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RESEARCH ARTICLE

Effect of mesenchymal stromal cells transplantation on the outcomes of patients with knee osteoarthritis: A systematic review and meta-analysis

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Abstract

Cell therapy has been explored as a new regenerative treatment for osteoarthritis in the field of regenerative medicine. However, the efficacy of stem cell transplantation from different sources for the treatment of knee osteoarthritis (KOA) remains controversial. This study integrates and evaluates the previously published data of stem cell transplantation for KOA to explore the curative effect of different stem cells. We conducted a meta-analysis of randomized controlled trials on stem cell therapy for KOA. Measures of efficacy included Visual Analog Scale (VAS), Lequesne index, Lysholm Knee Scoring Scale (LKSS), and Western Ontario and McMaster University Osteoarthritis Index (WOMAC). Joint injury was evaluated through the Whole-Organ Magnetic Resonance Imaging Score (WORMS) system. We analyzed 16 studies involving 875 KOA patients. The stem cell treatment showed significant VAS reduction from the third month onwards. Subgroup analysis suggested the most significant pain relief at different postoperative months came from adipose-derived and umbilical cord-derived stem cells. Autologous adipose tissue resulted in better pain alleviation compared with allogenic. However, autologous bone marrow stem cells did not show increased pain relief over allogeneic ones. Combination therapy (HA and/or PRP) showed no effect. Autologous adipose-derived stem cells demonstrate the most effective recovery of knee joint function. In WORMS assessment, there was no significant difference between the stem cell group and control. Stem cell transplantation proved safe and effective for KOA treatment. Different sources stem cells have a good effect on alleviating knee joint pain, restoring knee joint function, and minimizing patient trauma.

KEYWORDS

knee osteoarthritis, stem cell transplantation, systematic review and meta-analysis

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 09 September 2022 and was last updated on 09 September 2022 (registration number INPLASY202290046).

Rong-hui Xie and Shi-guo Gong contributed equally to the work.

1 | INTRODUCTION

Knee osteoarthritis (KOA) is a degenerative and chronic joint disorder characterized by joint stiffness, swelling, pain, and limited joint activity, eventually leading to physical function impairment and disability.[1] In the early stage of KOA, conservative treatments such as physical therapy and medication are commonly suggested to delay disease progression and reduce clinical symptoms, while in the late stage, knee arthroplasty can be considered.[2] In recent years, advances in molecular biology, cell biology, and precision medicine have provided novel therapeutic options for osteoarthritis. Especially in the field of regenerative medicine, cell therapy has been explored as a new regenerative treatment for osteoarthritis.[3]

At present, a variety of drugs are available to provide clinically relevant pain relief for patients with KOA, such as nonsteroidal anti-inflammatory drugs (NSAIDs), tramadol, and duloxetine recommended by most rheumatology/arthritis guidelines.[4,5] However, long-term medication can cause some gastrointestinal, cardiovascular, and other adverse reactions, drug resistance, and safety problems. Intra-articular injections can effectively alleviate the adverse reactions of drug metabolism in vivo and resolve the problem of medication compliance. A large array of intra-articular injection products have been proposed to provide symptomatic relief, including corticosteroids (CS), platelet-rich plasma (PRP), hyaluronic acid (HA), botulinum toxin type A, autologous conditioned serum (ACS), and stromal vascular fraction (SVF).[6–8] The results of current randomized controlled trials (RCTs) on cell therapy for KOA are still inconclusive, especially regarding the functional results.[9] The majority of the latest research mainly focuses on stem cells derived from multiple sources, such as mesenchymal stem cells,[10] adipose stem cells,[11] and umbilical cord mesenchymal stem cells,[12] but the safety and efficacy of stem cells in the treatment of KOA have not been rigorously demonstrated. It is still necessary to systematically evaluate the efficacy and cartilage repair ability of stem cell therapy for KOA.[13] Recently, a meta-analysis of RCTs provides evidence that intra-articular injection of mesenchymal stem cells (MSCs) shows a superior ability to regenerate damaged cartilage and improve functional impairment, and the cell quantity and concomitant treatment may have an impact on the results.[14] Another meta-analysis shows that expanded MSCs can relieve pain in the short term (6–12 months), but there still lacks sufficient evidence of functional improvement and cartilage repair.[15] Bone marrow mesenchymal stem cells transplantation for the treatment of KOA can significantly reduce the degree of pain in patients, down-regulate the release of inflammatory mediators in the knee joint fluid.[16] Adipose tissue-derived MSC can reduce knee pain and improve physical function and overall cartilage quality in OA.[17] Human umbilical cord mesenchymal stem cells (hUC-MSCs) secret extracellular vesicles and participates in OA treatment by transmitting bioactive molecules related to migration, proliferation, apoptosis, inflammatory reaction, extracellular matrix synthesis and cartilage repair.[18]

This study aimed to evaluate the clinical efficacy of MSC therapy by using the Visual Analog Scale (VAS), Lequesne index, Lysholm Knee Score Scale (LKSS), Western Ontario and McMaster University Osteoarthritis Index (WOMAC). Moreover, imaging manifestations of joint damage were assessed according to the Whole-Organ Magnetic Resonance Imaging Score (WORMS).

2 | MATERIALS AND METHODS

2.1 | Search strategy, study design, and eligibility criteria

The relevant studies published before September 2022 were searched from the foreign databases of Cochrane, Embase, Ovid Medline, Proquest, PubMed, Scopus, Web of Science, and Chinese databases including China National Knowledge Internet (CNKI) and SinoMed. The search terms included "Osteoarthritis, Knee" OR "Knee Osteoarthritides" OR "Knee Osteoarthritis" OR "Osteoarthritis of Knee" OR "Osteoarthritis of the Knee" AND "Stem Cell Transplantations" OR "Transplantations, Stem Cell" OR "Transplantation, Stem Cell" OR "Stem Cell Transplantation." Participant or population: patients with osteoarthritis of the knee. Intervention: stem cell transplantation. Comparison control: without stem cell transplantation. The study design included RCTs or cohort studies.

Eligibility criteria: (1) RCTs or cohort studies, (2) limited to human studies, (3) containing information on treatment outcomes, and (4) describing prognostic details and comparing characteristics of patients treated with and without stem cell therapy. Exclusion criteria: (1) animal or cell experiments, (2) no or insufficient reported data, (3) reviews, case reports, evaluations, editorials, and letters, and (4) duplicate experiments.

2.2 | Data selection criteria and quality assessment

Data selection and quality assessment were performed independently by two reviewers using standardized methods. Any discrepancies were adjudicated by a third party after referring to the original publication. The quality of eligible literature was evaluated using the modified Jadad scoring scale with a scoring system of 1–7 points, with 4–7 indicative of high quality and 1–3 indicative of low quality. The modified Jadad scale was scored for literature random sequence generation, allocation concealment, methods of blinding, and descriptions of participant withdrawals or dropouts.

2.3 | Definition of outcome measures

Pain level: VAS evaluates the pain level of patients with a total score of 0–10: no pain (0), mild pain (1–3), moderate pain (4–7), and severe pain (8–10). The higher the score the more severe the pain.

The Lequesne index is commonly used to assess the patient's knee function in terms of walking ability, swelling, and tenderness. The higher the score, the worse the knee function.

Knee function: the LKSS is one of the most effective questionnaires employed to evaluate the patient's recovery of knee function on the affected side, including eight items of walking gait, frequency of knee locking, frequency of pain, stair climbing, need for external support, body stability, joint swelling, and squatting ability. A total score (ranged 0–100 points) was calculated from the patient's answers. A lower score was indicative of poorer knee function.

The WOMAC assesses the pain severity, severity of joint stiffness, and difficulty performing daily functional activities, with a total of 24 items. Effectively, the WOMAC score is decreased compared with the pretreatment score, accompanied by the patient's self-reported relief of pain symptoms and improved joint function.

The knee joint was examined with a 1.5 T superconductive MRI scanner (Siemens). The thickness of the knee cartilage was measured. MRI slices were taken to assess the imaging manifestations of the joint injury according to the WORMS. The degree of signal involvement was graded from 0 to 3.

2.4 | Statistical analysis

The Stata statistical software was used for the meta-analysis. The effect size of less than 1.00 and the *p* value of less than 0.05 meant statistical significance. The heterogeneity of effect-size estimates from the individual studies was evaluated by using the Q test. The random-effect model, which was admitted to be more conservative, was chosen in the presence of significant heterogeneity. Otherwise, the fixed-effect model was used. Subgroup analyses of VAS were conducted according to different follow-up periods. After deleting any one of the papers, the pooled results of the remaining papers were not different from those without deletion, which meant that the sensitivity analysis was passed. The publication bias of included studies was assessed with funnel plots, Egger's test, and Begg's test.

3 | RESULTS

3.1 | Literature retrieval results

A relevant literature retrieval through the above-mentioned Chinese and English databases yielded 1177 publications. All the literature was imported into EndNote X9 to remove 537 duplicates, 201 reviews or briefs, and 252 pieces of literature involving animal and cell experiments. After preliminary screening, 95 were excluded due to irrelevance, and the remaining 92 were read in full text. Further, 76 were excluded based on patient, intervention, comparison, outcome study (PICOS) principles, inclusion or exclusion criteria, and data extraction criteria, finally resulting in 16 publications,[16–31] as detailed in Figure 1.

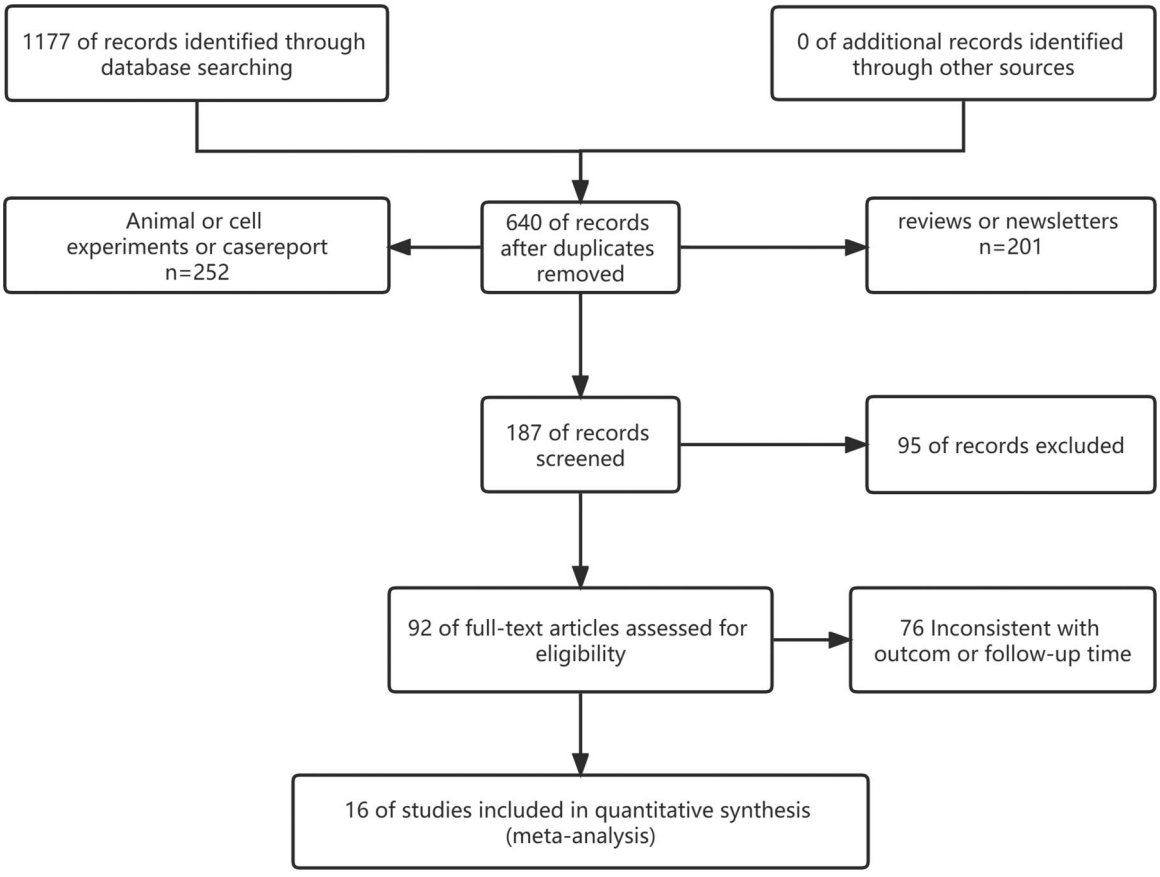

FIGURE 1 Flow diagram showing the study identification, screening, and inclusion process.

TABLE 1 Jadad scale for the eligible trials.

Study	Random sequence production	Allocation concealment	Blinding method	Withdrawal	Score
Bai et al.[16]	2	1	0	1	4
Cheng et al.[19]	2	1	0	1	4
Ha et al.[18]	2	1	0	1	4
Lyu et al.[20]	2	1	0	1	4
Tan et al.[21]	2	1	0	1	4
Tang[22]	2	1	0	1	4
Zhang et al.[17]	2	1	0	1	4
Zhao[23]	2	1	0	1	4
Chen et al.[24]	2	1	2	1	6
Kim et al.[25]	2	1	0	1	4
Kuah et al.[26]	2	2	2	1	7
Lamo-Espinosa et al.[27]	2	1	1	1	5
Lamo-Espinosa et al.[28]	2	1	0	1	4
Li et al.[29]	1	1	0	1	3
Matas et al.[30]	2	1	0	1	4
Vega et al.[31]	2	1	0	1	4

A total of 16 pieces of literature were included, most of which had clear randomization methods, allocation concealment, design of outcome indicators, and treatment of missing values, but only 4 of them mentioned the implementation of blinding methods. One piece of literature was evaluated as low-quality, and the remaining 15 were high-quality. The low-quality study was not shown the random sequence production, but in the study there was no significant difference in the general information between the two groups. The details of the Jadad scoring scale are shown in Table 1.

3.2 | Baseline patient characteristics

The characteristics of included studies were shown in Table 2, involving a total of 875 KOA patients (441 in the stem cell transplantation group and 434 in the control group). The male patients were about 336. The mean age of enrolled patients ranged from 51 to 69 years. The sample size ranged from a minimum of 4 to a maximum of 57. In the meta-analysis, there was no significant difference in demographics of the study participants beween the stem cell transplantation group and the control group.

Of all the trials, nine studies evaluated the efficacy of bone marrow-derived mesenchymal stromal cell (BMSC) transplantation in patients with KOA, two studies evaluated the efficacy of umbilical cords MSC (UcMSC) transplantation in patients with KOA, and five studies evaluated the efficacy of adipose-derived stem cell (ADSC) transplantation in patients with KOA. The number of stem cells injected was 5×10^6 to 400×10^6, except that five studies did not specify the number of cells injected, but the average injection volume of stem cells was 10^6 or more. The injection route was intra-articular injection. The sources of stem cell were autologous and allogeneic.

3.3 | VAS

Ten pieces of literature (28 studies) were tested for heterogeneity with $I^2 = 51\% > 50\%$ and $p < 0.1$ for the Q-test, suggesting the existence of heterogeneity between the literature selected. Then, sensitivity analysis was performed, and four distinct groupings were seen (Figure 2A), that is, different sensitivity profiles based on different follow-up times. Therefore, it was highly suspected that different follow-up times caused heterogeneity. Next, meta-regression was continued to examine whether different follow-up times had a significant effect on the effect size. Due to the high suspicion of heterogeneity caused by different follow-up times, a meta-regression was conducted with the effect size as the dependent variable and the follow-up time as the independent variable ($p = 0.002 < 0.05$). Based on this finding, subgroup analysis was performed.

The 10 pieces of literature (28 studies) were divided into four groups according to the follow-up time, the above subgroup analysis results revealed the heterogeneity among the four groups, implying that the follow-up time affected the results of the meta-analysis. Among them, the group with 12 h of follow-up had the least heterogeneity and the largest effect size of −0.94 for the pooled nine results ($z = 8.53$, $p < 0.05$), implying that stem cell transplantation

TABLE 2 Clinical information from the eligible trials in the meta-analysis.

Study	No. of patients (male)		Age ($\bar{x} \pm s$, years)		BMI ($\bar{x} \pm s$, kg/m^2)		Disease course ($\bar{x} \pm s$, years)		Control arm	Stem cell arm (Regimens dose)	Stem cell source	Outcomes
	S	C	S	C	S	C	S	C				
Bai et al.[20]	57 (22)	57 (20)	65.3 ± 5.7	64.2 ± 6.8	–	–	1.5 ± 0.7	1.3 ± 0.7	AO	AO + BMSCs(UK)	Autologous bone marrow (50 mL)	LKSS score
Cheng et al.[19]	20 (8)	20 (9)	54.6 ± 6.2	52.9 ± 5.3	22.1 ± 1.6	21.5 ± 1.5	–	–	HA	PRP + BMSCs(UK)	Autologous bone marrow (100 mL)	VAS, WOMAC
Ha et al.[18]	45 (15)	44 (14)	56.8 ± 6.1	55.6 ± 3.6	25.5 ± 2	25.4 ± 2.8	26.5 ± 3.4	25.6 ± 2.6	PRP	PRP + UcMSCs(5×10^6)	Cord blood	VAS
Lyu et al.[20]	40 (14)	40 (13)	55.9 ± 8.1	55.1 ± 6.8	–	–	6.9 ± 3.4	7.1 ± 3.5	HA	BMSCs($(38.2 \pm 12.3) \times 10^6$)	Autologous bone marrow (50 mL)	WOMAC
Tan et al.[21]	36 (10)	36 (9)	53.4 ± 6.9	53.8 ± 5.7	–	–	5.5 ± 2.1	5.5 ± 2	AO	AO+BMSCs ($(20.0 \sim 30.0) \times 10^6$)	Autologous bone marrow (60 mL)	Lequesne index
Tang[22]	10 (3)	10 (5)	62 ± 8.3	59.7 ± 7.1	26 ± 2.9	26.4 ± 2.1	–	–	AO+Microfracture +HA	AO+Microfracture + HA + ADSCs(50×10^6)	Autologous adipose tissue samples (30 mL)	WOMAC
Zhang et al.[17]	36 (6)	36 (8)	53.4 ± 12.7	56.9 ± 14.5	23.8 ± 3.8	24.4 ± 2.8	–	–	HA	HA + ADSCs(UK)	Autologous adipose tissue samples (40 mL)	VAS、WOMAC
Zhao[23]	43 (25)	43 (26)	51.3 ± 4.5	51.8 ± 4.3	–	–	–	–	AO	AO + BMSCs(UK)	Autologous bone marrow	Lequesne index
Chen et al.[24]	17 (2)	8 (3)	68.6 ± 6.5	70.5 ± 8.4	26.7 ± 4.2	25.5 ± 3.5	3.7 ± 7.2	2.4 ± 2.4	HA	ADSCs(32×10^6)	Allogeneicadi-pose-derived stem cells	VAS、WO-MAC、WORMS
Kim et al.[25]	30 (11)	30 (11)	63 ± 3.2	63.2 ± 3.8	26.4 ± 1.5	26.6 ± 1.5	–	–	HA	ADSCs(7.1×10^6)	Autologous adipose tissue samples (140 mL)	VAS、LKSS score
Kuah et al.[26]	8 (6)	4 (1)	50.8 ± 7.3	55 ± 10.4	27.7 ± 2.1	25.5 ± 2.8	–	–	cell culture media	ADSCs(39×10^6)	Allogeneic adipose-derived stem cells	VAS、WOMAC

(Continues)

TABLE 2 (Continued)

Study	No. of patients (male)		Age ($\bar{x} \pm s$, years)		BMI ($\bar{x} \pm s$, kg/m^2)		Disease course ($\bar{x} \pm s$, years)		Control arm	Stem cell arm (Regimens dose)	Stem cell source	Outcomes
	S	C	S	C	S	C	S	C				
Lamo-Espinosa et al.[27]	24 (17)	26 (16)	56 ± 16.3	54.6 ± 27.4	27 ± 3	25.3 ± 4.1	–	–	PRP	PRP + BMSCs (400×10^6)	Autologous bone marrow (100 mL)	VAS、WOMAC、WORMS
Lamo-Espinosa et al.[28]	10 (4)	10 (7)	65.9 ± 8.2	60.3 ± 4.4	27.1 ± 5	29.6 ± 3.4	9 ± 5.9	6 ± 4.4	HA	HA + BMSCs(10×10^6)	Autologous bone marrow (100 mL)	VAS、WOMAC、WORMS
Li et al.[29]	40 (12)	46 (20)	67.3 ± 5.4	66.5 ± 6.3	25.3 ± 2.9	25.8 ± 3	7.2 ± 2.9	7.1 ± 3	AO + HA	AO + BMSCs(UK)	Autologous bone marrow (50 mL)	LKSS score
Matas et al.[30]	10 (4)	9 (4)	56.1 ± 6.8	54.8 ± 4.5	27.6 ± 2.6	27.9 ± 3.4	–	–	HA	UcMSCs(20×10^6)	Cord blood	VAS、WOMAC、WORMS
Vega et al.[31]	15 (6)	15 (5)	56.6 ± 9.2	57.3 ± 9.1	–	–	–	–	HA	BMSCs(40×10^6)	Allogeneic bone marrow	VAS、Lequesne index

Abbreviations: ADSC, adipose-derived stem cell; AO, arthroscopic operation; BMSC, bone marrow mesenchymal stem cells; C, control group; HA, hyaluronic acid; LKSS, Lysholm Knee Score Scale; PRP, platelet-rich plasma; S, stem cell group; UcMSC, umbilical cord mesenchymal stem cell; UK, unknow; VAS, Visual Analog Scale; WOMAC, Whole-Organ Magnetic Resonance Imaging Score.

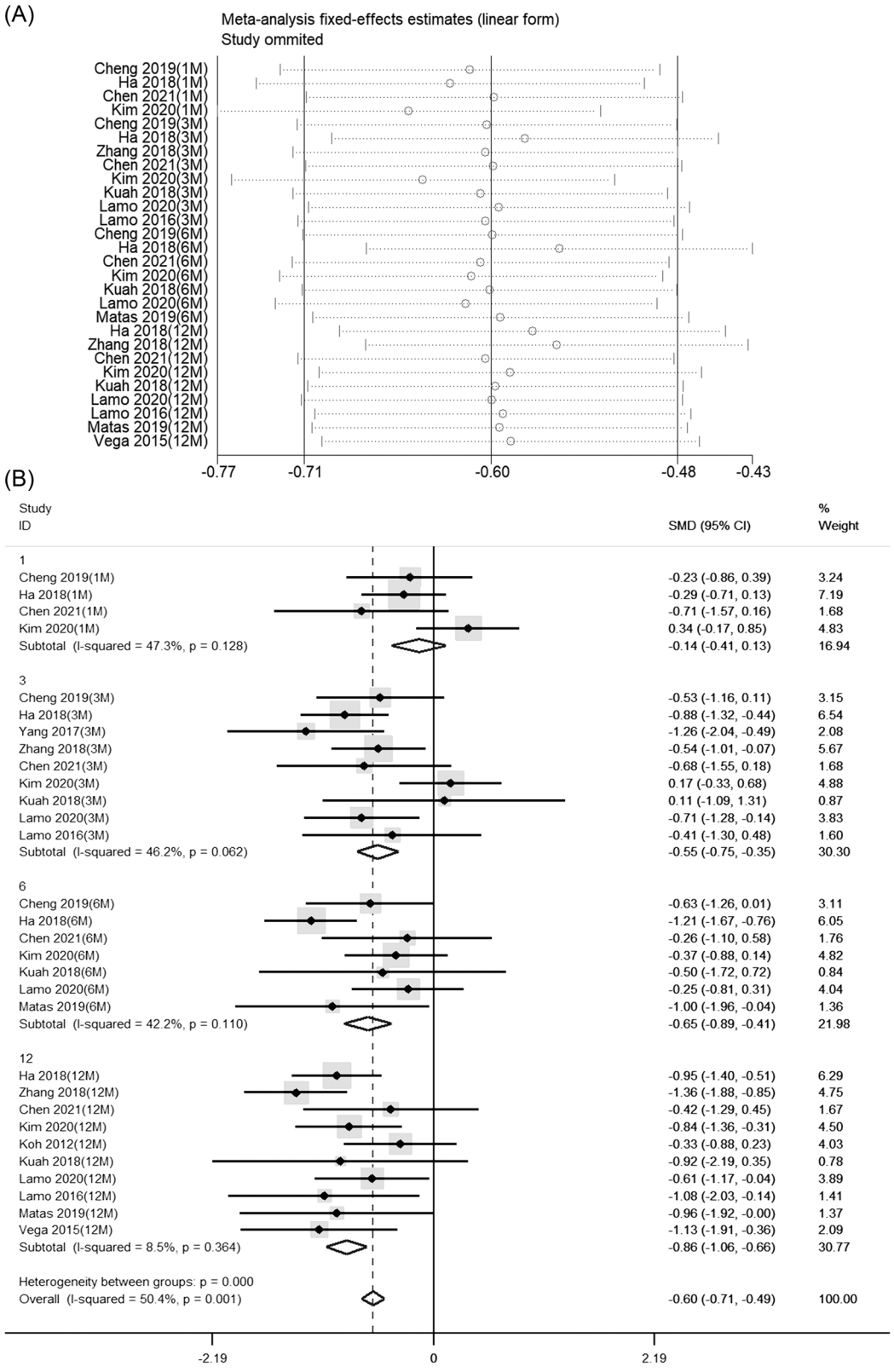

FIGURE 2 Meta analysis of VAS. (A) The sensitivity analysis of VAS. (B) Subgroup analysis in VAS between patients undergoing MSC therapy and controls at: (1) months, (2) 3 months, (3) 6 months, and (4) 12 months. Random effects models were used. MSC, mesenchymal stem cell; VAS, Visual Analog Scale.

significantly reduced KOA pain, followed by the groups with 6 months, 3 months, and 1 month of follow-up in descending order. The effect size for the groups with 6 and 3 months of follow-up was −0.65 and −0.50, respectively ($z = 5.34$ and $z = 4.63$, both $p < 0.05$), implying an improvement in KOA pain with stem cell transplantation. The effect size for the group with 1 month of follow-up was −0.14 ($z = 1.02$, $p = 0.31$). It was suggested that the longer the follow-up period, the more likely the effect would be exaggerated. All the above analyses demonstrated that stem cell transplantation significantly reduced KOA pain (Figure 2B).

The VAS results indicate that knee joint pain decreases with increasing recovery time after treatment. The subgroup analysis reveals that ADSCs showcase the greatest reduction in pain sensation at postoperative 1 month and postoperative 12 months.[17,24] Furthermore, cord-blood-derived stem cells lead to the greatest reduction in pain sensation at postoperative 3 months and postoperative 6 months.[18] Autologous adipose tissue is better at relieving pain than allogeneic adipose tissue of ADSCs.[17,24–26] Stem cells derived from autologous bone marrow cells were no better at relieving pain than stem cells derived from allogeneic bone marrow,[28,31] and combination therapy (HA and/or PRP) in the analyses has no effect.[19,27]

3.4 | Lequesne index

The Lequesne index results only include three studies that investigate stem cells sourced from bone marrow, with two using autologous bone marrow and one using allogeneic bone marrow. There was no heterogeneity in the results between autologous and allogeneic cells, even control group of HA to treat.[31] These results do not allow for a determination of the optimal choice. Three pieces of literature were tested for heterogeneity with $I^2 = 57.9\% > 50\%$ and $p = 0.09 < 0.1$ for the Q-test, suggesting the heterogeneity among the literature selected. These pieces of literature were subjected to sensitivity analysis, as shown in Figure 3A. From Figure 3B, the literature of Tang 2013 demonstrates a different sensitivity profile, suggesting that the literature of Tang 2013 may exaggerate the effect size. Due to the small number of included literature, subgroup analysis was not conducted and random effects were selected for meta-analysis (Figure 3A). The results showed that the Lequesne index was 5.69 in the experimental group, which was significantly lower than that in the control group ($t = -10.61$, $p = 0.01 < 0.05$), indicating that the experimental group had better knee functions than the control group.

3.5 | LKSS score

Three pieces of literature (six studies) were tested for heterogeneity, with $I^2 = 67.9\% > 50\%$ and $p = 0.01 < 0.05$ for the Q-test, suggesting the heterogeneity among the literature selected. Sensitivity analysis was performed on the three pieces of literature, and the results indicated the existence of the accuracy and stability (Figure 4A), so random effects were selected for the meta-analysis. The results of the meta-analysis given by random effects showed that the LKSS score in the experimental group was 4.13, significantly higher than that in the control group ($t = 3.03$, $p = 0.03 < 0.05$), indicating that the knee function recovery in the experimental group was better than that in the control group, as shown in Figure 4B.

The LKSS score results only include studies that investigate stem cells sourced from bone marrow and adipose tissue. Specifically, Bai et al.'s 16 study, which uses bone marrow-derived stem cells, showcases the best knee joint recovery, with an ES (95% confidence interval [CI]) of 8.55 (3.84, 13.26). All of the cells are autologous, and control group of HA to treat has no effect.[25,29]

3.6 | WOMAC score

Regarding the included literature on WOMAC score, the $I^2 < 50\%$ for the heterogeneity test and the p value > 0.05 for the Q-test suggested that there was no heterogeneity among the literature selected for this study. Hence, fixed effects were selected for meta-analysis. To ensure the accuracy and stability of the study, sensitivity analysis was performed. As shown in Figure 5A–D, none of the literature caused much interference with the results of this meta-analysis, implying the good stability of this study.

The pooled MD value of the total WOMAC score was −5.86 with a 95% CI of −7.68 to −4.03 ($t = -5.05$, $p < 0.05$), suggesting a reduction in the total WOMAC score in the stem cell treatment group compared with the control group, as well as relief of pain symptoms and improvement in joint function after treatment. Details are shown in Forest Figure 6A.

The MD of the WOMAC functional summary was −2.84 with a 95% CI of −4.58 to −1.10 (t = −2.18, $p = 0.04 < 0.05$), suggesting that the WOMAC functional score was decreased in the stem cell treatment group compared with the control group and that the patient's joint function was improved after treatment. Details are shown in Forest Figure 6B.

The MD value of WOMAC stiffness summary was −0.42 with a 95% CI of −0.71 to −0.12 (t = −2.77, $p = 0.01 < 0.05$), suggesting a reduction in the WOMAC stiffness score in the stem cell treatment group compared with the control group after treatment and an improvement in joint stiffness in patients. Details are shown in Forest Figure 6C.

The MD of WOMAC pain summary was −1.32 with a 95% CI of −1.83 to −0.80 (t = −3.98, $p = 0.001 < 0.05$), suggesting a reduction in the WOMAC pain score in the stem cell treatment group compared with the control group and relief of self-reported pain symptoms in patients after treatment. Details are shown in Forest Figure 6D.

In the WOMAC score results, except for the WOMAC pain score, ADSCs demonstrate the most effective recovery of knee joint function. However, the WOMAC pain score shows that cord-derived stem cells have the best restorative efficacy. In the WOMAC score results , autologous ADSCs demonstrate the most effective recovery of knee joint function.[17]

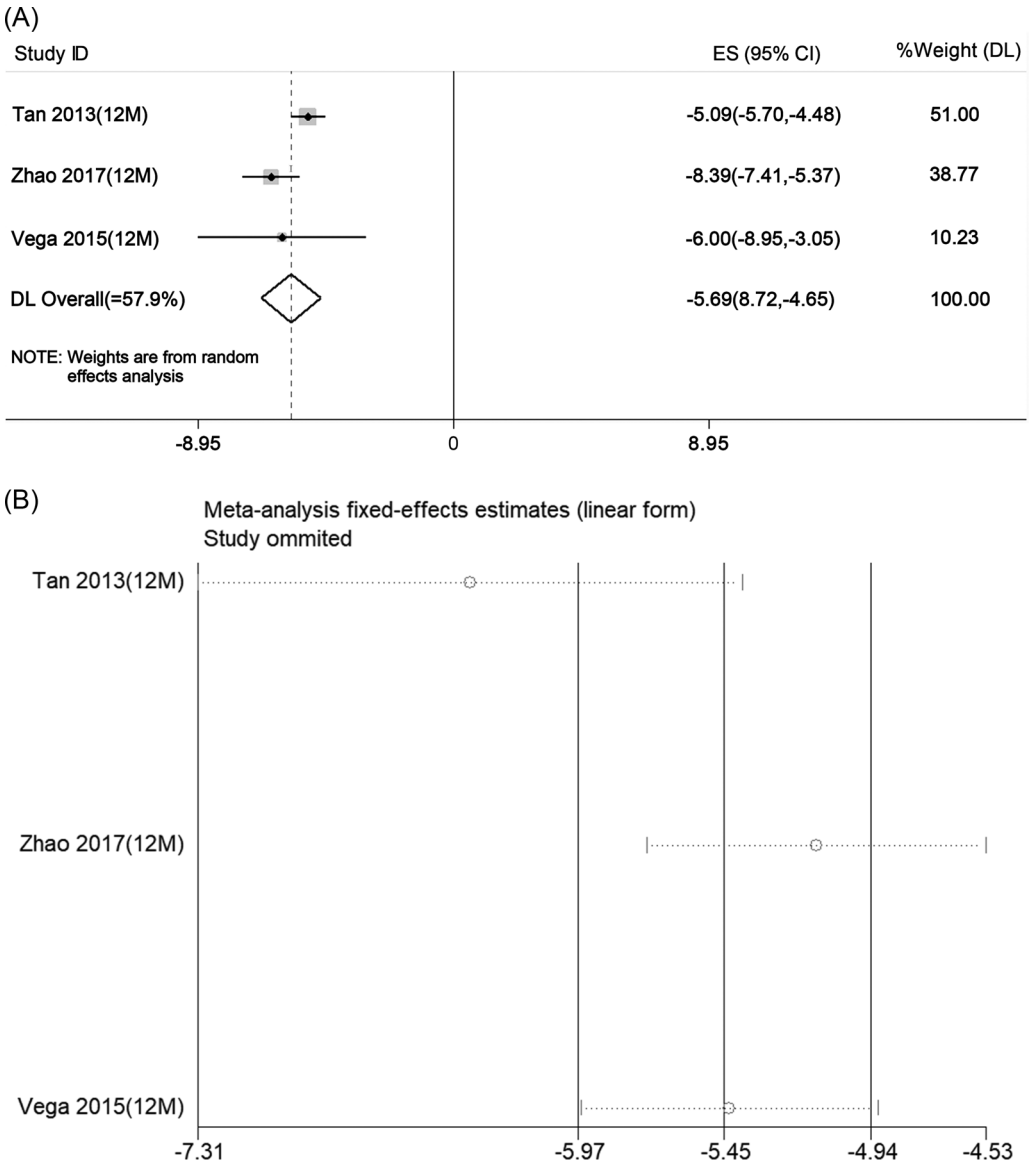

FIGURE 3 Meta analysis of Lequesne index. (A) Random effects models of Forest plot. (B) The sensitivity analysis of Lequesne index.

3.7 | WORMS

Four pieces of literature (seven studies) were tested for heterogeneity, with $I^2 = 0\% < 50\%$ and $p = 0.90 > 0.1$ for the Q-test, suggesting that there was no heterogeneity between the literature selected for this study, so fixed effects were selected for meta-analysis. To ensure the accuracy and stability of the study, sensitivity analysis was performed. As shown in Figure 7A, none of the literature caused much interference with the results of this meta-analysis, implying that this study had good stability.

The pooled MD value of the four literatures (seven studies) was 1.96 with a 95% CI of −2.99 to 6.92 ($t = 0.78$, $p = 0.47 > 0.05$), suggesting that the difference in the imaging performance of joint injury assessed by the WORMS between the stem cell transplantation group and the control group was not statistically significant. Details are shown in Forest Figure 7B.

3.8 | Publication bias

The funnel plot of our study was basically symmetrical. Egger's test and Begg's test yielded p values mostly greater than 0.05, and only Begg's test for WORMS indicated publication bias with $p = 0.018 < 0.05$ (Figure 8, Table 3). It was judged that none of the included literature in this study, except WORMS, had publication bias.

4 | DISCUSSION

KOA is the most prevalent chronic joint disease, exceeding the sum of other arthritis such as rheumatoid arthritis and ankylosing spondylitis. Extensive cartilage destruction and abnormal subchondral bone metabolism are primary events in the pathogenesis of osteoarthritis, resulting in clinical manifestations of joint pain,

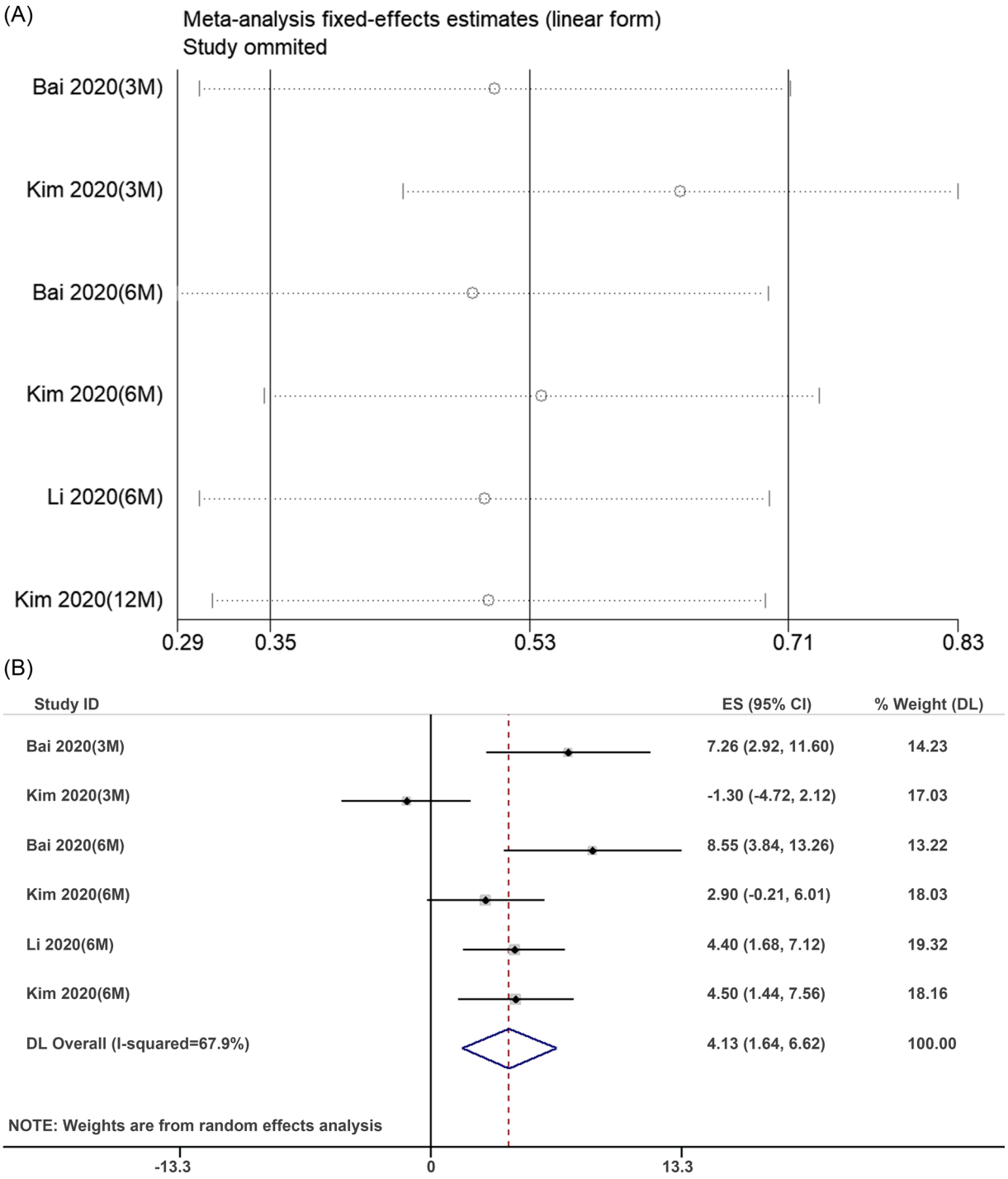

FIGURE 4 Meta analysis of LKSS score. (A) The sensitivity analysis of LKSS score. (B) Random effects models of Forest plot for LKSS score. LKSS, Lysholm Knee Scoring Scale.

limitation of movement, and joint deformity.[32,33] Moreover, this progressive condition leads to a workforce decline in young adults, accounting for a high amount of direct and indirect socioeconomic costs worldwide.[34]

This study comprehensively analyzed the VAS, WOMAC, Lequesne, and LKSS scores of various cell-based therapies for KOA, and used the WORMS to assess the joint injury. The results indicated that the VAS score of patients receiving stem cell transplantation was significantly reduced from 3 months onwards ($p < 0.05$). Patients receiving MSC treatment also showed a significant decrease in WOMAC and Lequesne scores ($p < 0.05$) and an increase in LKSS scores ($p < 0.05$). However, there was no statistically significant difference between the stem cell transplantation group and the control group in the WORMS assessment of joint injury ($p > 0.05$). Different types of stem cells have their advantages and disadvantages in the treatment of KOA. Some comprehensive analyses based

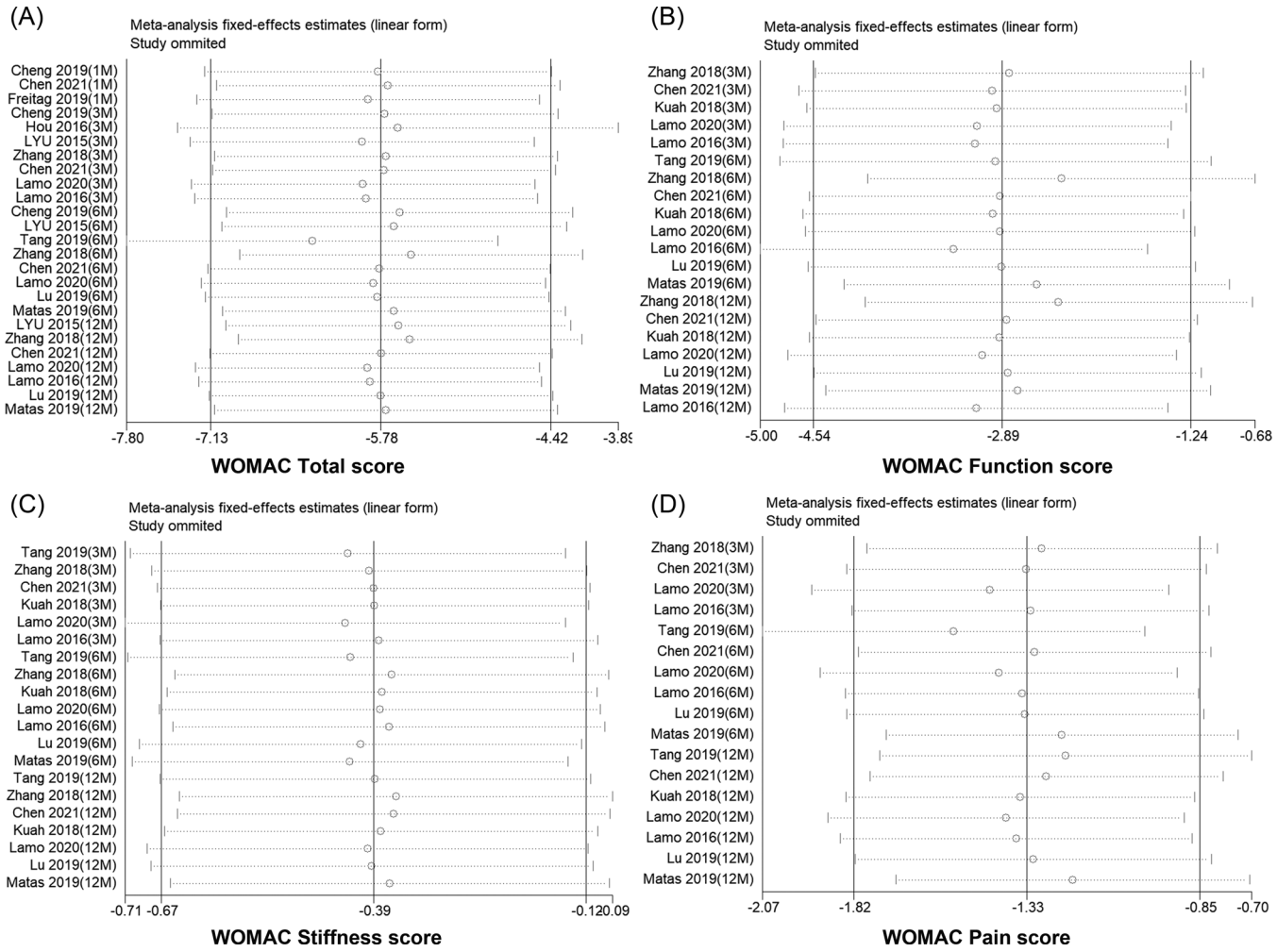

FIGURE 5 The sensitivity analysis of WOMAC score. (A-D) The sensitivity analysis of the WOMAC total score, WOMAC function score, WOMAC stifness score and WOMAC pain score. WOMAC, Whole-Organ Magnetic Resonance Imaging Score.

on RCTs and non-RCTs consider MSCs ideal treatment methods, because they can provide pain relief and functional improvement over a relatively long follow-up period (<28 months).[35] The comparison before and after treatment also shows that injection of BMSCs improves function and relieves pain, but fails to improve the range of motion.[36] However, there is a lack of standards for cell applications, especially regarding the cell type and source, cell dosage, cell quality identification, cell vehicle, and effect evaluation criteria. The establishment of cell application standards is the basis for further RCT design.[37] Therefore, this study was designed to analyze the effect and safety of cell therapy for OA, thereby providing guidance for further RCT design and even conferring a reference for cell therapy standards in the treatment of OA.

MSC transplantation possesses distinct advantages in the treatment of OA such as wide tissue source, culture expansion, multilineage differentiation capacity, tissue specificity of differentiated cells, anti-inflammatory and recruitment effects, low risk of tumorigenesis, and low immunogenicity. Nevertheless, the number of relevant RCTs is currently limited and further clinical studies are needed to confirm their efficacy.[38,39] MSCs can be isolated from various tissues including bone marrow and adipose tissues, with the ability to differentiate into osteoblasts, chondrocytes, and adipocytes.[40] It is still unclear whether BMSC transplantation carries specific mutations and causes carcinogenesis. In a previous study with a follow-up of 6–32 months, no complications such as infection, immune rejection, or carcinogenesis occurred in both the experimental group and control group,[20] indicating the safety of autologous BMSC transplantation. However, the patients showed significant painful swelling 30 min after transplantation and the VAS score was higher than that of the control group, and 18 patients (45%) required symptomatic medication (clonoxicam, celecoxib, etc.).[20] It may be due to the presence of a large number of cytokines. Neither platelet lysates nor stem cells cause immune rejection, but the presence of diverse cytokines can directly stimulate the synovium and induce synovial inflammation, thus increasing exudate, local skin temperature, and pain.[41]

hUcMSCs have superiorities including low immunogenicity and strong multidirectional differentiation potential.[42,43] Related studies have demonstrated that hUcMSCs implanted in joints can form

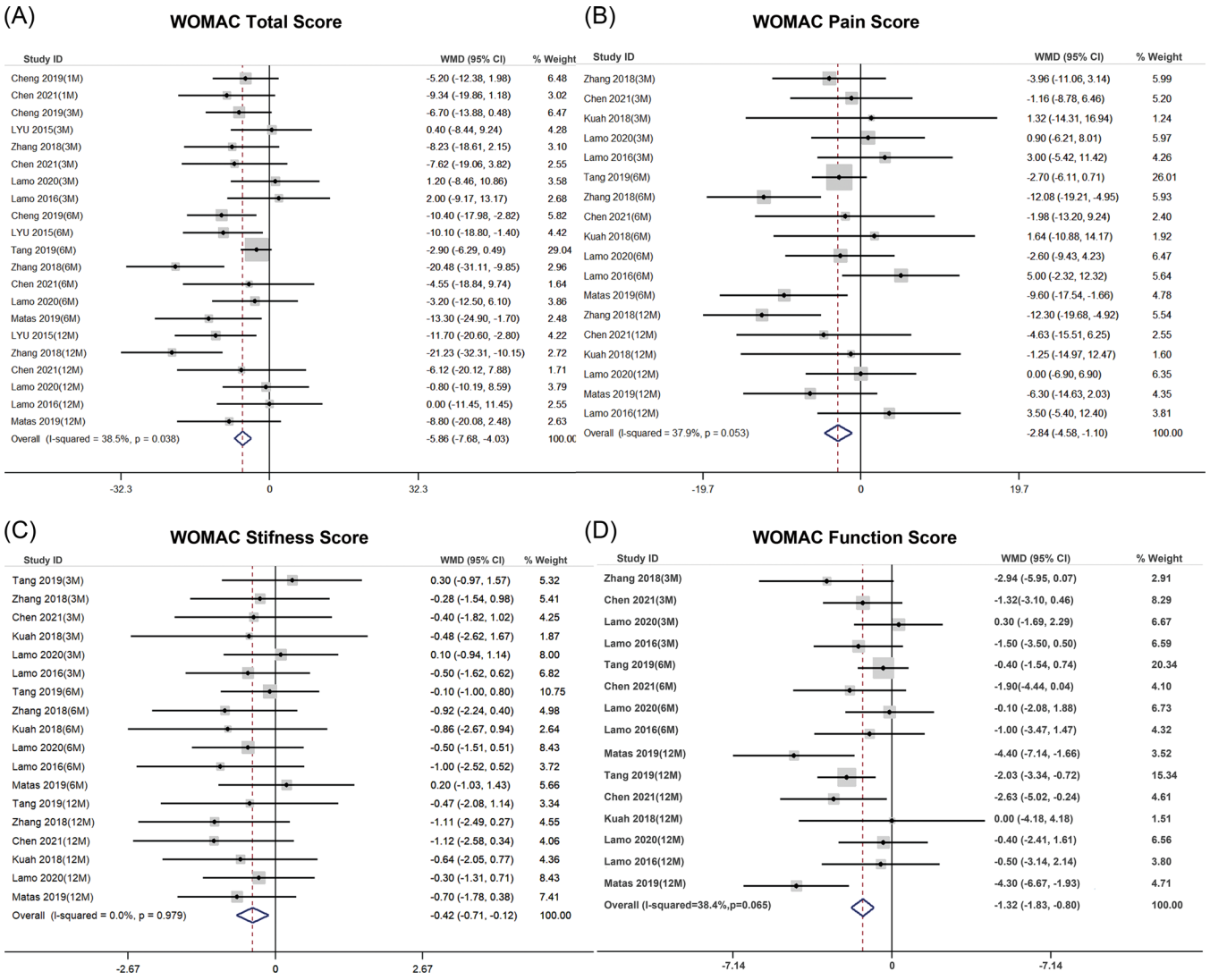

FIGURE 6 Fixed effects models of Forest plot for WOMAC score. (A-D) The forest plot for the WOMAC tatal score, WOMAC pain score, WOMAC stifness score and WOMAC function score. WOMAC, Whole-Organ Magnetic Resonance Imaging Score.

hyaline cartilage and form bone tissue under the cartilage.[42] hUcMSC transplantation for the treatment of severe OA can reduce joint pain and improve joint function more rapidly, significantly, and durably than sodium hyaluronate, and the efficacy of four injections is better than that of two injections.[44] hUcMSCs are promising candidates for OA treatment owing to their advantages of high cell yield, ethical access, noninvasive harvest procedure, favorable proliferation capacity, pluripotent differentiation property, low immunogenicity, and nontumorigenicity.[30,44,45] Since the umbilical cord is derived from the ectodermal developmental stage, hUcMSCs have certain characteristics of embryonic cells.[44] Also, hUcMSCs can maintain immune characteristics both before and after three-directional differentiation.[46] The occurrence of KOA is associated with various factors such as aging, inflammation, overload exercise, osteophytes, genetics, obesity, and environment, leading to chronic, aseptic, and progressive changes in knee joint cartilage, mainly manifested as cartilage degeneration and subchondral sclerosis.[47]

ADSCs combined with HA injections exerted analgesic effects in the short term, thus reducing KOA pain, but HA did not promote the effect of ADSCs in the long term. The decrease in WORMS score after injection was positively correlated with the decrease in cartilage damage score and the improvement in VAS and WOMAC scores, suggesting that the improvement in clinical performance may be attributed to cartilage repair.[17] However, differences in adipose tissue source, treatment course, administration method, dosage, and final MRI evaluation method may lead to huge differences in results. Therefore, follow-up MRI observation with a large sample size is needed to prove the exact effect of ADSCs on cartilage repair. In addition, MSCs can secrete a variety of factors to exert anti-inflammatory and immunomodulatory effects.[48] This study observed signs of cartilage repair in MRI evaluation, but the sample size was small. Briefly, ADSCs have the potential to repair cartilage, but a larger sample size is needed to confirm this.[17] In addition, the effects of the dosage, administration mode, and administration frequency of ADSCs on their efficacy still need further exploration.

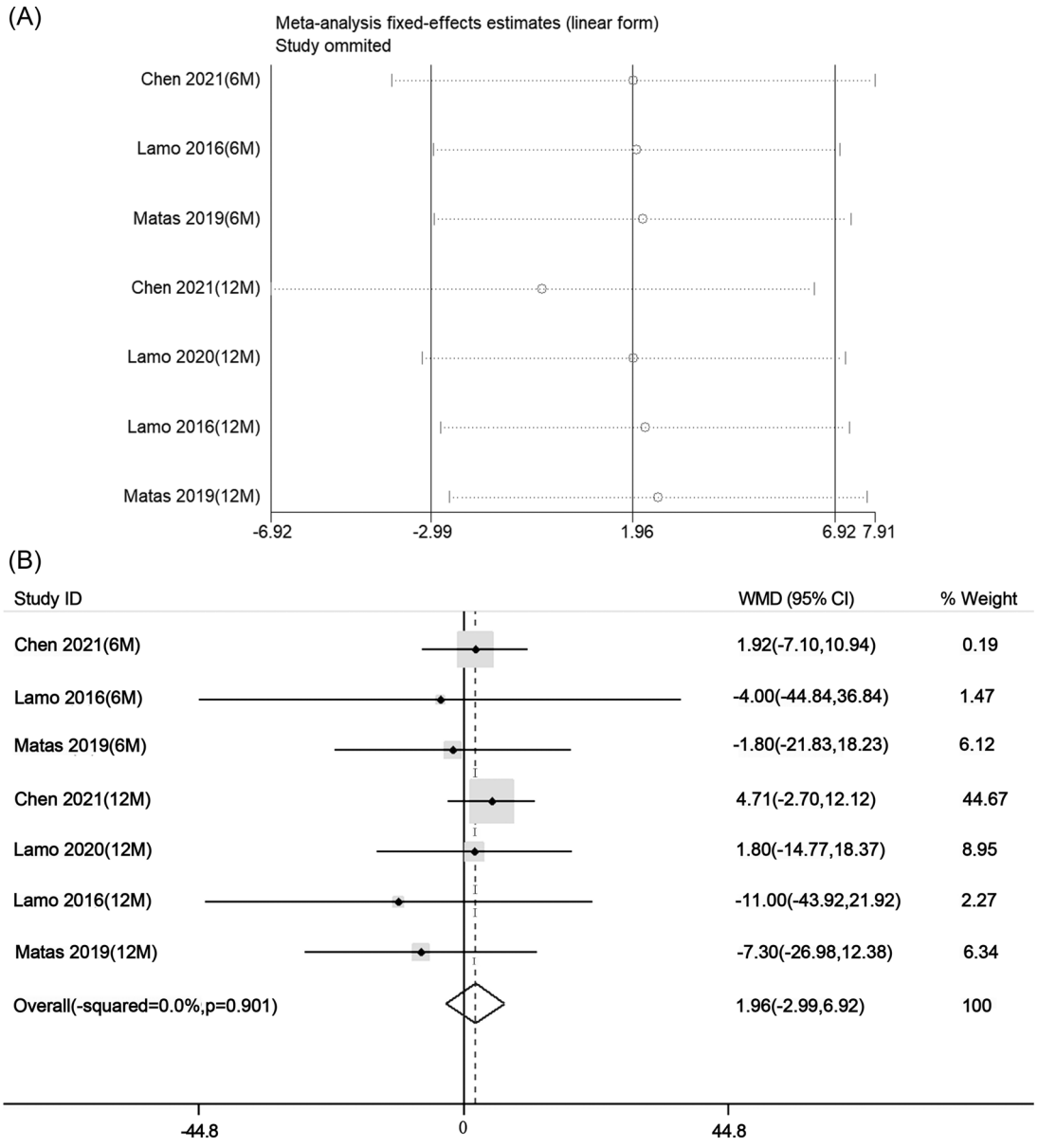

FIGURE 7 Meta analysis of WORMS. (A) The sensitivity analysis of WORMS. (B) Fixed effects models of Forest plot for WORMS. WOMAC, Whole-Organ Magnetic Resonance Imaging Score.

There are many studies on the use of PRP in treatment, and this study includes three studies related to PRP therapy.[18,19,27] Cheng[19] and Lamo-Espinosa's[27] studies differ only in the control group, with the former using conventional HA as the control and the latter using PRP as the control, while both experimental groups used a combination of PRP and bone marrow mesenchymal stem cells. The results of the WOMAC total score showed that, 3 months after surgery, the WMD (95% CI) of the former was −6.70 (−13.88, 0.48), which was better than that of the latter, which was −1.20 (−8.46, 10.86), in terms of knee joint function recovery. Six months after surgery, the WMD (95% CI) of the former was −10.40 (−17.98, −2.82), which was better than that of the latter, which was −3.20 (−12.50, 6.10), in terms of knee joint function recovery. Further analysis showed that PRP was more effective than HA in restoring knee joint function. However, there was a contradiction between the two studies in terms of VAS results, and the results of 3 and 6 months after surgery were opposite, making it impossible to determine which was more effective, PRP or HA, in relieving joint pain. The difference between Ha[18] and Lamo-Espinosa's[27] studies was the source of stem cells, with both experimental groups using stem cells in combination with PRP for treatment, and the control group using PRP alone for treatment. The VAS results showed that umbilical cord mesenchymal stem cells[18] were more effective in relieving knee joint pain than bone marrow mesenchymal stem cells.[27] Although the studies of Ha[18] and Cheng[19] have significant differences, the former study only reflects the impact of umbilical cord mesenchymal stem cells if the impact of the control group is excluded, whereas the latter study is the sum of the difference between bone marrow mesenchymal stem cells and two different interventions, PRP and HA. The VAS results showed that the

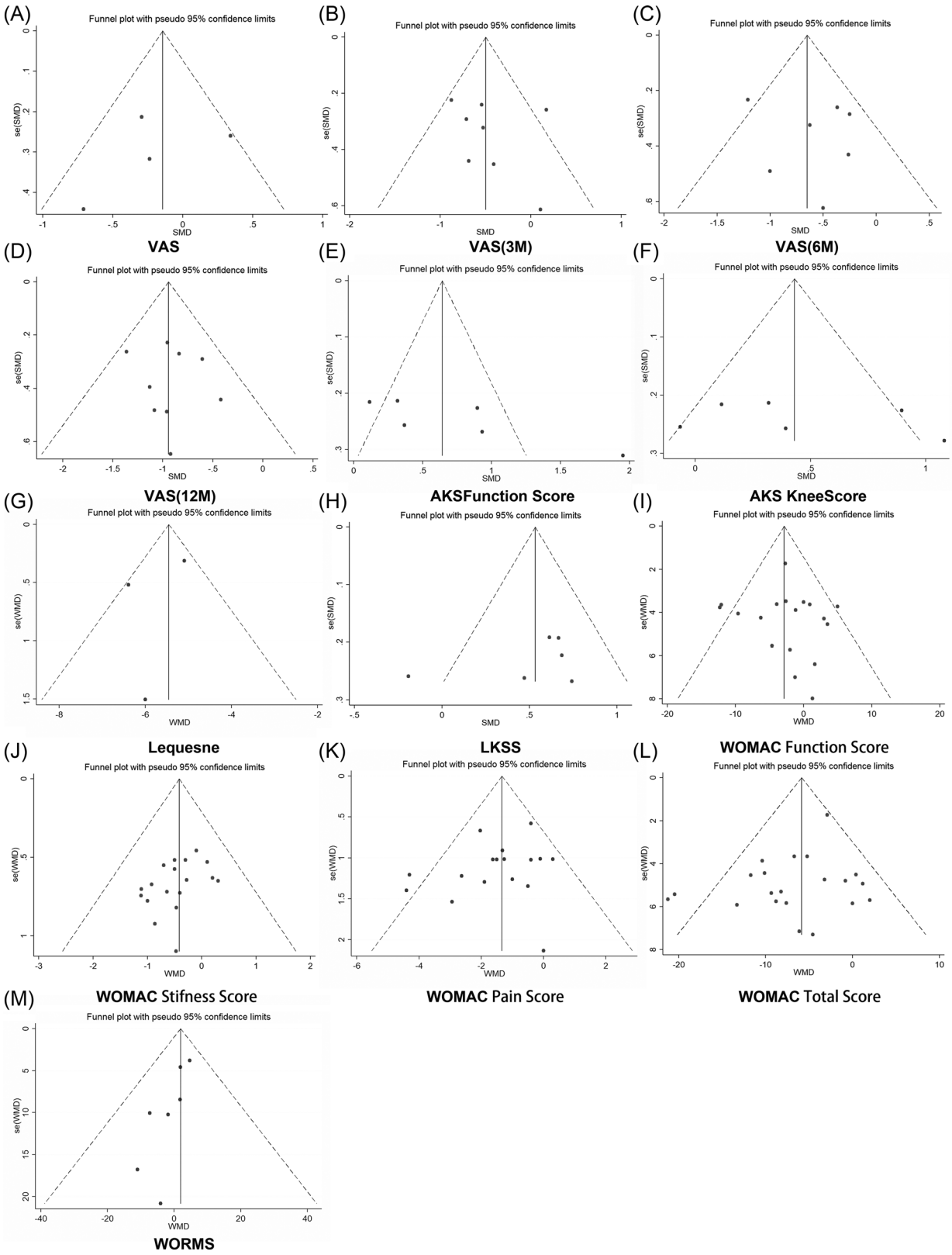

FIGURE 8 Funnel diagram. (A-D) The funnel diagram for the VAS, VAS (3M), VAS (6M) and VAS (12M). (E and F) The funnel diagram for the ASK function score and AKS Knee score. (G) The funnel diagram for the Lequesne. (H) The funnel diagram for the LKSS. (I-L) The funnel diagram for the WOMAC function score, WOMAC stifness score, WOMAC pain score and WOMAC tatal score. (M) The funnel diagram for the WORMS.

TABLE 3 Egger's and Begg's tests for publication bias.

Outcome	Group	Egger's test *p* value	Begg's test *p* value
VAS	1 month	0.734	0.641
	3 month	0.174	0.571
	6 month	1.000	0.618
	12 month	0.602	0.711
AKS	Knee score	0.452	0.535
	Functional score	0.133	0.047
Lequesne		1.000	0.618
LKSS		1.000	0.384
WOMAC	Total score	0.487	0.128
	Function	0.495	0.720
	Stiffness	0.161	0.079
	Pain	0.322	0.275
WORMS		0.133	0.018

Note: The *p* value less than 0.05 was considered statistically significant.
Abbreviations: LKSS, Lysholm Knee Score Scale; VAS, Visual Analog Scale; WOMAC, Whole-Organ Magnetic Resonance Imaging Score.

former was superior to the latter in relieving knee joint pain. Moreover, studies had shown that human umbilical cord blood mesenchymal stem cells were more effective than bone marrow concentrate in cartilage regeneration of medial unilocular KOA after high tibial osteotomy.[49]

5 | CONCLUSION

The study included 16 eligible publications with a total of 875 KOA patients, including 441 in the stem cell transplantation group and 434 in the control group. Stem cell transplantation significantly reduced VAS scores from 3 months onwards. MSC treatment also led to a significant decrease in WOMAC and Lequesne scores and an increase in LKSS scores. These results suggested the great potential of MSC therapy in the treatment of KOA. However, the WORMS assessment of joint injury showed no significant difference between the stem cell transplantation group and the control group. There was a publication bias in WORMS. Therefore, the safety and efficacy of MSC therapy require rigorous validation with a larger sample size before clinical application. From the perspectives of relieving knee joint pain, promoting knee joint function recovery, and reducing patient trauma, umbilical cord-derived stem cells should be considered as a priority option, followed by ADSCs, and finally bone marrow-derived stem cells.

AUTHOR CONTRIBUTIONS

Rong-hui Xie and Shi-guo Gong designed the study, analyzed the data and wrote the manuscript. Jiao Song, Ping-ping Wu, and Wen-Long Hu contributed to the research design, acquisition, analysis, and interpretation of the data and critically revised the manuscript. All authors were involved in data interpretation and discussion of the research progress, wrote the manuscript and approved the final version. All authors were involved in drafting the paper, and have read and approved the final submitted manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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