

Efficacy of bone marrow stem cells combined with core decompression in the treatment of osteonecrosis of the femoral head

A PRISMA-compliant meta-analysis

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Abstract

Background: This study used the meta-analytic approach to assess the safety and treatment efficacy of bone marrow stem cells (BMSCs) with core decompression (CD) for osteonecrosis of the femoral head (ONFH) based on randomized controlled trials (RCTs).

Methods: Electronic database of PubMed, Embase, Google Scholar, China National Knowledge Infrastructure (CNKI), and Wanfang database was searched up to December 26, 2019 for relevant RCTs about combined utilization of BMSCs and CD versus CD alone for ONFH. Gray literature sources were also searched. We conducted a meta-analysis following the guidelines of the Cochrane Reviewer's Handbook. Two independent reviewers performed the data extraction and assessed study quality. Our outcomes included the Harris hip scores (HHS) at 12 months, HHS at 24 months, necrotic area of femoral head, conversion to total hip arthroplasty (THA), visual analog pain scale at final follow-up, and adverse effects. The meta-analysis was performed with Stata 12.0.

Results: A total of 15 published studies with 688 patients fulfilled the requirements of inclusion criteria. Across all populations, participants in combined utilization of BMSCs group showed a statistical significance with higher HHS at 12 months (standard mean difference [SMD] 0.53, 95% confidence interval [CI] 0.29–0.77) and 24 months (SMD 0.57, 95% CI 0.36–0.77). Similarly, participants in combined utilization of BMSCs group had more advantages in reducing necrotic area of femoral head (SMD –1.05, 95% CI –1.73 to –0.38) and the rate of conversion to THA (risk ratio [RR]=0.53, 95% CI 0.38–0.74, $P=.000$). No significant differences were identified regarding postoperative adverse effects postoperatively (RR=1.03, 95% CI 0.64–1.67, $P=.893$).

Conclusion: Compared with CD treated alone in the treatment of ONFH, combined utilization of CD and autologous BMSCs implantation has a better pain relief and clinical outcomes and can delay the collapse of the femoral head more effectively.

Abbreviations: AEs = adverse effects, ARCO = Association Research Circulation Osseous, BMSCs = bone marrow stem cells, CD = core decompression, CI = confidence interval, CNKI = China National Knowledge Infrastructure, HHS = Harris hip scores, ONFH = osteonecrosis of the femoral head, PRISMA = preferred reporting items for systematic review and meta-analyses, RCTs = randomized controlled trials, RR = risk ratio, SMD = standard mean difference, THA = total hip arthroplasty, VAS = visual analog pain scale.

Keywords: bone marrow cells implantation, core decompression, meta-analysis, osteonecrosis of femoral head

Editor: Johannes Mayr.

The authors report no conflicts of interest.

S-IW and Y-bH contributed equally to this article and should be listed as co-first author.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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How to cite this article: Wang Sl, Hu Yb, Chen H, Tao B, Bu Gy, Zhang Yq, Zhang Js. Efficacy of bone marrow stem cells combined with core decompression in the treatment of osteonecrosis of the femoral head: A PRISMA-compliant meta-analysis. *Medicine* 2020;99:25(e20509).

Received: 14 January 2019 / Received in final form: 27 February 2020 / Accepted: 28 April 2020

<http://dx.doi.org/10.1097/MD.00000000000020509>

1. Introduction

Osteonecrosis of the femoral head (ONFH) is progressive and debilitating disease that characterized by the progressive necrosis of bone cells and the bone marrow.^[1,2] The incidence of newly diagnosed cases of ONFH has remained stable at approximately 20,000 to 30,000 per year.^[3] ONFH results from the rise in intraosseous pressure and blood supply decrease to the femoral head.^[4,5] The pathogenesis of ONFH is still unclear but it can be seen as a vascular and bone disease.

Effective treatment of early ONFH is still a difficult and urgent problem in the field of orthopedics. Core decompression (CD) is the most common procedure used to treat early stage of ONFH. CD could significantly reduce the pressure in the bone, opens up the hardening zone that hinders the repair of osteonecrosis. Finally, this operation could stimulate the formation of blood vessels around the decompression tunnel and delays the progression of osteonecrosis. Although CD has already been employed for >5 decades, its efficacy remains controversial.^[6,7]

The levels of the number and activity of mesenchymal stem cells in both the hematopoietic and the stromal compartments of the bone marrow have been shown to be depressed in patients with ONFH.^[8] Thus, the implantation of bone marrow containing various stem cells with the ability to differentiate into multiple cell lineages into the necrotic lesion of the femoral head was considered as a promising therapy for ONFH.^[9] CD combining with autologous BMSCs implantation is supposed to be more effective than CD alone. Some clinical trials confirmed the superiority of the combined utilization of BMSCs and CD.^[10,11] Although other studies^[12,13] could not detect a benefit from the additional implantation of autologous BMSCs.

However, there exists a little consensus as to which method is the more efficacious treatment for ONFH. It is therefore meaningful to draw a direct comparison between additional implantation of autologous BMCs for patients with ONFH. This study compares the therapeutic effects of these 2 therapies on reducing pain intensity, clinical outcomes, and safety.

2. Materials and methods

This work was done according to the preferred reporting items for systematic review and meta-analyses (PRISMA) guidelines.^[14] And this work did not involve straight contact with individuals; therefore, ethical approval is not necessary.

2.1. Search strategy

Two authors independently explored the electronic literature databases of PubMed, Embase, Google Scholar, China National Knowledge Infrastructure (CNKI), and Wanfang from the inception dates to December 26, 2019 to identify studies comparing combined utilization of BMSCs and CD versus CD alone for ONFH alone. The search keywords included “bone marrow stromal stem cells,” “stromal cells, mesenchymal,” “mesenchymal stromal cells,” “bone marrow stromal cell,” “Mesenchymal Stem Cells[Mesh],” “core decompression” and “osteonecrosis of the femoral head,” “ONFH.” Related articles and reference lists of all selected studies were reviewed to avoid original miss. Moreover, the reference reports of previous systematic reviews, meta-analysis, and randomized controlled trials (RCTs) were manually reviewed to avoid initial miss. Gray literature sources were also searched.

2.2. Inclusion and exclusion criteria

Studies were included if: patients were diagnosed with ONFH (ARCO stage 1 to 3); trials comparing combined utilization of BMSCs and CD group to CD alone group; outcomes including: HHS at 12 months, HHS at 24 months, necrotic area of femoral head, conversion to total hip arthroplasty (THA), visual analog pain scale (VAS) at final follow-up, and adverse effects (AEs).

The exclusion criteria were as follows: the study shared the same data set; the evaluation methods did not address the major outcome; the participants included in the study had co-morbidities and/or other joint diseases such as hypertension and rheumatoid arthritis.

2.3. Data extraction

Data of included trials were extracted by 2 investigators independently using a standardized form including lead author, publication year, sample size, age, diagnostic criteria, disease stages, etiological factors, intervention, outcomes, follow-up. Moreover, we collected BMSCs isolated method, number of BMSCs delivered, and collecting or administering BMSCs methods. Clinical outcomes containing HHS at 12 months, HHS at 24 months, necrotic area of femoral head, conversion to THA, VAS at final follow-up, and AEs. Differences and disagreements were resolved by consensus. If the trials had >2 groups, we only extracted the interest reported information and data.

2.4. Risk of bias and quality assessment

The quality of the included RCTs was assessed independently by the 2 reviewers. based on the Cochrane Collaboration tool for assessing risk of bias. The tool included the following items: randomization sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. All disagreements were resolved by the third reviewer.

2.5. Statistical analysis

Analysis was conducted using Stata 12.0 (Stata Corp., College Station, TX). For continuous outcome data, a standard mean difference (SMD) and 95% confidence interval (CI) were calculated by means and SDs. For dichotomous outcomes, risk ratio or relative risk (RR) and 95% CI were calculated as the summary statistics. The statistical heterogeneity was determined by the χ^2 test and I^2 . The value of $I^2 < 25\%$ indicated low statistical heterogeneity; $25\% \leq I^2 < 50\%$ indicated moderate statistical heterogeneity; $50\% \leq I^2 < 75\%$ indicated high statistical heterogeneity.^[15] $P < .05$ was considered to be statistically significant. A random-effects analysis was used to synthesize data when heterogeneity was existing; a fixed-effects analysis was used to synthesize data when heterogeneity was absent.

3. Results

3.1. Search results

By retrieving electronic database comprehensively, a total of 535 articles were identified initially. Of these, 142 articles were from PubMed, 598 articles were from Embase, 512 articles were from Google Scholar, 203 articles were from CNKI, 28 articles were

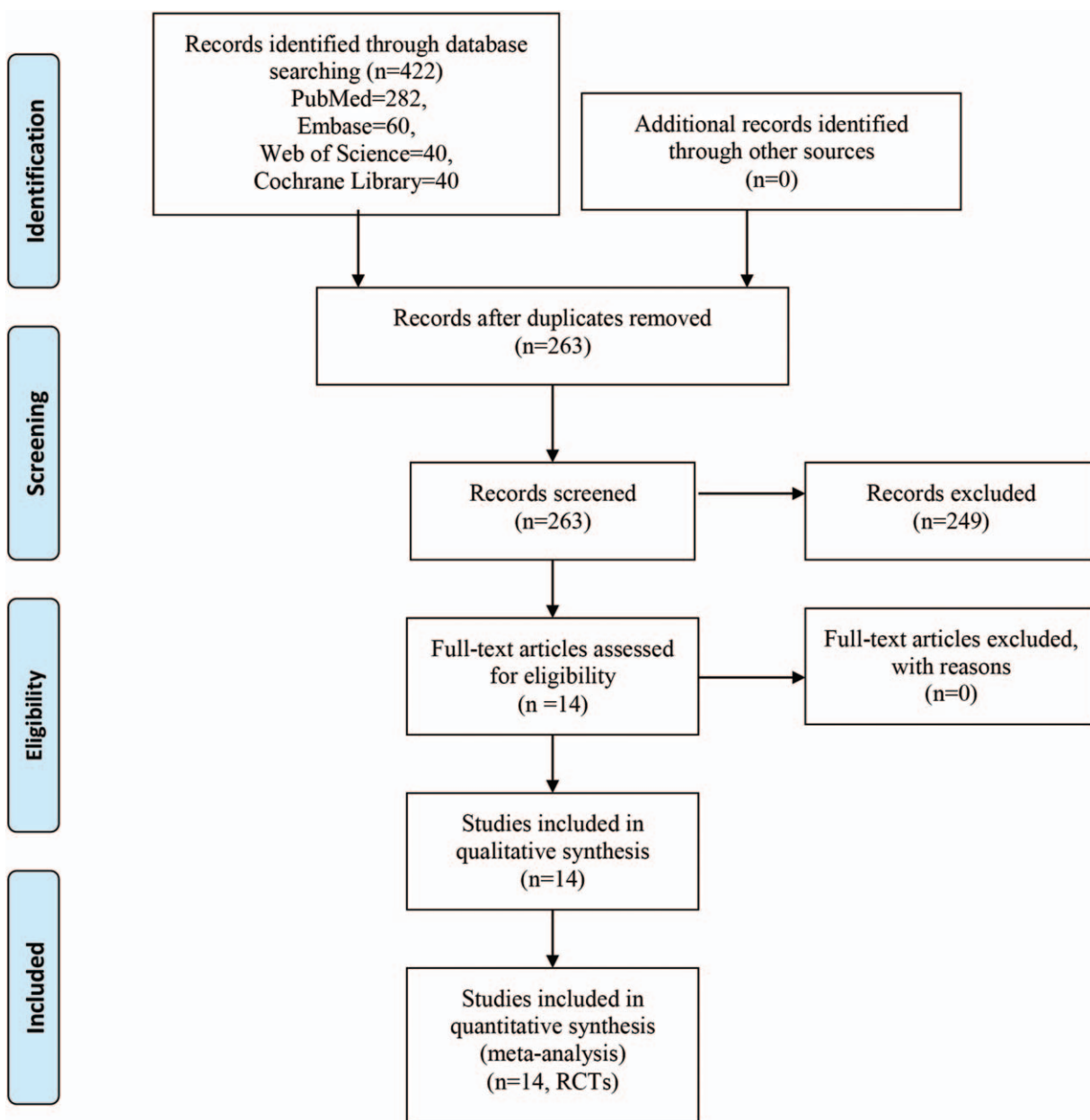


Figure 1. The search results and selection procedure. RCT = randomized controlled trial.

from the Wanfang, 123 articles were excluded for duplicates. Four hundred eleven articles were excluded by scanning the titles and the abstracts. Finally, a total of 15 articles^[10,12,13,17-27] including 688 patients were included in this meta-analysis. There were 351 patients in the combined utilization of BMSCs and CD group, and 337 patients in the CD alone group. A flowchart of articles selection is shown in Figure 1.

3.2. General characteristic of the included studies

The basic characteristics of the included articles are shown in Table 1. Included studies were published from 2004 to 2019. Sample size of the included studies ranged from 8 to 51. Mean age of the OFNH cases ranged from 26.8 to 49.7. Thirteen studies

used Association Research Circulation Osseous (ARCO) diagnostic criteria, 1 study used Steinberg diagnostic criteria, and the rest 1 study used Ficat diagnostic criteria. Follow-up duration ranged from 12 to 60 months. BMSCs isolated, number, and collecting methods can be seen in Table 2. All of the included studies placed BMSCs into gelatin sponge and pushed through the trephine to close the hole.

3.3. Risk of bias of included researches

Details about the risk of bias graph and bias summary can be obtained in Figure 2 and Figure 3 separately. Table 3 lists the reasons accounting for these biases. To assess the random sequence generation, the risk of bias was ambiguous in 8 of 15

Table 1

General characteristic of the included studies.

Study	Sample size (E/C, hips)	Age, y	Diagnostic criteria	Disease stages (hips)	Etiological factors	Intervention	Outcomes	Follow-up, mo
Gangji et al, 2011 ^[16]	13/11	42.2/45.7	ARCO	I/II	NS	E: CD + BMSCs; C: CD	3, 4, 5, 6	60
Gangji et al, 2004 ^[10]	10/8	40.9/48.8	ARCO	NS	NS	E: CD + BMSCs; C: CD	4, 5, 6	24
Hauzeur et al, 2018 ^[21]	19/19	48.0/49.7	ARCO	NS	E: S (12), A (8), Dr (2), Id (1); C: S (13), A (7), Dr (0), Id (3)	E: CD + BMSCs; C: CD	4, 5, 6	24
Papke et al, 2016 ^[13]	11/14	44.3/44.5	ARCO	II	NS	E: CD + BMSCs; C: CD	1, 2, 5	24
Sen et al, 2012 ^[17]	26/25	NS	ARCO	I/II	Tr (17), S (20), A (8) I (2), P (2), Cs (2)	E: CD + BMSCs; C: CD	1, 2	24
Tabatabaee et al, 2015 ^[18]	14/14	37.0/26.8	ARCO	E: I (3), II (9), III (2); C: I (2), II (7), III (5)	E: S (10), I (4); C: S (9), I (5)	E: CD + BMSCs; C: CD	4, 5, 6	24
Zhao et al, 2012 ^[9]	53/51	32.7/33.8	ARCO	E: IC (3), IIA (15), IIB (24); IIC (11) C: IC (2), IIA (15), IIB (22); IIC (12)	E: Tr (8), S (11), A (11), Cd (6), I (17); C: Tr (12), S (13), A (8), Cd (5), I (13)	E: CD + BMSCs; C: CD	1, 2, 3, 4	60
Chang et al, 2010 ^[25]	8/8	NS	ARCO	E: IIA (2), IIB (2); IIC (3), IIIA (1); C: IIA (4), IIB (2); IIC (1), IIIA (1)	S (2), A (3), U (3)	E: CD + BMSCs; C: CD	4, 6	12
Sun et al, 2008 ^[26]	17/15	NS	ARCO	I (8), II (24)	Tr (7), S (9), A (10), U (2)	E: CD + BMSCs; C: CD	2, 3, 5	18
Yang et al, 2015 ^[23]	44/38	35.3/37.6	ARCO	E: I (16), II (28); C: I (16), II (22)	Tr (6), S (36), A (38), U (2)	E: CD + BMSCs; C: CD	1, 4, 6	18
Zhao et al, 2016 ^[24]	18/18	NS	Steinberg	NS	NS	E: CD + BMSCs; C: CD	1, 2, 3, 5, 6	24
Guo et al, 2008 ^[22]	12/12	NS	ARCO	III (24)	S (7), A (4), Tr (3), U (6)	E: CD + BMSCs; C: CD	3, 4, 6	12
Ma et al, 2014 ^[21]	25/24	35.6/34.8	Ficat	E: I (3), II (17), III (5); C: I (4), II (15), III (5)	E: S (15), A (4), I (6); C: S (15), A (3), I (6)	E: CD + BMSCs; C: CD	1, 2, 4, 5	24
Rastogi et al, 2013 ^[20]	30/30	33.0/34.7	ARCO	E: IB (2), IC (5), IIA (0), IIB (3), IIC (8), IIIA (0), IIIC (7); C: IB (2), IC (5), IIA (0), IIB (5), IIC (8), IIIA (0), IIIB (5), IIIC (7)	NS	E: CD + BMSCs; C: CD	4, 6	24
Liu, 2019 ^[27]	51/50	44.9/41.6	ARCO	NS	NS	E: CD + BMSCs; C: CD	1, 2, 3, 4, 5, 6	24

1 = HHS at 12 months, 2 = HHS at 24 months, 3 = necrotic area of femoral head, 4 = conversion to THA, 5 = visual analog pain scale at final follow-up, 6 = adverse effects, A = alcohol abuse, Cd = catinon disease, Cs = Cushing, I = idiopathic, P = pregnancy, S = steroids, Sm = smoking, Tr = trauma, U = unknown aetiology

Table 2
Detailed information about the BMSCs administration and CD performed.

Author	MSC isolated	No. of MSC delivered	Collecting or administering MSCs	CD
Gangji et al, 2011 ^[16]	NS	22.4×10^7	NS	3 mm Trephine through the femoral neck into the necrotic region in the femoral head, 2–3mm away from the cartilage
Gangji et al, 2004 ^[10]	Concentrated	92×10^7	Spectra cell separator	3 mm Trephine, till 2 or 3 mm from joint cartilage
Hauzeur et al, 2018 ^[12]	Concentrated	19.45×10^6	sorted on a Spectra cell separator	Hungerford technique
Pepke et al, 2016 ^[13]	Sepax centrifugation device	118×10^6	bone marrow biopsy device	Steinberg technique (1984) using a 9.5-mm trephine; the proximal deep part of tunnel was filled with the distal part of the core
Sen et al, 2012 ^[17]	Ficoll interface separator	5×10^8	Ficoll interface separator	A 10-mm diameter trephine was placed into the mid-line of the trochanter and driven toward the necrotic site
Tabatabaee et al, 2015 ^[18]	Centrifuged	2×10^6	NS	8 mm Michele trephine, to remove 2 cores of bone; the first was put aside to be used as a graft
Zhao et al, 2012 ^[19]	Centrifuged	2×10^6	Stryker's Navigation System	Decompression and grafting procedure; the patients wore capacitive coupling units
Chang et al, 2010 ^[25]	Centrifuged	2.9×10^6	NS	Drilling of the femoral head after intraosseous venography
Sun et al, 2008 ^[26]	Centrifuged	5×10^8	NS	10 mm Channel; cancellous bone grafts were harvested from the anterior iliac crest and cancellous bone chips were packed into the defect
Yang et al, 2015 ^[23]	Sepax centrifugation device	2.9×10^6	NS	Curettage, autologous bone grafting (autograft) from the greater trochanter and proximal femur using a 8-mm hollow—core drill
Zhao et al, 2016 ^[24]	Centrifuged	5×10^8	Ficoll interface separator	A decompression tunnel was made using a trephine through the trochanter and femoral neck into the necrotic region in the femoral head, 2–3mm away from the cartilage
Guo et al, 2008 ^[22]	NS	5×10^8	NS	3 mm Trephine through the femoral neck into the necrotic region in the femoral head, 2–3mm away from the cartilage
Ma et al, 2014 ^[21]	Centrifuged	2×10^6	NS	10 mm Channel; cancellous bone grafts were harvested from the anterior iliac crest and cancellous bone chips were packed into the defect
Rastogi et al, 2012 ^[20]	Ficoll density separation method	2.9×10^6	NS	3 mm Trephine, till 2 or 3 mm from joint cartilage
Liu, 2019 ^[27]	Concentrated	118×10^6	NS	NS

BMSCs = bone marrow stem cells, CD = core decompression, MSC = mesenchymal stem cells, NS = not stated.

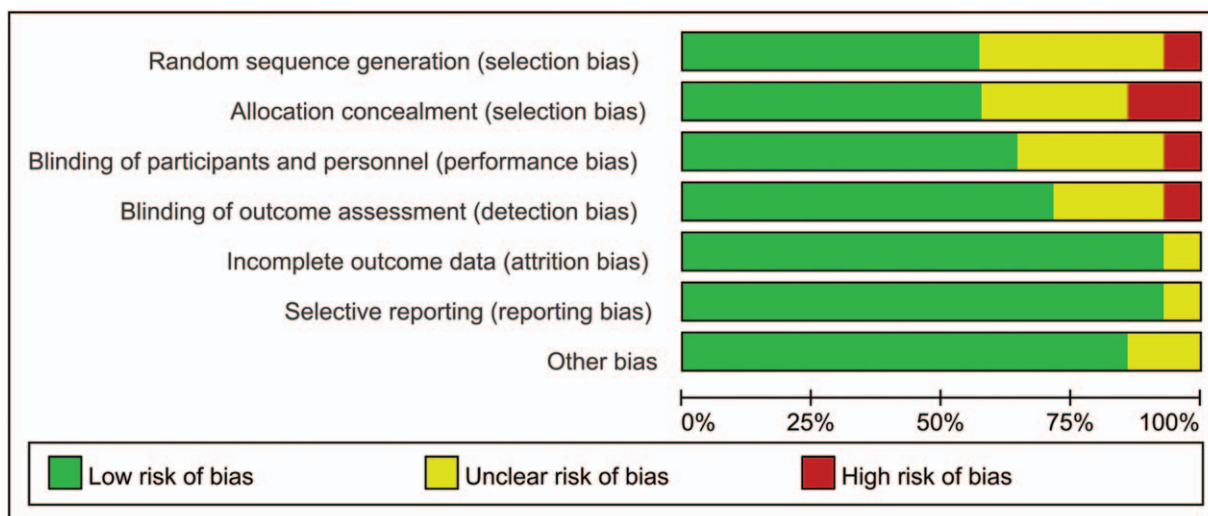


Figure 2. Risk of bias graph review authors' judgements about each risk of bias item presented as percentages across all included studies.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chang 2010	+	+	+	+	+	+	+
Gangji 2004	-	+	+	+	+	+	+
Gangji 2011	+	+	+	+	+	+	+
Guo 2008	?	?	?	?	+	+	+
Hauzeur 2018	+	+	+	+	+	+	+
Ma 2014	?	?	?	?	+	+	+
Pepke 2016	+	+	+	+	+	+	+
Rastogi 2012	+	+	+	+	+	+	+
Sen 2012	?	+	+	+	+	+	+
Sun 2008	?	-	-	-	+	+	?
Tabatabaee 2015	+	+	+	+	+	+	+
Yang 2015	?	?	?	?	?	?	?
Zhao 2012	+	-	+	+	+	+	+
Zhao 2016	+	?	?	+	+	+	+

Figure 3. Risk of bias summary review authors' judgements about each risk of bias item for each included study.

studies. To assess the allocation concealment, the risk of bias was ambiguous and large in 8 and 2 of 15 studies separately.

For the blinding of participants and personnel assessment, the risk of bias of 9 trials was ambiguous and 6 of 15 trials had a high risk of bias. In terms of the blinding of outcomes assessment, the risk of bias was ambiguous in 14 of 15 researches. For not complete outcome data, the risk of bias of 1 of 15 trials was ambiguous. In the selective reporting assessment, the risk of bias was ambiguous in 1 of 15 studies. There were 2 studies with ambiguous risk of bias in other items.

4. Results of meta-analysis

4.1. HHS at 12 and 24 months

The forest plot for meta-analysis of HHS at 12 and 24 months is presented in Figure 4. The overall results indicated that the HHS in the combined utilization of BMSCs and CD group was higher than that of the CD alone group at 12 months (SMD = 0.53, 95% CI 0.29–0.77, $P = .000$; P for heterogeneity = .228, $I^2 = 26.4\%$) and 24 months (SMD = 0.57, 95% CI 0.36–0.77, $P = .000$; P for heterogeneity = 0.581, $I^2 = 0.0\%$).

4.2. Necrotic Area of Femoral Head

The necrotic area of femoral head was available in 6 trials. A significantly reduction in the necrotic area of femoral head after the treatments was seen in combined utilization of BMSCs and CD group than CD alone group (WMD = -1.05, 95% CI -1.73 to -0.38, $P = .002$, $I^2 = 84.8\%$) (Fig. 5). These data together suggest that the combined utilization of BMSCs and CD has a superior efficacy in eliminating necrotic area of femoral head than CD alone.

4.3. Conversion to THA

The forest plot for meta-analysis of conversion to THA is presented in Figure 5. The results demonstrated that the rate of conversion to THA was significantly less in combined utilization of BMSCs and CD group than CD alone group (RR = 0.53, 95% CI 0.38–0.74, $P = .000$; P for heterogeneity = .229, $I^2 = 22.5\%$, Fig. 6).

4.4. VAS at final follow-up

The forest plot for meta-analysis of VAS at final follow-up is presented in Figure 7. The results demonstrated that the VAS at final follow-up was significantly less in combined utilization of BMSCs and CD group than CD alone group (SMD = -0.93, 95% CI -1.59 to -0.28, $P = .005$; P for heterogeneity = .000, $I^2 = 86.2\%$).

Table 3 Summary of risk of bias.

Risk of bias	No. of RCTs and why
Selection bias	Six studies did not describe the method of randomization and allocation concealment
Performance bias	Five studies had patients who were aware of the interventions.
Detection bias	One Four RCTs did not mention the personnel responsible for outcome measures, and 1 study employed the physician aware of the intervention details for follow-up measures,
Attrition bias	In 1 RCT, >20% of patients were lost to follow-up
Reporting bias	One RCT did not report results of all predefined measures
Other bias	Two RCTs did not have sample size calculations before interventions, and did not recruit enough patients per the calculated sample size

RCT = randomized controlled trial.

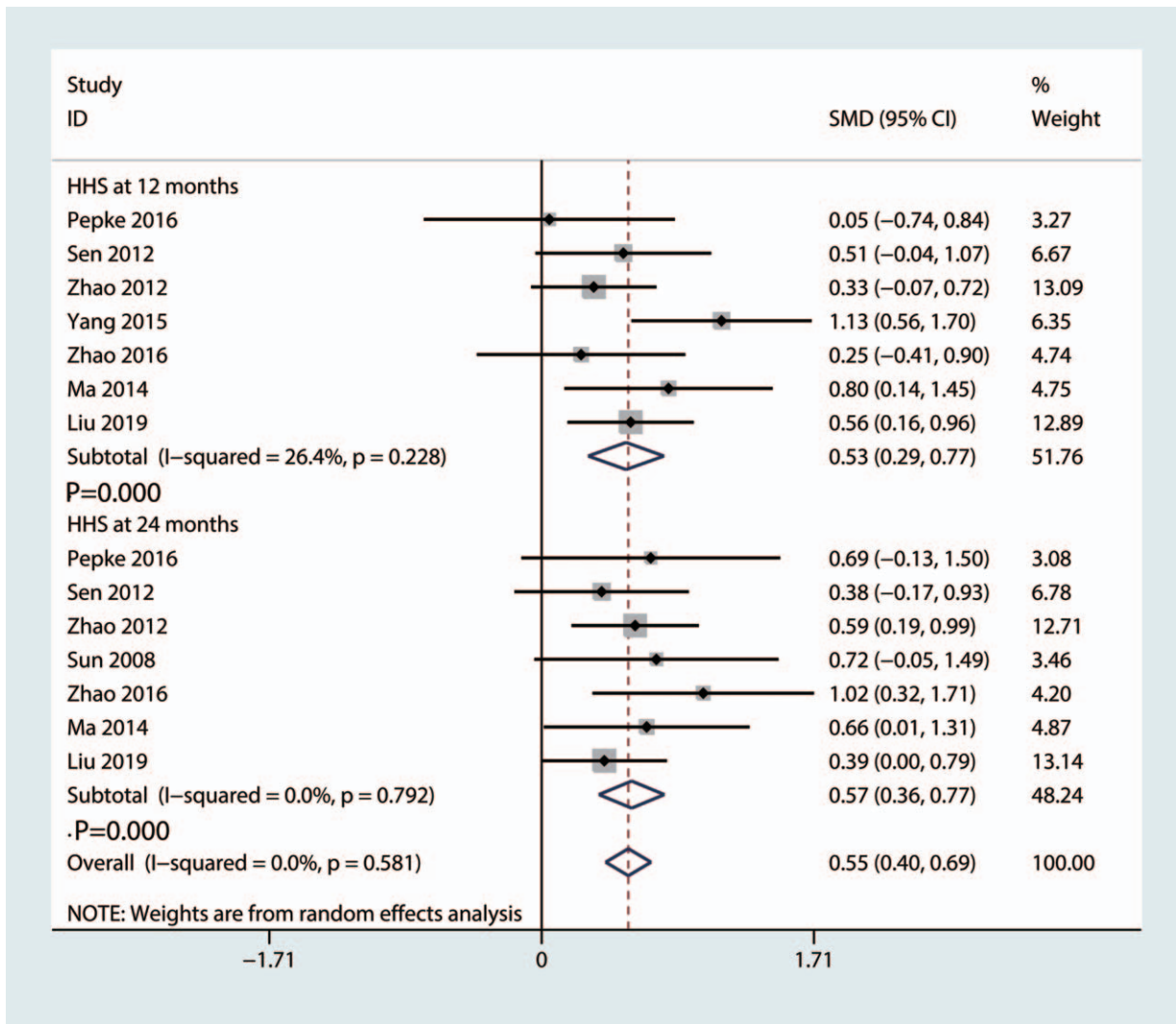


Figure 4. A forest plot diagram showing HHS at 12-months and 24-months postoperatively. CI = confidence interval, HHS = Harris hip scores, SMD = standard mean difference.

4.5. AEs

The forest plot for adverse events of all the included studies is shown in Figure 8. The overall results indicated that there were no significant differences in the combined utilization of BMSCs and CD group and CD alone group at final follow-up (RR = 1.03, 95% CI 0.64–1.67, P=.893; P for heterogeneity=.977, I²= 0.0%).

4.6. Subgroup analysis, sensitivity study, and publication bias

Table 4 presents the results of subgroup analyses. The findings of increased HHS at 24 months were consistent in all subgroup analyses except for the included stage III ONFH (not included stage III was superior than included stage III).

Figure 9 presents sensitivity study for HHS at 24 months. The HHS at 24 months remained consistent through sensitivity analyses.

For the meta-analysis of combined utilization of BMSCs and CD on HHS at 24 months, there was no evidence of publication

bias by inspection of the funnel plot (Fig. 10) and formal statistical tests (Egger test, P=.56; Begg test, P=.49).

5. Discussion

Our meta-analysis comprehensively and systematically reviewed the current available literature and found that: combined utilization of BMSCs and CD compared with CD alone significantly increased HHS at 12 and 24 months, reduced necrotic area of femoral head and the rate of conversion to THA; combined utilization of BMSCs and CD significantly reduced VAS at final follow-up; combined utilization of BMSCs and CD has no influence on the occurrence of adverse effects. Moreover, subgroup analysis found that combined utilization of BMSCs and CD was superior than CD alone in stage 1 to 2 ONFH, otherwise stage 3 ONFH.

Only 2 related meta-analyses were released.^[28,29] Although the main finding of our meta-analysis was consistent with previous meta-analyses, differences between ours and the previous ones should be noted. First, these previous meta-analyses included no

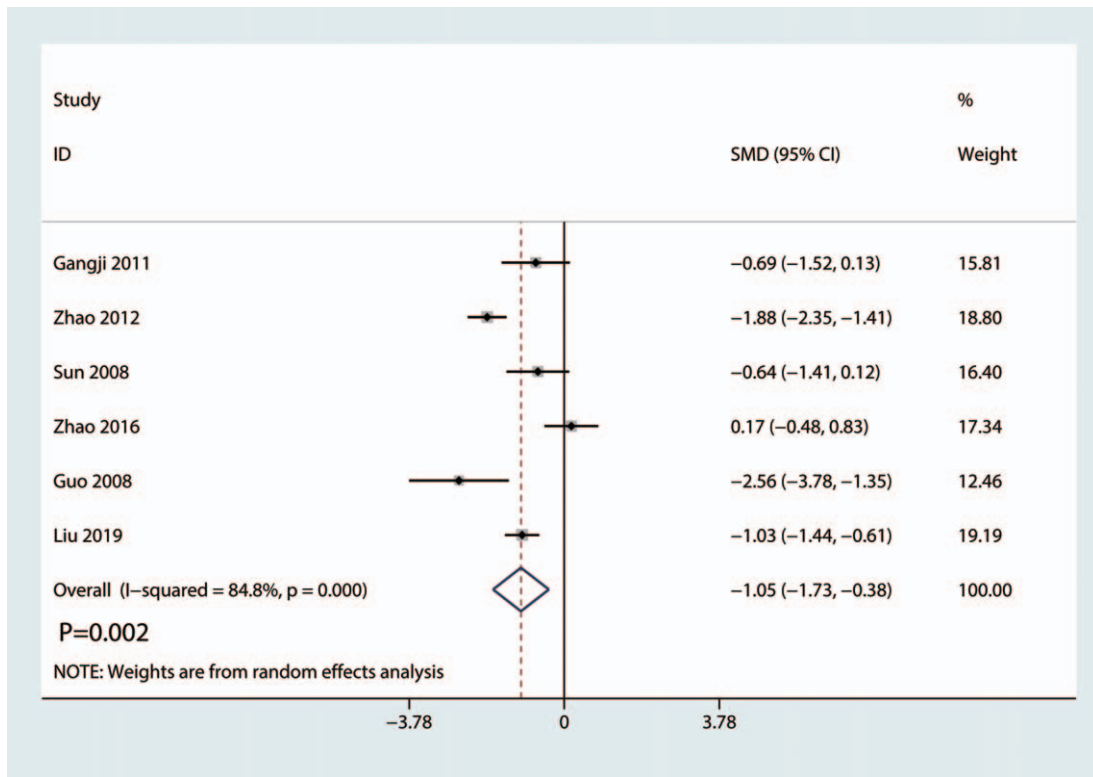


Figure 5. A forest plot diagram showing necrotic area of femoral head postoperatively. CI = confidence interval, SMD = standard mean difference.

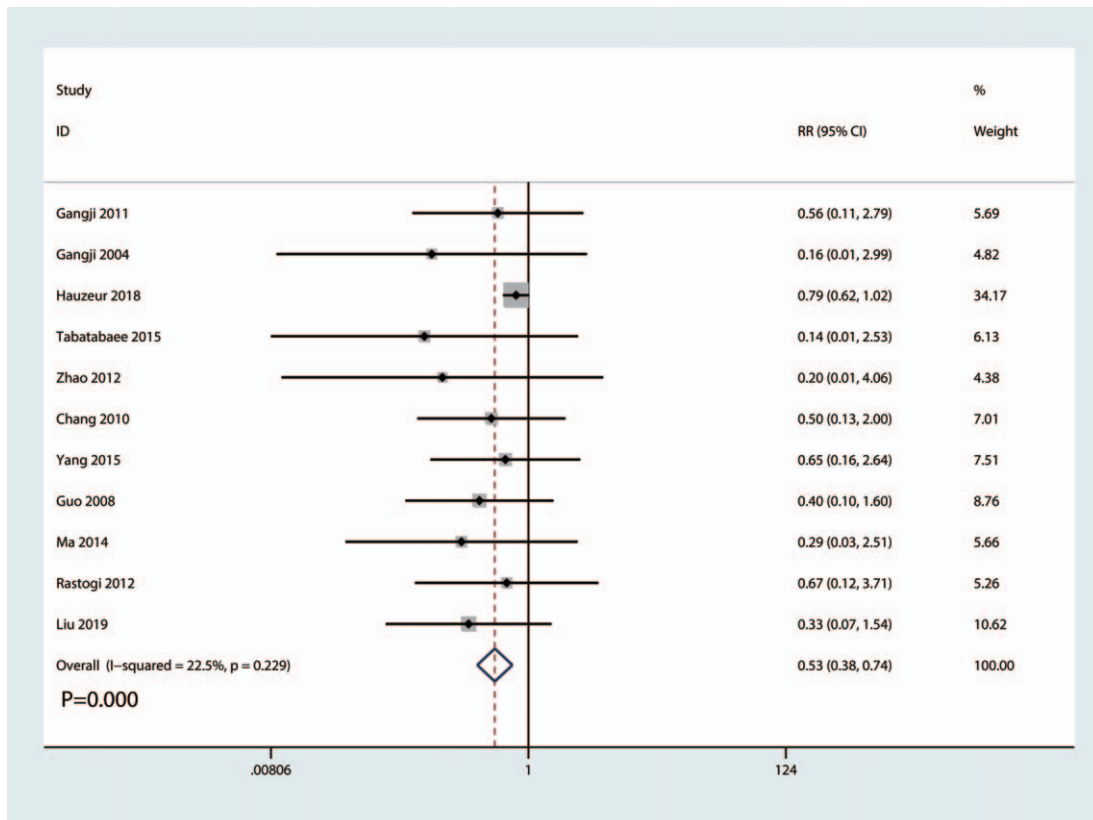


Figure 6. A forest plot diagram showing the rate conversion to THA postoperatively. CI = confidence interval, RR = risk ratio.

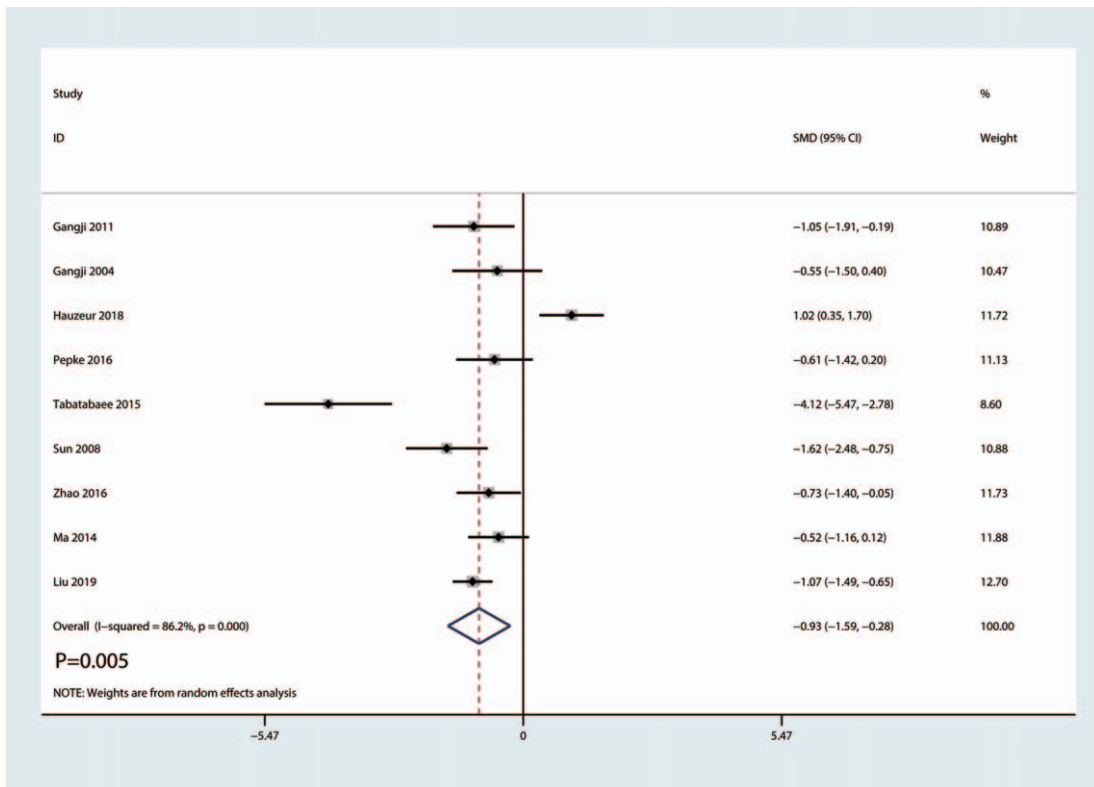


Figure 7. A forest plot diagram showing visual analog pain scale at final follow-up postoperatively. CI = confidence interval, SMD = standard mean difference.

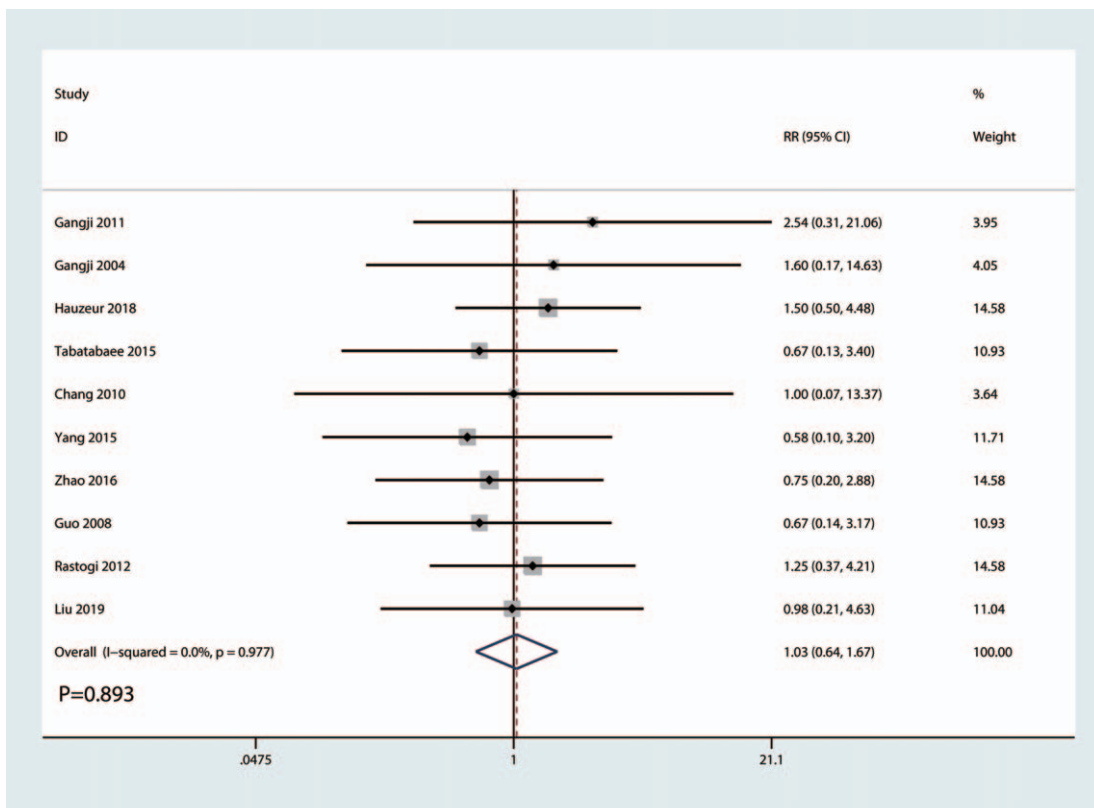


Figure 8. A forest plot diagram showing adverse effects postoperatively. CI = confidence interval, RR = risk ratio.

Table 4
Subgroup analysis for HHS at 24 months.

Subgroup	SMD (95% CI)	P	I ² (%)	Test of interaction, P
Risk of bias				
Low	0.46 (0.19–0.73)	.001	0.0	.102
Unclear/high	0.68 (0.37–1.00)	.000	0.0	
Sample				
n <40	0.85 (0.41–1.28)	.000	0.0	.136
n >40	0.47 (0.24–0.71)	.000	0.0	
Effect model				
Fixed-effects model	0.88 (0.39–1.09)	.000	0.0	.096
Random-effects model	0.55 (0.31–0.89)	.000	0.0	
Included stage III				
Yes	0.52 (0.28–0.76)	.000	0.1	.024
No	0.65 (0.26–1.03)	.000	0.0	
Centrifuge				
Yes	0.54 (0.29–0.80)	.001	0.0	.134
No	0.58 (0.22–0.94)	.000	0.0	
No. of BMSCs				
<2 × 10 ⁷	0.53 (0.28–0.77)	.000	0.0	.263
>2 × 10 ⁷	0.62 (0.25–1.00)	.001	0.0	

BMSCs = bone marrow stem cells, CI = confidence interval, HHS = Harris hip scores, SMD = standard mean difference.

more than 5 trials and 359 patients. In comparison, our current meta-analysis included 15 trials totaling 688 patients. Li et al^[29] conducted a related meta-analysis on the fusion of CD and BMSCs for ONFH cases. Nevertheless, this meta-analysis included non-RCTs and RCTs to achieve analysis and thus selection bias could not be avoided.

We selected HHS at 12 and 24 months as primary outcomes. Results found that, compared to CD alone, combined utilization of BMSCs and CD could significantly increase HHS at 12 and 24 months. HHS is a comprehensive tool that used to assess the clinical outcome of ONFH patients. Moreover, 6 studies assess

the necrotic area of femoral head; result found that combined utilization of BMSCs and CD could significantly reduce the necrotic area of femoral head ($P < .05$). Therefore, the rate of conversion to THA was corresponding reduced in combined utilization of BMSCs and CD group. A meta-analysis comparing CD with conservative treatment showed that performing CD for ONFH is effective for preventing a femoral collapse in short term.^[30] Hua et al^[31] conducted a meta-analysis and revealed that CD is an effective and safe method of treating ONFH. Based on subgroup analysis, we found that combined utilization of BMSCs and CD was associated an increase in HHS in stage 1 to 2

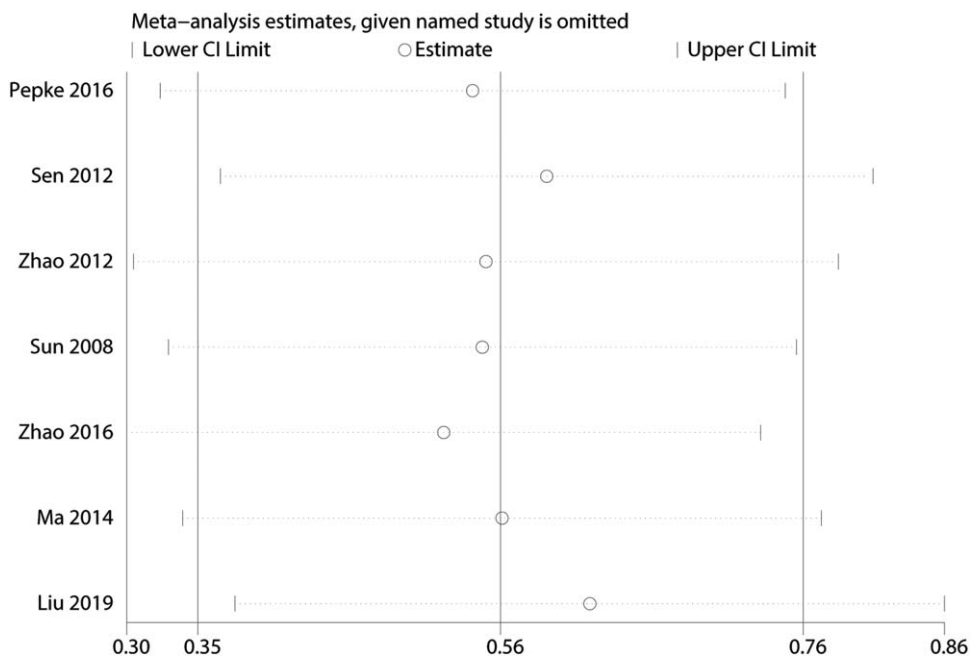


Figure 9. Sensitivity analysis for HHS at 24-months. CI = confidence interval.

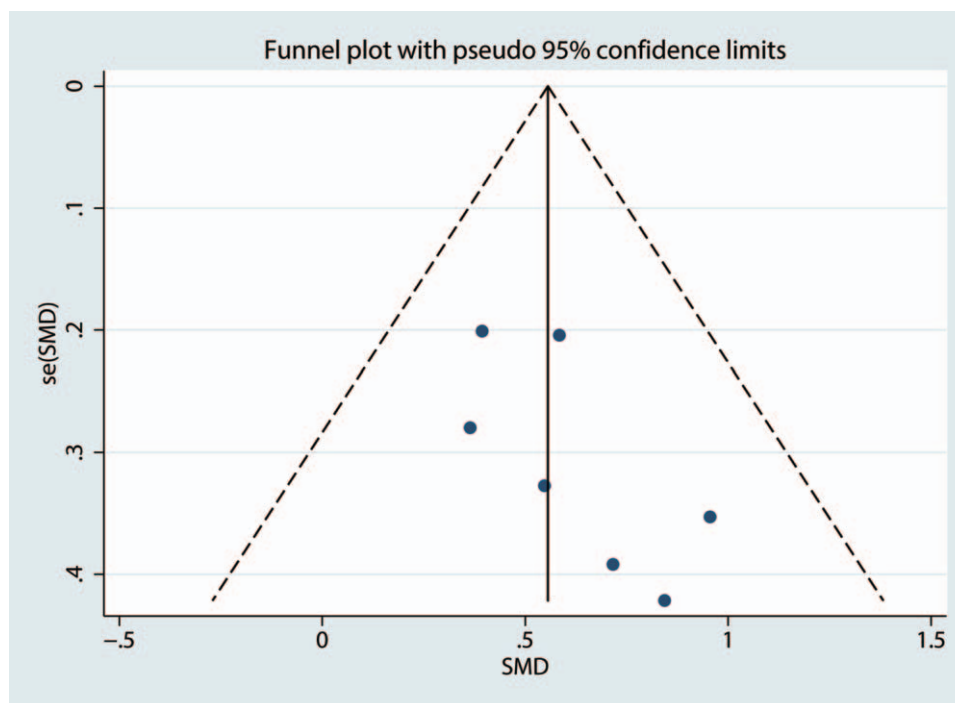


Figure 10. Funnel plot for HHS at 24-months. SMD = standard mean difference.

than stage 3 ONFH. Kang et al^[32] revealed that implantation of BMSCs into the femoral head at an early stage of ONFH lowers the THA conversion rate.

The present study has several strengths. Firstly, to our knowledge, it is the most comprehensive systematic review and meta-analysis and up to date assessment of the combined utilization of BMSCs and CD versus CD alone in ONFH patients. Also, we concluded data results by subanalysis and sensitivity analysis to ensure the accuracy of the outcomes.

There are still some limitations of our meta-analysis. The total number of participants was not large enough so that bigger-scale clinical trials were needed to be practised. Meanwhile, The BMSCs isolated, collecting and number administrated in each study were differed from each other, which will made bias of the results. Finally, due to the lack of primary studies with a relative long follow-up, it is difficult to determine the status of the ONFH treated by these 2 strategies at a time point >2 years. Hence, some other trials with longer follow-up should be performed in the future.

6. Conclusion

This systematic review and meta-analysis found that combined utilization of BMSCs and CD appeared to be more efficacious in the treatment of ONFH than CD only, delayed ONFH progression, reduced necrotic area of femoral head, decreased the need for THA, and improved Harris hip score. However, more rigorously designed and higher RCTs with larger sample size are necessary for better confirming the effectiveness of combined utilization of BMSCs and CD on ONFH.

Author contributions

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