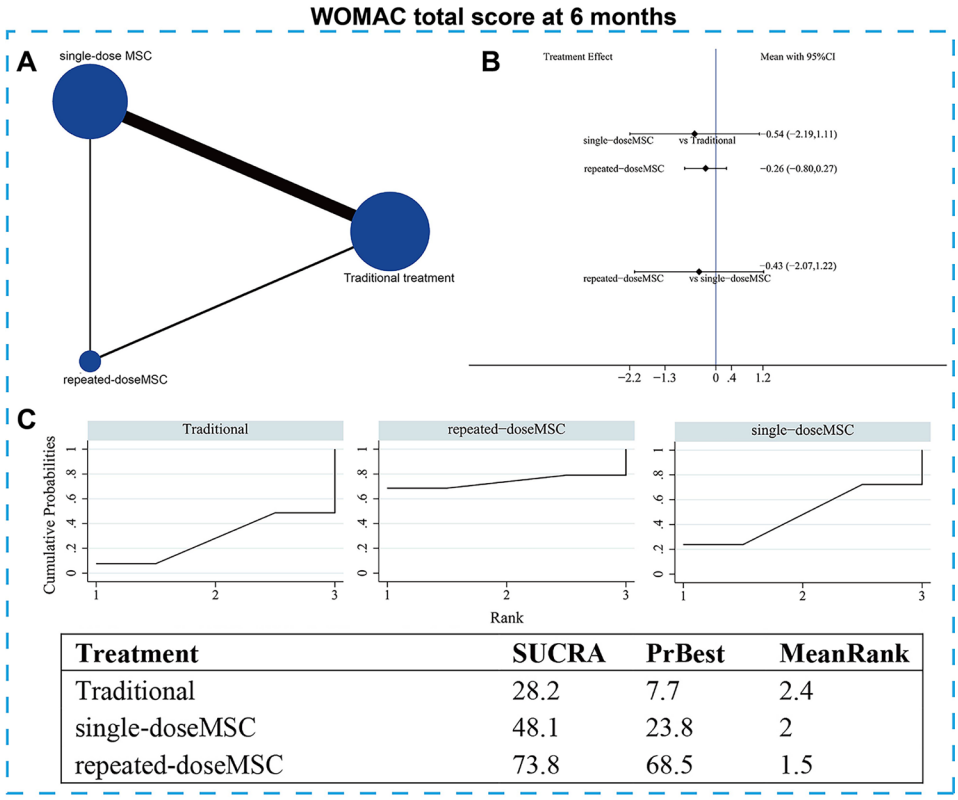
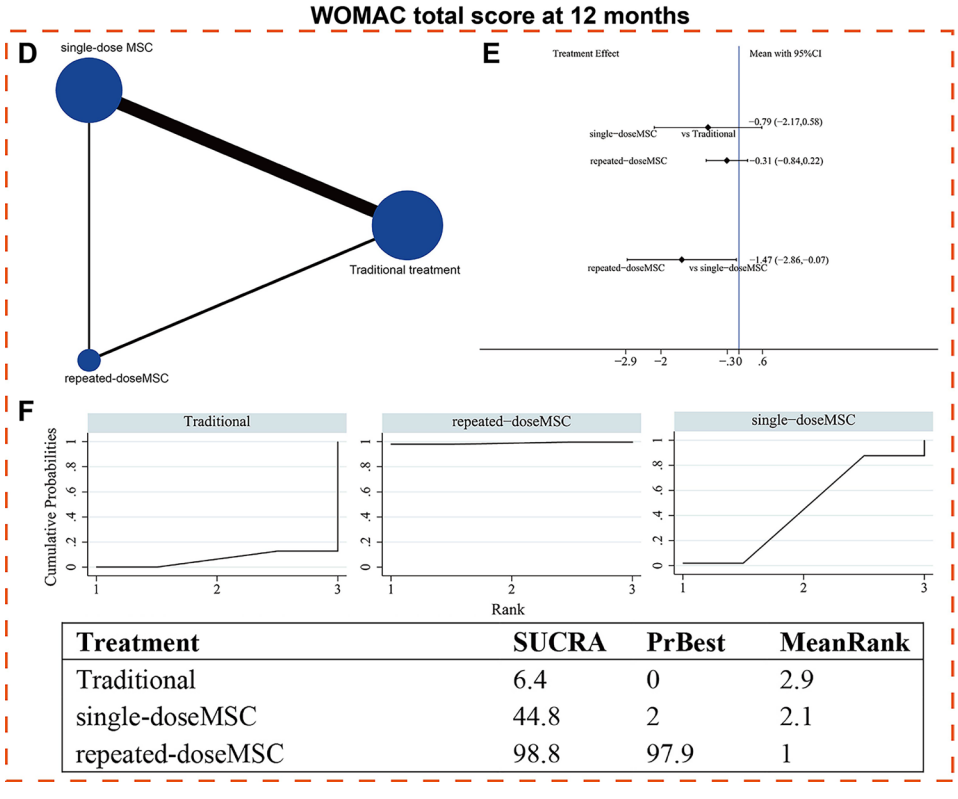


Fig. 9 Forest plots illustrating the effect of single and repeated MSC injections on WORMS score (articular cartilage) at 12 months

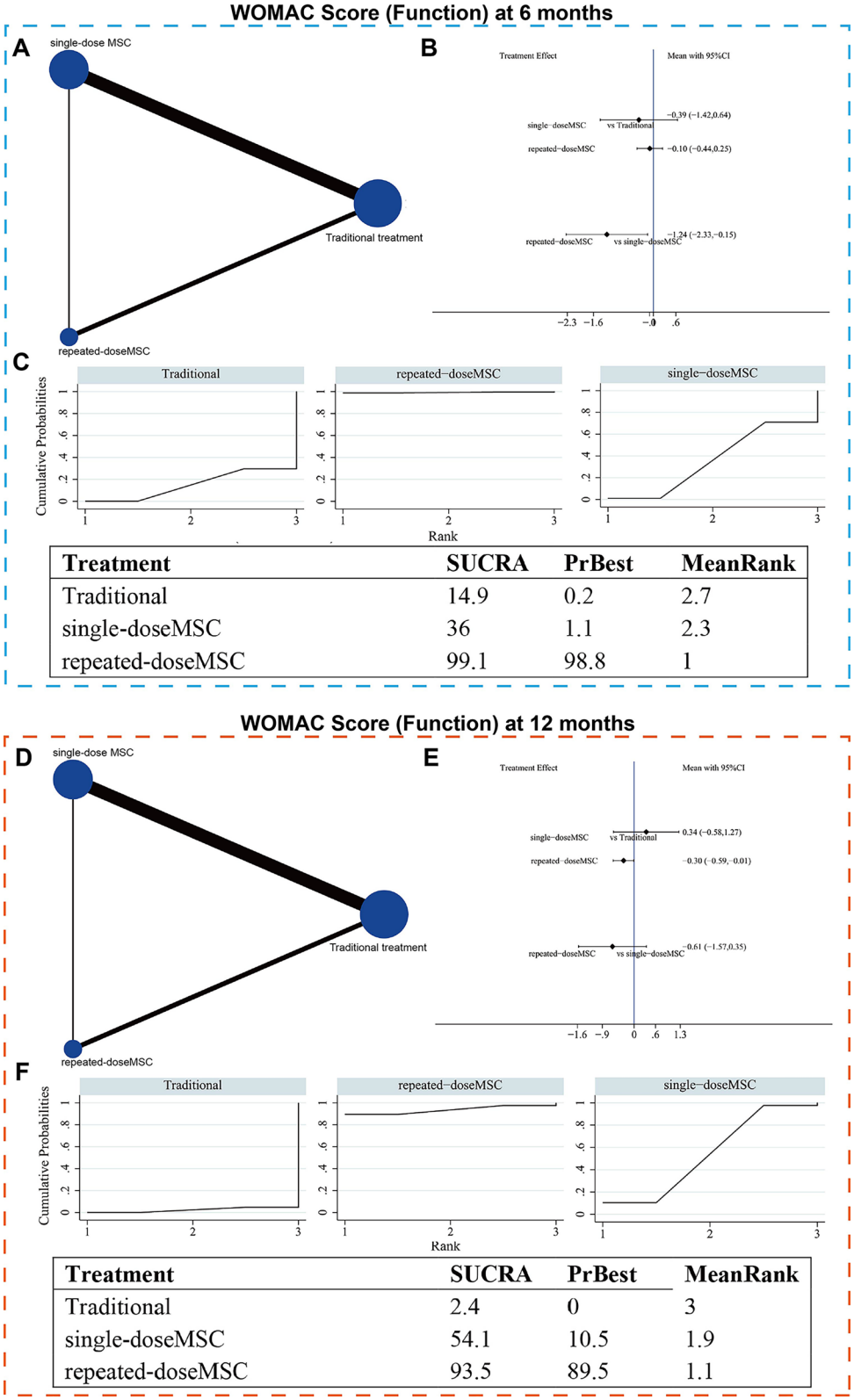


Treatment	SUCRA	PrBest	MeanRank
Traditional	28.2	7.7	2.4
single-doseMSC	48.1	23.8	2
repeated-doseMSC	73.8	68.5	1.5



Treatment	SUCRA	PrBest	MeanRank
Traditional	6.4	0	2.9
single-doseMSC	44.8	2	2.1
repeated-doseMSC	98.8	97.9	1

Fig. 10 Network meta-analysis of single and repeated MSC injections on WOMAC total score at 6 and 12 months. **A** Evidence network diagram of WOMAC total score at 6 months. **B** Forest plot showing the comparative evidence for single and repeated MSC treatments. **C** SUCRA curve and area under the curve (%) for WOMAC total score at 6 months after single and repeated MSC injections. **D** Evidence network diagram of WOMAC total score at 12 months. **E** Forest plot showing the comparative evidence for single and repeated MSC treatments. **F** SUCRA curve and area under the curve (%) for WOMAC total score at 12 months after single and repeated MSC injections



Treatment	SUCRA	PrBest	MeanRank
Traditional	14.9	0.2	2.7
single-doseMSC	36	1.1	2.3
repeated-doseMSC	99.1	98.8	1

Treatment	SUCRA	PrBest	MeanRank
Traditional	2.4	0	3
single-doseMSC	54.1	10.5	1.9
repeated-doseMSC	93.5	89.5	1.1

Fig. 11 Network meta-analysis of single and repeated MSC injections on WOMAC score (Function) at 6 and 12 months. **A** Evidence network diagram of WOMAC score (Function) at 6 months. **B** Forest plot showing the comparative evidence for single and repeated MSC treatments. **C** SUCRA curve and area under the curve (%) for WOMAC score (Function) at 6 months after single and repeated MSC injections. **D** Evidence network diagram of WOMAC score (Function) at 12 months. **E** Forest plot showing the comparative evidence for single and repeated MSC treatments. **F** SUCRA curve and area under the curve (%) for WOMAC score (Function) at 12 months after single and repeated MSC injections

to – 0.01; low certainty) (Fig. 11E). Based on SCURA ranking results, the repeated MSC injection group was ranked as the best treatment for reducing the WOMAC score (Function) with a probability of $P = 93.5$ (Fig. 11F). Single MSC injection ranked second with a probability of $P = 54.1$. These results suggest that repeated MSC injection may be the best option for improving the WOMAC score (Function) at both 6 and 12 months.

WOMAC score of pain

WOMAC score (Pain) at 6 months. A total of 11 datasets involving 276 patients were included. The main evidence for all pairwise comparison protocols regarding WOMAC score (Pain) is shown in Fig. 12A. The network forest plot illustrates the results of the three pairwise comparisons, showing no statistical difference in treatment effects between the single and repeated MSC injection groups (Fig. 12B). Based on SCURA ranking results, the repeated MSC injection group was ranked as the best treatment for reducing the WOMAC score (Pain) with a probability of $P = 75.1$ (Fig. 12C). This was followed by single MSC injection ($P = 56.8$) and conventional therapy ($P = 18.1$). These results suggest that repeated MSC injection may be the best option for improving the WOMAC score (Pain) at 6 months.

WOMAC score (Pain) at 12 months. In the network meta-analysis, a total of 11 datasets involving 276 patients were included. The network evidence plot for the three intervention protocols is shown in Fig. 12D. The network forest plot illustrates the results of the three pairwise comparisons, showing no statistical difference in treatment effects between the single and repeated MSC injection groups (Fig. 12E). Based on SCURA ranking results, the repeated MSC injection group was ranked as the best treatment for reducing the WOMAC score (Pain) with a probability of $P = 89.6$ (Fig. 12F). This was followed by conventional therapy ($P = 39.6$) and single MSC injection ($P = 20.7$). These results suggest that repeated MSC injection may be the best option for improving the WOMAC score (Pain) at both 6 and 12 months.

WOMAC score of stiffness

WOMAC score (Stiffness) at 6 months. A total of 10 datasets involving 246 patients were included. The main evidence for all pairwise comparison protocols regarding WOMAC score (Stiffness) is shown in Fig. 13A. The network forest plot illustrates the results of the three pairwise comparisons, showing no statistical difference in treatment effects between the single and repeated MSC injection groups (Fig. 13B). Based on SCURA ranking results, the repeated MSC injection group was ranked as the best treatment for reducing the WOMAC score (Stiffness) with a probability of $P = 62.9$ (Fig. 13C). This was followed by conventional therapy ($P = 47.8$) and single MSC injection ($P = 39.3$).

WOMAC score (Stiffness) at 12 months. In the network meta-analysis, a total of 10 datasets involving 246 patients were included. The network evidence plot for the three intervention protocols is shown in Fig. 13D. The network forest plot showed that, compared to the conventional therapy group, repeated MSC injection may effectively reduce the WOMAC score (Stiffness) at 12 months (SMD = – 0.32, 95% CI – 0.62 to – 0.02; low certainty) (Fig. 13E). Based on SCURA ranking results, the repeated MSC injection group was ranked as the best treatment for reducing the WOMAC score (Stiffness) with a probability of $P = 85.7$ (Fig. 13F). This was followed by single MSC injection ($P = 59.9$) and conventional therapy ($P = 4.40$). These results suggest that repeated MSC injection may be the best option for improving the WOMAC score (Stiffness) at both 6 and 12 months.

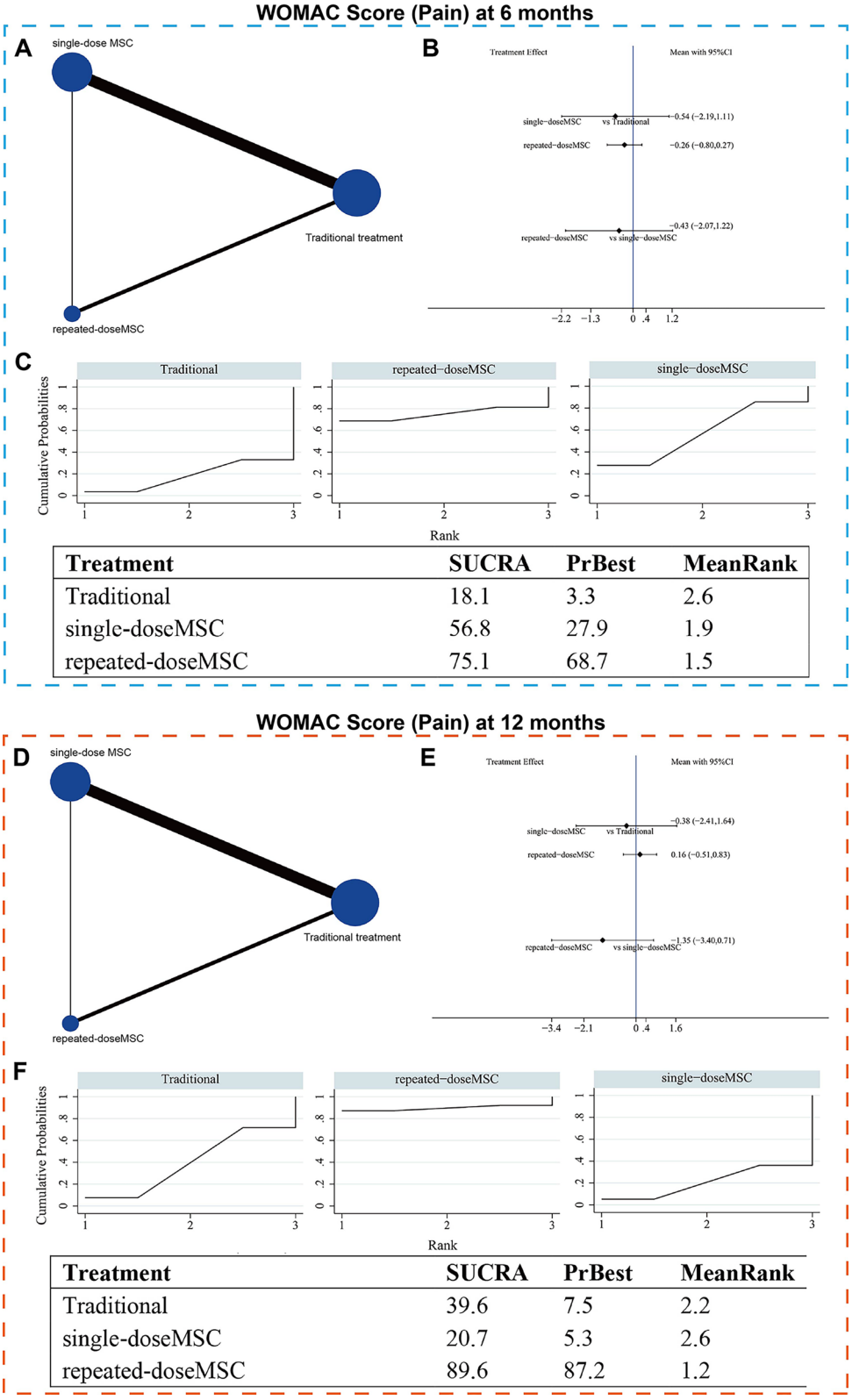
VAS score

VAS score at 6 months. A total of 17 datasets involving 482 patients were included. The main evidence for all pairwise comparison protocols regarding the VAS score is shown in Fig. 14A. Among these, repeated MSC injection significantly reduced the VAS score at 6 months compared to conventional therapy (SMD = – 0.77, 95% CI – 1.26 to – 0.28; low certainty) (Fig. 14B). Based on SCURA ranking results, the repeated MSC injection group was ranked as the best treatment for reducing the VAS score with a probability of $P = 94.7$ (Fig. 14C). This was followed by single MSC injection ($P = 54.5$) and conventional therapy ($P = 0.8$). These results suggest that repeated MSC injection may be the best option for improving the VAS score at 6 months.

VAS score at 12 months. The network meta-analysis included a total of 14 datasets involving 360 patients. The network evidence plot for the three intervention protocols is shown in Fig. 14D. The network forest plot showed that, compared to the conventional therapy group, repeated MSC injection may effectively reduce the VAS score at 12 months (SMD = – 0.90, 95% CI – 1.57 to – 0.23; low certainty) (Fig. 14E). Based on SCURA ranking results, the repeated MSC injection group was ranked as the best treatment for reducing the VAS score with a probability of $P = 95.4$ (Fig. 14F). Single MSC injection ranked second with a probability of $P = 53.7$. These results suggest that repeated MSC injection may be the best option for improving the VAS score at both 6 and 12 months.

AE and SAE

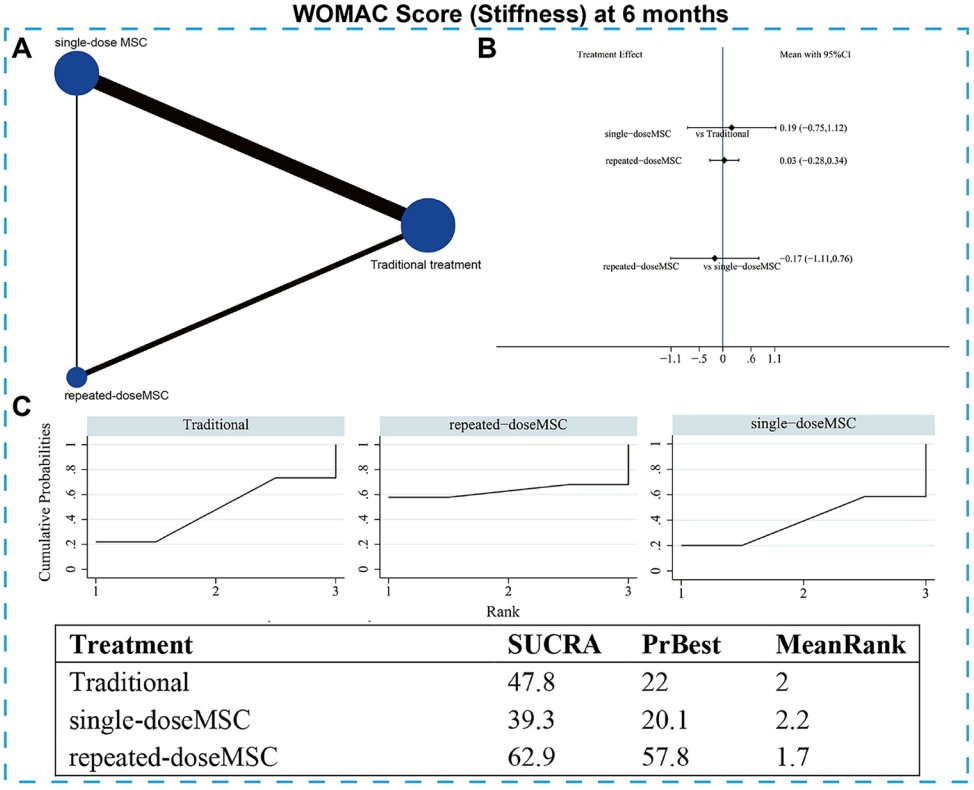
In the traditional meta-analysis of related adverse events, the single injection group includes 9 studies (12 datasets) involving 308 patients, while the repeated injection



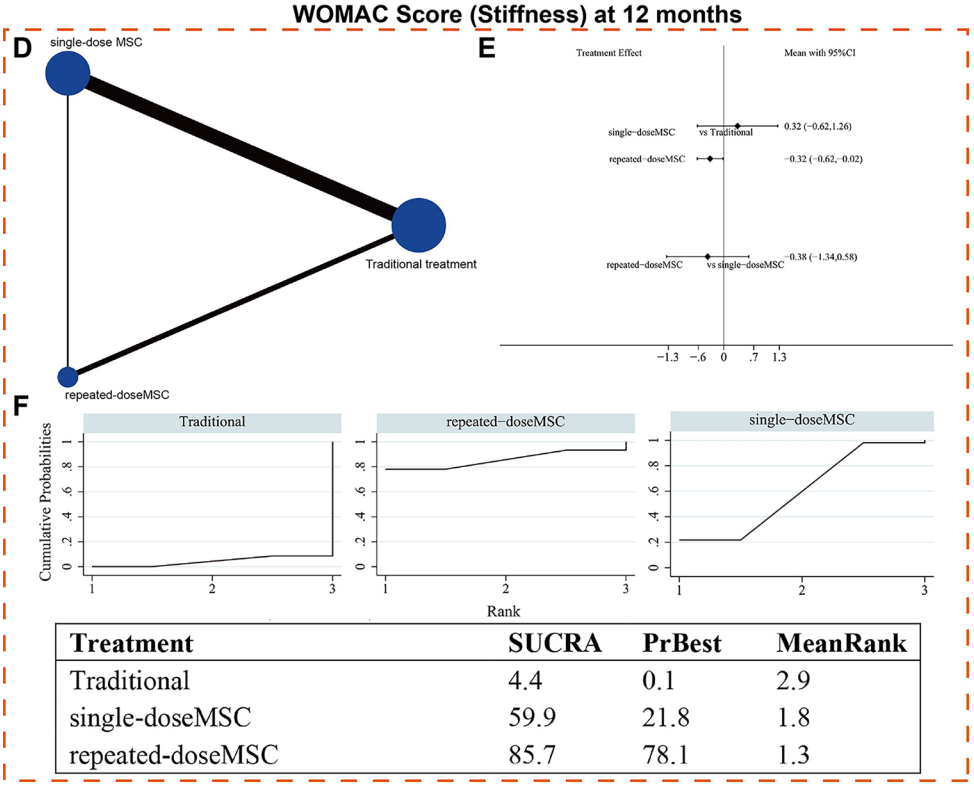
Treatment	SUCRA	PrBest	MeanRank
Traditional	18.1	3.3	2.6
single-doseMSC	56.8	27.9	1.9
repeated-doseMSC	75.1	68.7	1.5

Treatment	SUCRA	PrBest	MeanRank
Traditional	39.6	7.5	2.2
single-doseMSC	20.7	5.3	2.6
repeated-doseMSC	89.6	87.2	1.2

Fig. 12 Network meta-analysis of single and repeated MSC injections on WOMAC score (Pain) at 6 and 12 months. **A** Evidence network diagram of WOMAC score (Pain) at 6 months. **B** Forest plot showing the comparative evidence for single and repeated MSC treatments. **C** SUCRA curve and area under the curve (%) for WOMAC score (Pain) at 6 months after single and repeated MSC injections. **D** Evidence network diagram of WOMAC score (Pain) at 12 months. **E** Forest plot showing the comparative evidence for single and repeated MSC treatments. **F** SUCRA curve and area under the curve (%) for WOMAC score (Pain) at 12 months after single and repeated MSC injections

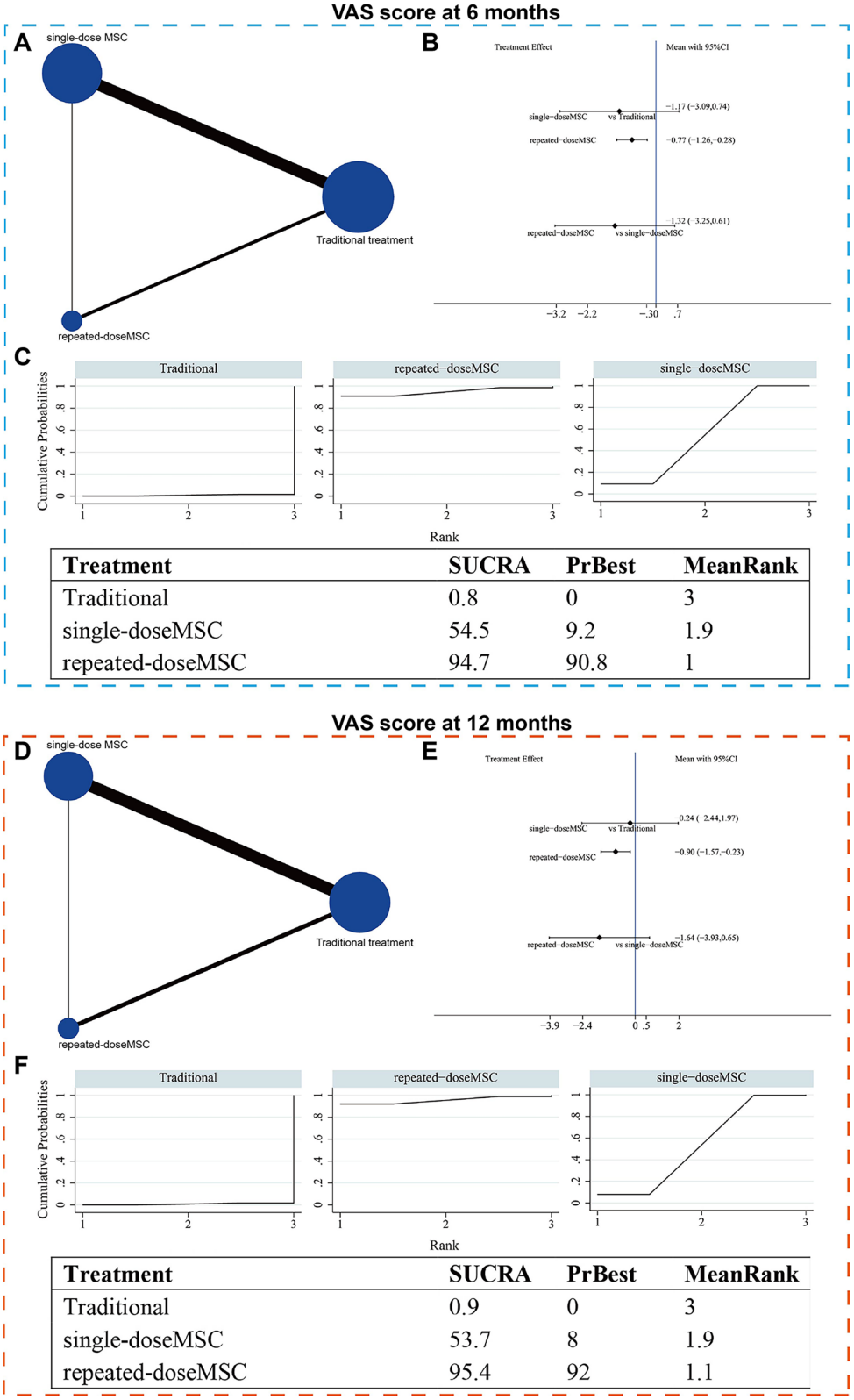


Treatment	SUCRA	PrBest	MeanRank
Traditional	47.8	22	2
single-doseMSC	39.3	20.1	2.2
repeated-doseMSC	62.9	57.8	1.7



Treatment	SUCRA	PrBest	MeanRank
Traditional	4.4	0.1	2.9
single-doseMSC	59.9	21.8	1.8
repeated-doseMSC	85.7	78.1	1.3

Fig. 13 Network meta-analysis of single and repeated MSC injections on WOMAC score (Stiffness) at 6 and 12 months. **A** Evidence network diagram of WOMAC score (Stiffness) at 6 months. **B** Forest plot showing the comparative evidence for single and repeated MSC treatments. **C** SUCRA curve and area under the curve (%) for WOMAC score (Stiffness) at 6 months after single and repeated MSC injections. **D** Evidence network diagram of WOMAC score (Stiffness) at 12 months. **E** Forest plot showing the comparative evidence for single and repeated MSC treatments. **F** SUCRA curve and area under the curve (%) for WOMAC score (Stiffness) at 12 months after single and repeated MSC injections



Treatment	SUCRA	PrBest	MeanRank
Traditional	0.8	0	3
single-doseMSC	54.5	9.2	1.9
repeated-doseMSC	94.7	90.8	1

Treatment	SUCRA	PrBest	MeanRank
Traditional	0.9	0	3
single-doseMSC	53.7	8	1.9
repeated-doseMSC	95.4	92	1.1

Fig. 14 Network meta-analysis of single and repeated MSC injections on VAS score at 6 and 12 months. **A** Evidence network diagram of VAS score at 6 months. **B** Forest plot showing the comparative evidence for single and repeated MSC treatments. **C** SUCRA curve and area under the curve (%) for VAS score at 6 months after single and repeated MSC injections. **D** Evidence network diagram of VAS score at 12 months. **E** Forest plot showing the comparative evidence for single and repeated MSC treatments. **F** SUCRA curve and area under the curve (%) for VAS score at 12 months after single and repeated MSC injections

group includes 4 studies (5 datasets) involving 115 patients. The pooled analysis showed that, compared to conventional therapy, both single and repeated MSC injections significantly increased the incidence of adverse events (OR = 5.72, 95% CI 2.52 to 13.01, $P < 0.0001$; low certainty) (I^2 = 48%) (Fig. 15A). Furthermore, the pooled results also indicated no significant difference in the incidence of adverse events between the different injection protocols ($P = 0.95$). For SAE, the single injection group includes 3 studies (4 datasets) involving 89 patients, while

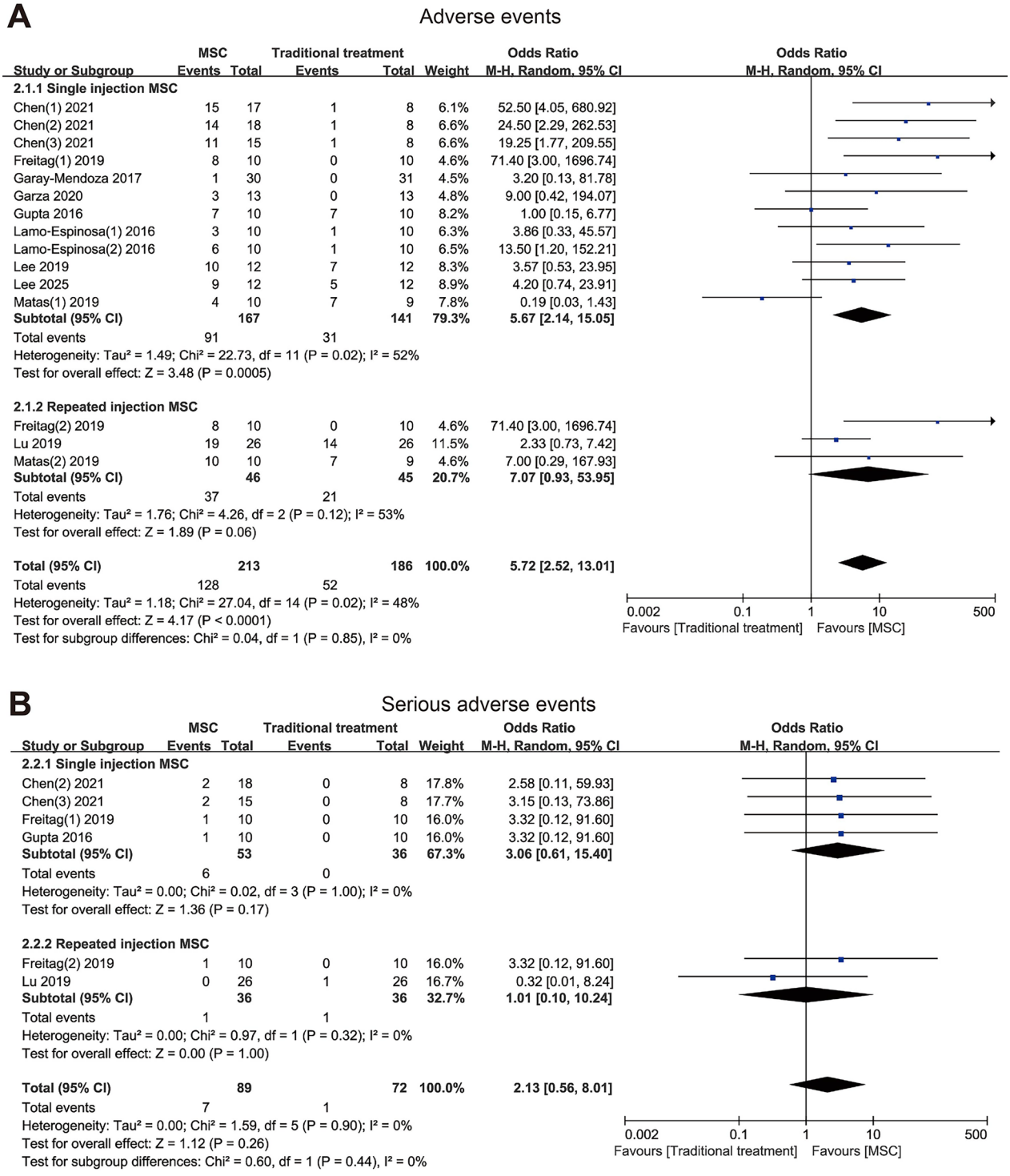


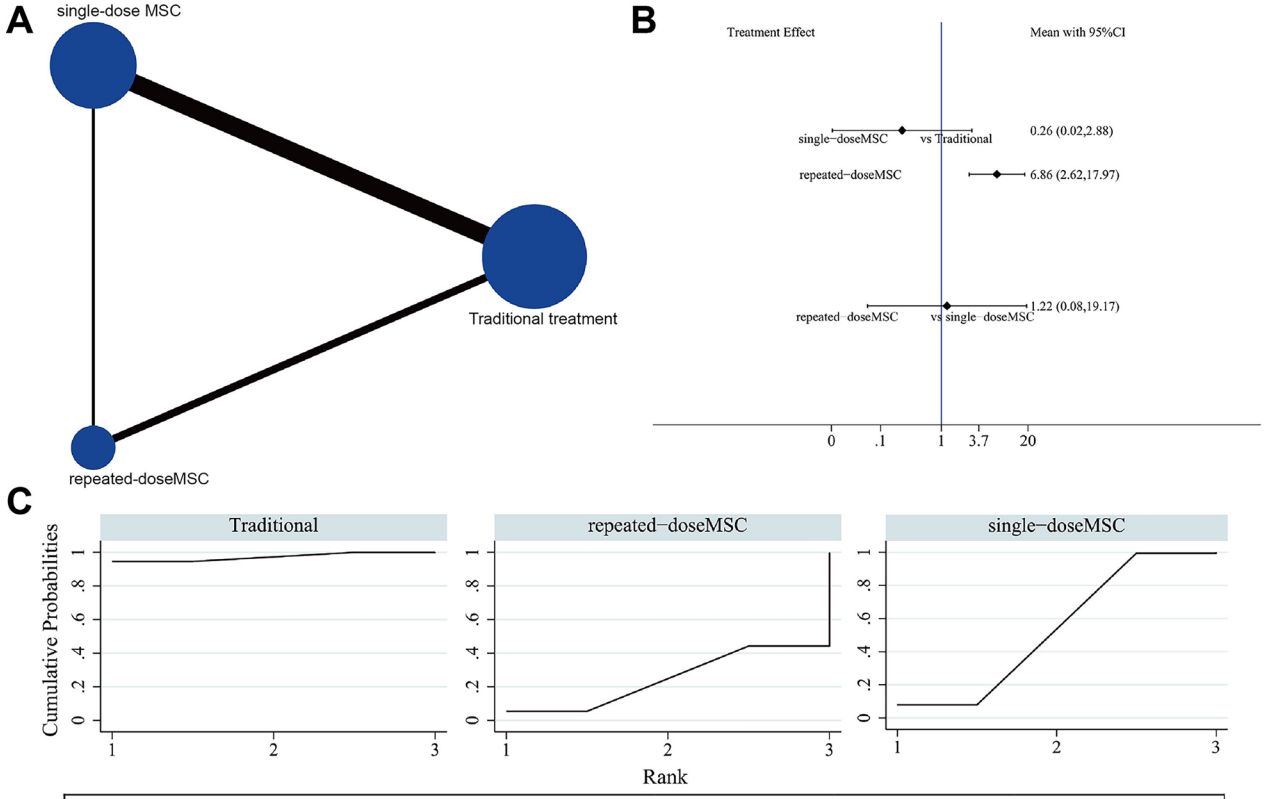
Fig. 15 Forest plot showing the comparative evidence for adverse events following single and repeated MSC injections in knee osteoarthritis. **A** Adverse events. **B** Serious adverse events

the repeated injection group includes 2 studies involving 72 patients. The pooled analysis showed that, compared to conventional therapy, neither single nor repeated MSC injections reduced the incidence of serious adverse events (OR = 2.13, 95% CI 0.56 to 8.01, $P = 0.26$) (Fig. 15B). Additionally, the pooled results indicated no significant difference in the incidence of serious adverse events between the different injection protocols ($P = 0.44$).

In the network meta-analysis, a total of 15 datasets involving 404 patients were included. The network evidence plot shows the pairwise comparisons for the three intervention methods (Fig. 16A). The network forest plot indicates that, compared to the conventional therapy group, repeated MSC injections may increase the incidence of adverse events (OR = 6.86, 95% CI 2.62 to 17.97; very low certainty) (Fig. 16B). Based on SCURA ranking results, the conventional therapy group was ranked as the best treatment for reducing adverse events with a probability of $P = 97.3$ (Fig. 16C). This was followed by single MSC injection ($P = 27.9$) and repeated MSC injection ($P = 24.8$). These results suggest that, compared to conventional therapy, repeated MSC injections may increase the occurrence of adverse events in patients with knee osteoarthritis.

Evaluation of evidence certainty using the GRADE method

In the comparison between single vs. repeated MSC injections, the GRADE assessment indicated that the evidence quality for repeated MSC injections in reducing the WOMAC total score at 12 months was "very low," and for reducing the WOMAC Function score at 6 months, the evidence quality was "low". In the comparison between repeated MSC injections and conventional therapy, the evidence quality for repeated MSC injections in reducing the WOMAC Function score at 12 months, WOMAC Function score at 12 months, VAS score at 6 months, and VAS score at 12 months was all assessed as "low", while the evidence certainty for increasing the



Treatment	SUCRA	PrBest	MeanRank
Traditional	97.3	94.6	1.1
single-doseMSC	27.9	0	2.4
repeated-doseMSC	24.8	5.4	2.5

Fig. 16 Network meta-analysis of adverse events following single and repeated MSC injections. **A** Evidence network diagram of adverse events. **B** Forest plot showing the comparative evidence for adverse events following single and repeated MSC treatments. **C** SUCRA curve and area under the curve (%) for adverse events following single and repeated MSC injections

incidence of adverse events was considered "very low". A summary of the findings from the NMA and the assessment of evidence certainty can be found in Table 3.

Sensitivity analysis

Additionally, sensitivity analysis was conducted to evaluate the robustness of the results from the traditional meta-analysis. Figure 17A shows the sensitivity analysis of the WOMAC scores at different time points (3 months, 6 months, and 12 months). When any single study was excluded, the pooled results from the remaining studies were consistent with the original results, demonstrating the robustness of the findings. Similarly, sensitivity analyses of the WOMAC score (Function), WOMAC score (Pain), and WOMAC score (Stiffness) at different time points (3 months, 6 months, and 12 months) also showed the robustness of the pooled results (Fig. 17B). Moreover, consistent conclusions were also observed in the pooled results for the VAS scores and adverse events at different time points (3 months, 6 months, and 12 months). Overall, the meta-analysis results for various outcome measures were stable (Figures S1 and S2). To further evaluate the robustness of the results, subgroup analyses were performed to assess the potential impact of studies with a high risk of bias on the pooled estimates. The results of the subgroup analyses showed no significant differences between the high-risk and low-risk bias subgroups in terms of VAS score at different time points, WOMAC total score, WOMAC pain score, WOMAC stiffness score, WOMAC function score, and adverse events (Figures S3–S9), further supporting the stability of the meta-analysis findings.

Publication bias

Funnel plots and Egger's test were used to assess publication bias. In the traditional meta-analysis, the funnel plots for most outcome measures were symmetrical, and Egger's test showed no significant evidence of publication bias (Figures S10-S14) (Table 4). For outcomes with a P-value < 0.05 in Egger's test, the trim-and-fill method was further employed to evaluate the potential impact of publication bias on the results (Figure S15). The analysis revealed that no studies were imputed for WOMAC total score at 6 months, WOMAC total score at 12 months, VAS score at 6 months, and VAS score at 12 months, and the pooled estimates remained unchanged before and after trimming. Therefore, there was no indication of publication bias according to the trim-and-fill method (no new studies added), suggesting that these results were robust. In the network meta-analysis, the funnel plots for all outcome measures were also symmetrical (Figures S16-S21). Overall, the analysis results of the included studies were robust.

Discussion

Main findings

KOA is a progressive disease that can ultimately lead to disability, with its incidence steadily increasing across various populations [55]. Aside from joint replacement surgery for advanced KOA, clinical management typically relies on non-surgical approaches to slow disease progression, including intra-articular injections of HA, PRP, and MSC. Given their multilineage differentiation potential, immunomodulatory and anti-inflammatory properties, and ability to enhance angiogenesis, MSCs have emerged as a promising therapeutic strategy to compensate for the limited regenerative capacity of cartilage in KOA [56, 57]. However, standardized protocols for MSC preparation and intervention are still lacking, which may lead to variability in therapeutic efficacy and safety among KOA patients. While Recent studies have investigated the effects of different MSC sources and dosages [25, 58], our focus is on comparing the efficacy and safety between different injection frequencies (single vs. repeated injections), aiming to provide evidence for the development of standardized intra-articular MSC intervention protocols.

To the best of our knowledge, this is the first study to compare the efficacy and safety of single versus repeated MSC injections for KOA patients using both traditional and network meta-analysis. A total of 16 randomized controlled trials (RCTs) involving 23 treatment arms and 622 patients were included in this study. Conventional meta-analysis revealed that, compared to baseline, both single and repeated MSC injections significantly improved pain (VAS score) and knee function scores (WOMAC and KOOS), including domains such as function, mobility, stiffness, quality of life, and symptoms at 3, 6, and 12 months. However, no significant differences in efficacy were observed between the single and repeated injection groups in direct comparisons. In the network meta-analysis, we found that repeated MSC injections demonstrated significant advantages over conventional treatments in reducing VAS pain scores at 6 months, WOMAC Function and Stiffness scores at 12 months, and VAS pain scores at 12 months. Among these indicators, SUCRA rankings showed that repeated MSC injections provided the most favorable therapeutic outcomes. Furthermore, compared to single injections, repeated MSC injections significantly improved WOMAC Function scores at 6 months and total WOMAC scores at 12 months. These findings suggest that, in clinical practice, repeated MSC injections may be more effective in alleviating pain and improving knee joint function in the early to mid-stages of KOA, thereby offering superior therapeutic benefits.

Table 3 Summary of findings

Outcome	Comparison	Direct estimate		Indirect estimate		NMA estimate		Comments
		SMD (95% CI)	Certainty in the evidence	SMD (95% CI)	Certainty in the evidence	SMD (95% CI)	Certainty in the Evidence	
WOMAC total score at 6 months	Single-dose MSC vs. conventional therapy	– 0.26 (– 0.91 to 0.39)	⊕ very low[a, b,c]	– 0.43 (– 1.20 to 0.33)	⊕ very low[a, d]	– 0.54 (– 2.19 to 1.11)	⊕ very low	Single or repeated MSC injections may not reduce the WOMAC total score at 6 months, but the evidence is highly uncertain.
	Repeated-dose MSC vs. conventional therapy	– 0.53 (– 0.95 to – 0.11)	⊕⊕ low[a, d]	– 0.24 (– 0.91 to 0.44)	⊕ very low[a]	– 0.26 (– 0.80 to 0.27)	⊕ very low	
	Repeated vs. single-dose MSC	0.09 (– 1.18 to 1.36)	⊕ very low[a, b,d]	– 0.35 (– 0.83 to 0.12)	⊕ very low[a]	– 0.43 (– 2.07 to 1.22)	⊕ very low	
WOMAC total score at 12 months	Single-dose MSC vs. conventional therapy	– 0.42 (– 0.92 to 0.07)	⊕ very low[a, b,c]	– 0.12 (– 0.91 to 0.67)	⊕ very low[a, d]	– 0.79 (– 2.17 to 0.58)	⊕ very low	Compared to a single MSC injection, repeated injections may reduce the WOMAC total score at 12 months, but the evidence is highly uncertain.
	Repeated-dose MSC vs. conventional therapy	– 1.34 (– 2.63 to – 0.06)	⊕ very low[a, b,d]	– 1.06 (– 1.76 to – 0.37)	⊕ very lowd[a]	– 0.31 (– 0.84 to 0.22)	⊕ very low	
	Repeated vs. single-dose MSC	– 0.74 (– 1.48 to 0.00)	⊕ very low[a, b,d]	– 0.45 (– 0.96 to 0.06)	⊕ very low[a]	– 1.47 (– 2.86 to -0.07)	⊕ very low	
WOMAC score (Function) at 6 months	Single-dose MSC vs. conventional therapy	– 0.12 (– 0.47 to 0.2)	⊕⊕⊕ Moderate[a]	0.94 (– 0.17 to 2.05)	⊕ very low[a, d]	– 0.39 (– 1.42 to 0.64)	⊕⊕⊕ Moderate	Compared to a single MSC injection, repeated injections may reduce the WOMAC Function score at 6 months, but the evidence certainty is low.
	Repeated-dose MSC vs. conventional therapy	0.06 (– 1.53 to 1.64)	⊕ very low[a, b,d]	– 1.05 (– 2.03 to – 0.08)	⊕⊕ low[a]	– 0.10 (– 0.44 to 0.25)	⊕⊕ low	
	Repeated vs. single-dose MSC	– 0.96 (– 1.89 to – 0.03)	⊕⊕ low[a, d]	0.17 (– 0.48 to 0.83)	⊕ very low[a]	– 1.24 (– 2.33 to – 0.15)	⊕⊕ low	
WOMAC score (Function) at 12 months	Single-dose MSC vs. conventional therapy	– 0.27 (– 0.55 to 0.00)	⊕⊕⊕ Moderate[a]	1.42 (0.28 to 2.55)	⊕ very low[a, d]	0.34 (– 0.85 to 1.27)	⊕⊕⊕ Moderate	Compared to conventional therapy, repeated injections may reduce the WOMAC Function score at 12 months, but the evidence certainty is low.
	Repeated-dose MSC vs. conventional therapy	0.33 (– 1.01 to 1.68)	⊕ very low[a, b,d]	– 1.46 (– 2.47 to – 0.45)	⊕⊕ low[a]	– 0.30 (– 0.59 to – 0.01)	⊕⊕ low	
	Repeated vs. single-dose MSC	– 1.26 (– 2.23 to – 0.29)	⊕⊕ low[a, d]	0.49 (– 0.16 to 1.13)	⊕ very low[a]	– 0.61 (– 1.57 to 0.35)	⊕⊕ low	
WOMAC score (Pain) at 6 months	Single-dose MSC vs. conventional therapy	– 0.32 (– 0.81 to 0.18)	⊕⊕ low[a, b]	– 0.63 (– 1.67 to 0.40)	⊕⊕ low[a, d]	– 0.54 (– 2.19 to 1.11)	⊕⊕ low	Single or repeated MSC injections may not reduce the WOMAC Pain score at 6 months, but the evidence certainty is low.
	Repeated-dose MSC vs. conventional therapy	– 0.47 (– 1.03 to 0.08)	⊕⊕ low[b, d]	– 0.07 (– 0.99 to 0.85)	⊕⊕ low[a]	-0.26 (-0.80 to 0.27)	⊕⊕ low	
	Repeated vs. single-dose MSC	0.19 (– 0.69 to 1.07)	⊕⊕ low[a, d]	– 0.20 (– 0.81 to 0.42)	⊕⊕ low[a]	– 0.43 (– 2.07 to 1.22)	⊕⊕ low	
WOMAC score (Pain) at 12 months	Single-dose MSC vs. conventional therapy	0.12 (– 0.43 to 0.66)	⊕⊕ low[a, b]	0.56 (– 0.57 to 1.70)	⊕⊕ low[a, d]	– 0.38 (– 2.41 to 1.64)	⊕⊕ low	Single or repeated MSC injections may not reduce the WOMAC Pain score at 12 months, but the evidence is highly uncertain.
	Repeated-dose MSC vs. conventional therapy	– 0.69 (– 1.74 to 0.36)	⊕⊕ low[b, d]	– 1.18 (– 2.19 to – 0.17)	⊕⊕ low[a]	0.16 (– 0.51 to 0.83)	⊕⊕ low	
	Repeated vs. single-dose MSC	– 1.26 (– 2.23 to – 0.30)	⊕⊕ low[a, d]	– 0.67 (– 1.31 to – 0.03)	⊕⊕ low[a]	– 1.35 (– 3.40 to 0.71)	⊕⊕ low	
WOMAC score (Stiffness) at 6 months	Single-dose MSC vs. conventional therapy	0.05 (– 0.23 to 0.33)	⊕⊕ low[a, d]	0.12 (– 0.93 to 1.17)	⊕⊕ low[a, d]	0.19 (– 0.75 to 1.12)	⊕⊕ low	Single or repeated MSC injections may not reduce the WOMAC Stiffness score at 12 months, but the evidence is highly uncertain.
	Repeated-dose MSC vs. conventional therapy	– 0.35 (– 0.90 to 0.20)	⊕⊕ low[a, d]	– 0.41 (– 1.34 to 0.53)	⊕⊕ low[a]	0.03 (– 0.28 to 0.34)	⊕⊕ low	
	Repeated vs. single-dose MSC	– 0.47 (– 1.36 to 0.42)	⊕⊕ low[a, d]	– 0.37 (– 0.99 to 0.24)	⊕⊕ low[a]	– 0.17 (– 1.10 to 0.76)	⊕⊕ low	

Table 3 (continued)

Outcome	Comparison	Direct estimate		Indirect estimate		NMA estimate		Comments
		SMD (95% CI)	Certainty in the evidence	SMD (95% CI)	Certainty in the evidence	SMD (95% CI)	Certainty in the Evidence	
WOMAC score (Stiffness) at 12 months	Single-dose MSC vs. conventional therapy	− 0.12 (− 0.47 to 0.22)	⊕⊕ low[a, d]	0.55 (− 0.51 to 1.62)	⊕ very low[a, d]	0.32 (− 0.62 to 1.26)	⊕⊕ low	Compared to conventional therapy, repeated injections may reduce the WOMAC Stiffness score at 12 months, but the evidence certainty is low.
	Repeated-dose MSC vs. conventional therapy	− 0.08 (− 0.99 to 0.82)	⊕ very low[a, b,d]	− 0.95 (− 1.90 to 0.00)	⊕⊕ low[a]	− 0.32 (− 0.62 to − 0.02)	⊕⊕ low	
	Repeated vs. single-dose MSC	− 0.69 (− 1.60 to 0.21)	⊕⊕ low[a, d]	0.18 (− 0.44 to 0.81)	⊕ very low[a]	− 0.38 (− 1.34 to 0.58)	⊕⊕ low	
VAS score at 6 months	Single-dose MSC vs. conventional therapy	− 0.87 (− 1.35 to − 0.38)	⊕ very low[a, b,c]	− 0.50 (− 1.47 to 0.47)	⊕⊕ low[d]	− 1.17 (− 3.09 to 0.74)	⊕⊕ low	Compared to conventional therapy, repeated injections may reduce the VAS score at 6 months, but the evidence certainty is low.
	Repeated-dose MSC vs. conventional therapy	− 0.69 (− 1.50 to 0.12)	⊕⊕ low[b, d]	− 0.89 (− 1.80 to 0.01)	⊕ very low[a]	− 0.77 (− 1.26 to − 0.28)	⊕⊕ low	
	Repeated vs. single-dose MSC	− 0.16 (− 1.03 to 0.72)	⊕⊕⊕ Moderate[d]	0.09 (− 0.37 to 0.55)	⊕ very low[a]	− 1.32 (− 3.25 to 0.61)	⊕⊕⊕ Moderate	
VAS score at 12 months	Single-dose MSC vs. conventional therapy	− 0.91 (− 1.45 to − 0.36)	⊕ very low[a, b,c]	1.13 (− 0.01 to − 2.27)	⊕⊕ low[d]	− 0.24 (− 2.44 to 1.97)	⊕⊕ low	Compared to conventional therapy, repeated injections may reduce the VAS score at 12 months, but the evidence certainty is low.
	Repeated-dose MSC vs. conventional therapy	− 0.70 (− 1.87 to 0.47)	⊕⊕ low[b, d]	-2.32 (-3.42 to -1.23)	⊕ very low[a]	− 0.90 (− 1.57 to − 0.23)	⊕⊕ low	
	Repeated vs. single-dose MSC	− 1.78 (− 2.83 to − 0.73)	⊕⊕⊕ Moderate[d]	0.08 (− 0.41 to 0.57)	⊕ very low[a]	− 1.64 (− 3.93 to 0.65)	⊕⊕⊕ Moderate	
Adverse events	Single-dose MSC vs. conventional therapy	5.95 (2.96 to 11.97)	⊕⊕ low[a, c]	0.10 (− 1.93 to 2.13)	⊕ very low[a, d]	0.26 (0.02 to 2.88)	⊕⊕ low	Compared to conventional therapy, repeated injections may increase adverse events, but the evidence is highly uncertain.
	Repeated-dose MSC vs. conventional therapy	7.07 (0.93 to 53.95)	⊕ very low[a, b,d]	2.71 (0.80 to 4.61)	⊕ very low[a, d]	6.86 (2.62 to 17.97)	⊕ very low	
	Repeated vs. single-dose MSC	4.32 (0.98 to 19.16)	⊕ very low[a, b,d]	− 0.32 (− 1.49 to 0.86)	⊕ very low[a, d]	1.22 (0.08 to 19.17)	⊕ very low	

CI Confidence interval, *MSC* Mesenchymal stem cell, *NMA* Network meta-analysis, *OR* Odds ratio, *SMD* Standardized mean difference. ⊕⊕⊕⊕: high certainty; ⊕⊕⊕: moderate certainty; ⊕⊕⊕: low certainty; ⊕: very low certainty; (a) Certainty in the evidence downgraded by one level due to significant risk of bias; (b) Certainty in the evidence downgraded by one level due to inconsistency; (c) Certainty in the evidence downgraded by one level due to significant publication bias; (d) Certainty in the evidence downgraded by one level due to imprecision

Does a higher dose of MSCs lead to better therapeutic outcomes?

Mechanistically, MSCs and their secreted products (such as exosomes and cytokines) exert chondroprotective and regenerative effects through multiple pathways, including promoting chondrocyte differentiation, reducing apoptosis, enhancing metabolic activity, and modulating immune responses [59, 60]. Therefore, it is anticipated that administering a higher quantity of MSCs may yield enhanced therapeutic benefits. Essentially, strategies involving repeated or high-dose MSC injections can be considered equivalent to the administration of a large quantity of MSCs. In terms of injection frequency, Matas et al. [27] demonstrated that repeated MSC injections (administered every six months) significantly improved knee function and reduced pain compared to a single injection. Another study also found that two intra-articular MSC injections provided better joint stability than a single injection in KOA patients [39]. These findings align with our results, as the network meta-analysis (NMA) showed that repeated MSC injections significantly improved knee function scores at both 6 and 12 months compared to single injections.

In terms of MSC injection dosage, the commonly used dose is approximately 5×10^7 cells [61]. The studies included in our analysis involved injection doses ranging from 1×10^7 to 1×10^8 cells. Preliminary clinical trials have explored the impact of higher MSC doses on patient outcomes. Chahal et al. [62] observed that, over a 12-month follow-up, patients in the high-dose MSC group showed significant reductions in cartilage catabolic biomarkers and MRI-assessed synovitis. Another study with a two-year follow-up reported sustained clinical improvement in the high-dose group [63]. Similarly, Lamo-Espinosa et al. [45] found that patients receiving high-dose MSCs exhibited reduced joint damage. A recent meta-analysis comparing low ($0–25 \times 10^6$), medium ($25–50 \times 10^6$), and high ($> 50 \times 10^6$) cell doses demonstrated that high-dose

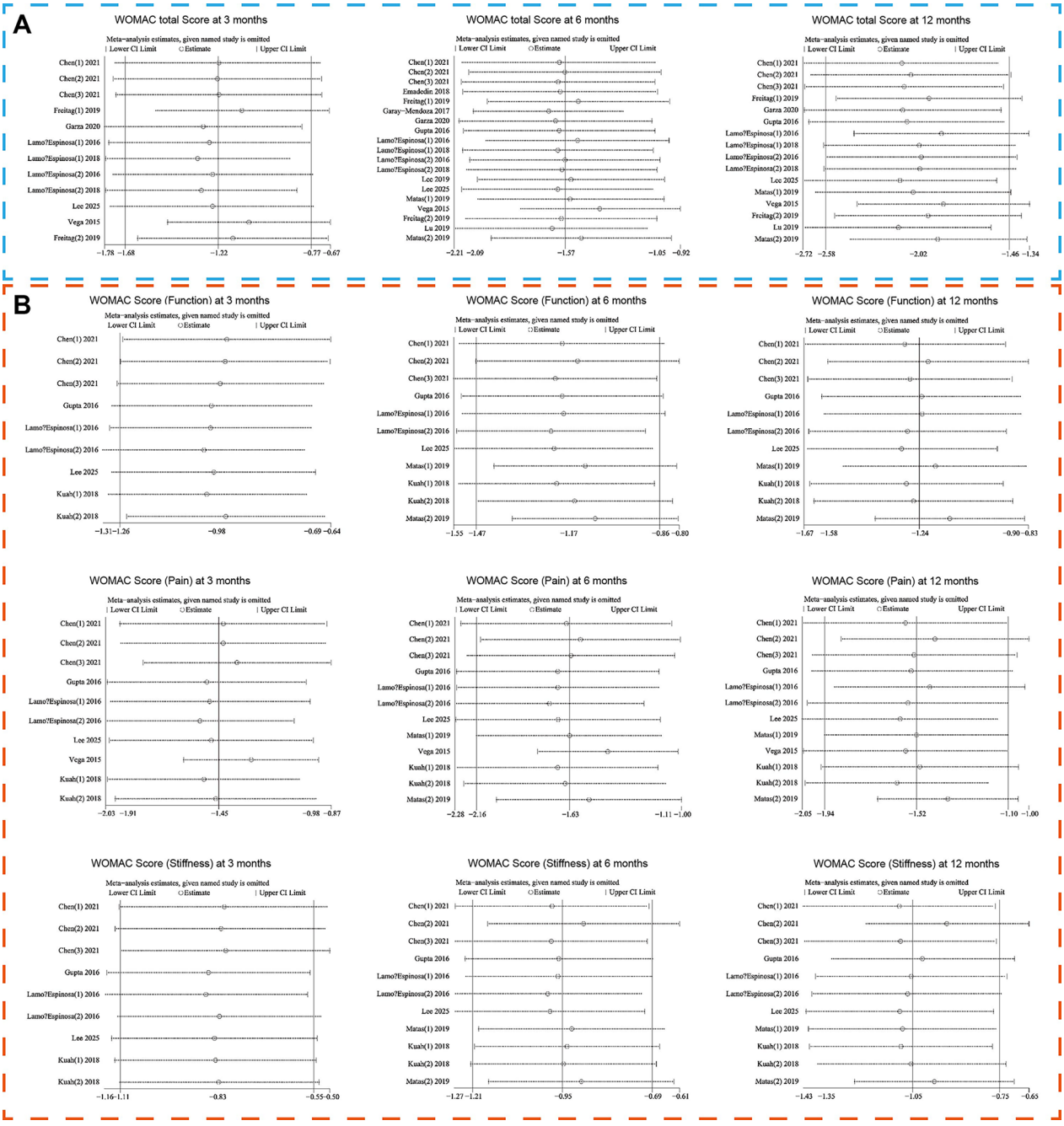


Fig. 17 Sensitivity analysis of different outcome measures in traditional meta-analysis. **A** WOMAC total score at 3, 9, and 12 months. **B** WOMAC score (Function), WOMAC score (Pain), and WOMAC score (Stiffness) at different time points (3, 6, and 12 months)

MSC treatment yielded the most favorable outcomes, particularly in improving early pain and functional impairment [25]. However, a small-sample clinical trial by Pers et al. [64] reported improvements in pain and function with low-dose MSCs, while the high-dose group did not show statistically significant benefits. Due to the non-randomized design and limited sample size, these findings should be interpreted with caution. Overall, current evidence suggests that high-dose MSC therapy may offer superior clinical benefits for KOA patients. Nevertheless, large-scale and long-term randomized controlled trials are still needed to confirm whether patients can consistently benefit from intra-articular injections of large quantities of MSCs.

Safety evaluation

Beyond clinical efficacy, safety assessment is a critical factor in evaluating the clinical applicability of MSC

Table 4 Analysis of publication bias for different outcome measures in traditional meta-analysis

Outcome	Egger's test (*p* value)	t value	Pooling model
WOMAC total Score at 3 months	**0.192**	− 1.400	Random
WOMAC total Score at 6 months	0.000	− 7.240	Random
WOMAC total Score at 12 months	0.000	− 8.720	Random
WOMAC score (Function) at 3 months	**0.392**	0.910	Random
WOMAC score (Function) at 6 months	**0.098**	− 1.850	Random
WOMAC score (Function) at 12 months	**0.054**	− 2.220	Random
WOMAC score (Pain) at 3 months	**0.558**	− 0.610	Random
WOMAC score (Pain) at 6 months	**0.101**	− 1.820	Random
WOMAC score (Pain) at 12 months	**0.053**	− 2.230	Random
WOMAC score (Stiffness) at 3 months	**0.222**	1.340	Random
WOMAC score (Stiffness) at 6 months	**0.291**	− 1.120	Random
WOMAC score (Stiffness) at 12 months	**0.326**	− 1.040	Random
VAS score at 3 months	**0.455**	− 0.780	Random
VAS score at 6 months	0.003	− 3.470	Random
VAS score at 12 months	0.003	− 3.640	Random

VAS Visual analogue scale, *WOMAC* Western Ontario and McMaster University Osteoarthritis Index

therapies. In terms of post-injection safety, our meta-analysis revealed that both single and repeated MSC injections were associated with a higher incidence of AEs compared to conventional treatments. Network meta-analysis further demonstrated that repeated MSC injections significantly increased the AE rate relative to standard therapy. According to the data, AEs were reported in all treatment arms involving MSCs: 91 cases in the single-injection group and 53 cases in the repeated-injection group. Most AEs were mild and localized, primarily involving post-injection site pain. Importantly, neither intervention showed a significantly increased rate of SAEs. The single-injection group reported six SAEs, while the repeated-injection group reported one. Notably, apart from one case of prepatellar bursitis [44] and two cases of prolonged pain lasting up to four weeks [39], the remaining SAEs were not deemed related to MSC administration. In a separate study, Pers et al. [64] reported a case of unstable angina in the MSC treatment group. Current data suggest that SAEs are more frequently associated with high-dose MSC treatments ($>5\times10^7$ cells). Therefore, while repeated MSC injections may enhance clinical outcomes, they also appear to increase the risk of injection-related AEs. Striking a balance between therapeutic efficacy and safety remains a critical issue that warrants further investigation.

Strengths and limitations

Our work represents the first comprehensive meta-analysis comparing the efficacy and safety of single and repeated MSC injections using both conventional and network methodologies, providing valuable insights for the clinical standardization of MSC intervention protocols. Firstly, in contrast to previous meta-analyses that focused on different MSC sources, treatment methods, and intervention doses, we comprehensively compared the efficacy and safety data of single versus multiple MSC injections for KOA, summarizing evidence of effectiveness for different injection frequencies. This is crucial for guiding clinical interventions. Secondly, we refined the measurement indicators based on different follow-up time points (3, 6, and 12 months). This time-point division provides further insight into the duration of benefit from single/repeated MSC injections for KOA patients, which was overlooked in previous meta-analyses. Moreover, while prior meta-analyses pointed to a dose-dependent increase in AEs [25], our study found that repeated MSC injections improved KOA outcomes without showing higher rates of AEs or SAEs compared to single injections. This result reflects the risk-benefit balance of multiple MSC injections and provides novel insights for personalized clinical interventions in KOA. For example, repeated MSC injections may benefit moderate to severe KOA patients with limited consideration for AE risks, whereas single injections may be more suitable for early KOA patients seeking short-term symptom relief. Of course, from a cost-effectiveness perspective, repeated injections may lead to higher patient costs, and future clinical applications should fully weigh these factors.

Therefore, this study integrated both traditional and network meta-analyses, overcoming the limitation of insufficient direct comparative evidence between single and repeated MSC injections. It provided a comprehensive comparison of the efficacy and safety of the two intervention strategies in the treatment of KOA. The analysis included a full range of outcome indicators commonly used to assess KOA and evaluated clinical efficacy at 3, 6, and 12 months, offering a thorough assessment of early- to mid-term outcomes for both single and repeated MSC injections. However, several limitations should be acknowledged. First, in order to obtain a sufficient number of comparison arms, the conventional treatment group included a variety of commonly used clinical medications and placebos, which may have introduced heterogeneity and affected the reliability of the pooled results. Second, most of the included RCTs were single-center studies with small sample sizes, lacking large-scale, multicenter trial data. Moreover, there was variability in the source and dosage of MSCs across studies, potentially contributing to significant heterogeneity in the outcomes. Therefore, future research should focus on conducting

large-scale, multicenter clinical trials with extended follow-up periods. In addition, further efforts are needed to standardize MSC preparation and intervention protocols to validate the clinical efficacy and safety of MSC-based treatments for KOA.

Conclusion

In this study, both single and repeated MSC injections improved knee joint function and reduced pain in KOA patients across different follow-up time points (3, 6 and 12 months) compared to baseline. Notably, repeated MSC injections demonstrated advantages over single injections and conventional therapies in alleviating early-stage pain and enhancing mid-term knee function. However, given the higher incidence of adverse events observed in the repeated injection group, further large-scale randomized controlled trials with extended follow-up durations are necessary to validate the efficacy and safety of different injection frequencies.

Abbreviations

AD-MSC	Adipose-derived mesenchymal stem cells
AE	Adverse event
BMSC	Bone marrow mesenchymal stem cells
BMI	Body mass index
CI	Confidence interval
HA	Hyaluronic acid
ITT	Intention-to-treat
I^2	I-squared (Heterogeneity Statistic)
KOA	Knee osteoarthritis
KOOS	Knee Injury and Osteoarthritis Outcome Score
MD	Mean difference
MeSH	Medical Subject Headings
MSC	Mesenchymal stem cell
NMA	Network meta-analysis
OA	Osteoarthritis
OR	Odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
SAE	Serious adverse event
SD	Standard deviation
SUCRA	Surface under the cumulative ranking
UC-MSC	Umbilical cord mesenchymal stem cells
VAS	Visual analogue scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
WORMS	Whole-Organ Magnetic Resonance Imaging Score

Supplementary Information

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Supplementary material 1.

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Author contributions

Li Deng, Chongyu Zhao and Ying Zhang conceived the study and wrote the manuscript. Li Li and Liming Zhou carried out the data collection and data analysis. Xiaoyu Mu and Haomin Sun assessed the quality of the studies. All authors reviewed the results and approved the final version of the manuscript.

Generative AI in scientific writing

The authors declare that they have not use AI-generated work in this manuscript" in this section.

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Data availability

The supplementary tables and figures presented in the study are included in the Supplementary Material, further inquiries can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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