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SYSTEMATIC REVIEW ARTICLE

Stem Cells in Rotator Cuff Injuries and Reconstructions: A Systematic Review and Meta-Analysis

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Abstract: ***Background:*** Multiple studies have focused on stem cell-based treatments for rotator cuff disorders; however, the outcomes are not consistent.

Objectives: This systematic review and meta-analysis were performed to evaluate the effects of stem cells on rotator cuff healing.

Methods: A detailed search of relevant studies was conducted in three databases including Pubmed/Medline, Cochrane library, and Embase databases, using the following keywords: "rotator cuff" or "Tissue Engineering" AND "stem cell" from inception to January 01, 2019. The standard mean difference (SMD) and 95% confidence interval (CI) for each individual study were extracted from the original studies or calculated based on relevant data and pooled to obtain integrated estimates using random effects modeling.

Results: A total of 22 studies were identified. The results demonstrated that the ultimate strain in the stem cell group was significantly higher than that in the control group at 4 and 8 weeks. Muscle weight in the stem cell group was higher than the control group at 8 weeks, while no significant differences were detected at 16 weeks. The stem cell group had lower visual analog scale scores (VAS) at 1, 3, and 6 months, and higher American shoulder and elbow surgeons score (ASES) at 3 months. In addition, the walking distance, time, and speed in the stem cell group were significantly superior to those in the control group.

***Conclusions*:** This meta-analysis confirms that stem cells improved the rehabilitation of rotator cuff disorders. However, larger-scale studies are needed to further support these findings.

Keywords: Rotator cuff, rotator cuff disorders, stem cell, tissue engineering, regenerative therapy, meta-analysis.

1. INTRODUCTION

The rotator cuff is one of the most complicated structures which frequently suffers from disorders in adults. It has been known that the pain caused by rotator cuff disorders represents the third most common musculoskeletal pain (16%), next to back (23%) and knee (19%) pain in adults [1]. Rotator cuff disorders are thought to be multi-factorial disorders caused by aging, degenerative changes, traumatic injury, genetic sensitivity, smoking, and some other factors [2, 3]. So far, the exact mechanism of rotator cuff diseases is still unknown.

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Treatments for rotator cuff tears include non-surgical treatments (rest, non-steroidal anti-inflammatory drugs, physical therapy, and corticosteroid injection) and surgical repair (arthroscopic operation and traditional open surgery) [4]. Historically, non-surgical methods were considered to be the most common treatment for patients who suffer from rotator cuff diseases, from a small scar to a full-thickness tear. Generally, a considerable number of patients (41%) show persistent symptoms after 1 year of non-operative treatments [5]. It is known that non-surgical treatments could only reduce the symptoms such as pain and improve restricted functions, but could hardly restore the structure of the rotator cuff or postpone the progress of these disorders. Currently, surgical repair is widely applied by physicians. In the United States, over 600,000 patients per year require rotator cuff related surgeries [6]. However, numerous pa-

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tients had their rotator cuff re-ruptured after operation [7]. Most of the rotator cuff tears occur near the enthesis, which hardly regenerates after surgery [8-11]. Given the high rate of re-rupture after surgical repair and the unsatisfactory outcomes of non-surgical treatments, alternative novel repair strategies need to be developed to boost the healing of rotator cuff disorders.

Currently, the application of biological adjuvants is considered as a promising alternative strategy to overcome the limitations of the traditional treatment methods. Stem cells are multipotent cells which are capable to differentiate into multiple cell types such as osteoblasts, adipocytes, and chondrocytes [12]. They also have the properties of self-renewal and provide exogenous biological cues for guiding tissue regeneration. Nourissat *et al*. delivered stem cells into a torn Achilles tendon, which resulted in better strength and tissue repair, revealing that stem cells played a positive role within the sites of the injury [13]. Moreover, numerous animal studies demonstrated that stem cell-based therapy holds great potential for tendon repair [13, 14].

Stem cells include many types, such as bone marrow-derived stem cells (BMSCs), adipose-derived stem cells (ADSCs), tendon stem/progenitor cells (TPSCs), umbilical cord blood-derived mesenchymal stem cells (UCB-MSCs), muscle-derived stem cells, and synovial-derived stem cells. Injection of BMSCs could decrease muscle degeneration, and to some extent improve the regeneration of rotator cuff [15]. Furthermore, several clinical studies demonstrated that BMSCs improved massive rotator cuff tear repair [16-19]. Thus BMSCs serve as a promising reparative cell candidate for boosting rotator cuff healing. ADSCs are another attractive stem cell candidate because of their easy isolation and high responsiveness to the distinct environment. Adipose tissue is abundant in human and other animal species which can be easily harvested with less invasive procedures compared to BMSCs [20]. Another study proved that TSPCs mixing with hydrogel or seeding onto scaffold tend to be a new paradigm in healing tendons [21, 22].

Scaffolds have been widely applied to deliver cells or drugs into injury sites to facilitate healing. Ambrosi *et al*. proved that rotator cuff repair with scaffold achieved effective and improved outcomes, especially for large-scale rotator cuff lesions [23]. Some hard scaffolds, like polyglycolic-acid (PGA) and polycaprolactone (PCL) have been used in some research and achieved promising outcomes as compared to the control group [24, 25]. Another kind of scaffold, hydrogel, formed from a network of natural or synthetic polymer chains, possesses a higher degree of molding and has been frequently investigated [20]. Literature has reported that hydrogels functionalized by stem cells can be applied as a promising treatment strategy for rotator cuff repair [26, 27].

So far, considerable controversy still persists among physicians on the optimal treatment for rotator cuff disease, and also there is no clear conclusion on whether stem cells can improve the healing of the rotator cuff in short, mid, or long term observation.

As such, the aim of the present study was to more critically and accurately evaluate all available scientifically published material, using strict inclusion and exclusion criteria, to evaluate the effect of stem cells on rotator cuff healing.

2. METHODS

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [28].

2.1. Data Sources and Search Strategy

Online published articles from inception to January 01, 2019 were searched in three databases including Pubmed/Medline, Cochrane library, and Embase databases. To build up the literature, the following Mesh-terms were used: "rotator cuff", "rotator cuff tear", "rotator cuff disorders" or "Tissue Engineering" AND "stem cell", "ADSC", "Adipose-derived stem cell", "BMSC", "Bone marrow stem cell", "TSPC", "Tendon stem progenitor cell", "BMAC", "bone marrow aspirate concentrate", "UCB-MSC" or "Umbilical cord blood-derived mesenchymal stem cell". Processes including electronic searches, reference lists screening, study selection, data extraction, assessment of the risk of bias, and summary estimates pooling were performed by two investigators (FX L and ZX Y) independently. Any disagreement was resolved by discussion or judgement of an arbitrator when consensus could not be reached. Due to this, all required data was retrieved from published articles. As such, informed consent and ethics approval were not required.

2.2. Study Screening and Selection

Studies were selected on the following inclusion criteria: 1) the study applies stem cells for rotator cuff repair; 2) the study needs to use animal models; 3) a qualitative or quantitative outcome to determine if stem cells have provided improvement in rotator cuff repair, and 4) English language.

Studies were excluded on the following criteria: 1) the study does not involve the use of any types of stem cell; 2) study protocols, letters, correspondence, and conference addressing; or 3) studies do not involve qualitative outcomes to determine if the stem cells have provided any improvement in rotator cuff repair.

2.3. Data Extraction

The following information was collected from the included articles: first author's family name, year of publication, number of participants in the trial group and control group, types of stem cells, other supplements used, methods of measurement, and evaluation of endpoint outcomes of interest: visual analog scale score (VAS), American shoulder and elbow surgeons score (ASES), muscle weight, stiffness, ultimate strain, ultimate load, tear size, trabecular thickness, walking distance, fast walking time, and walking speed. Standardized mean difference (SMD) and its 95% confidence interval (CI) were directly extracted from the original articles if provided or calculated from the relevant data of individual participants.

2.4. Study Risk of Bias Assessment

Quality assessment was performed in each included study using the modified Cochrane Collaboration tool to assess the

risk of bias for randomized controlled trials. Bias is assessed as a judgment (high, low, or unclear) for individual elements from five domains (selection, performance, attrition, reporting, and other). Discrepancies were resolved through discussion among the researchers.

2.5. Statistical Synthesis

Meta-analysis was implemented to conduct the quantitative analysis and produce forest plots using Revman for Windows, 5.3.5 Version (The Nordic Cochrane Centre, The Cochrane Collaboration). Evaluation parameters of interest involved the pooled SMD as well as related 95% CIs. The I^2 statistic was used to assess heterogeneity. Then sensitivity analyses were conducted by omitting studies one by one to assess the stability of the results and subgroup analyses were performed to address the source for heterogeneity.

3. RESULTS

3.1. Selection Process

A total of 827 articles were identified through the PubMed/Medline, Embase database, and Cochrane Library search. Fig. (**1**) shows the stepwise selection procedure and reasons for exclusions. All 580 titles and abstracts were read and then assessed for eligibility. After excluding 548 studies, 32 articles were downloaded as full-text. Among the 32 articles identified, a total of 22 articles [15, 21, 24-27, 29-44] including 19 studies [15, 24-27, 29-42] involving animals experiments and 3 [21, 43, 44] involving clinical trials met the predefined inclusion criteria and therefore were included in the meta-analysis. All included 22 articles [15, 21, 24-27, 29-44] were reviewed thoroughly and the main characteristics of all these articles are summarized in Table **1** and Table **2**.

3.2. Study Characteristic and Quality Assessment

All eligible studies were published in English. As for animal experiments, 4 studies [24, 30, 33, 38] used rabbits, one used dogs [40], and the remaining 14 [15, 25-27, 29, 31, 32, 34-37, 39, 41, 42] used rats. Sample sizes of these studies ranged from 14 to 112. For the types of the stem cell, seven studies [15, 25, 26, 31, 32, 35, 43] used BMSCs, 3 [29, 34, 44] used ADSCs, 2 [30, 33] used UCB-MSCs, and only 1 [21] used TSPCs. The baseline methodological and procedural

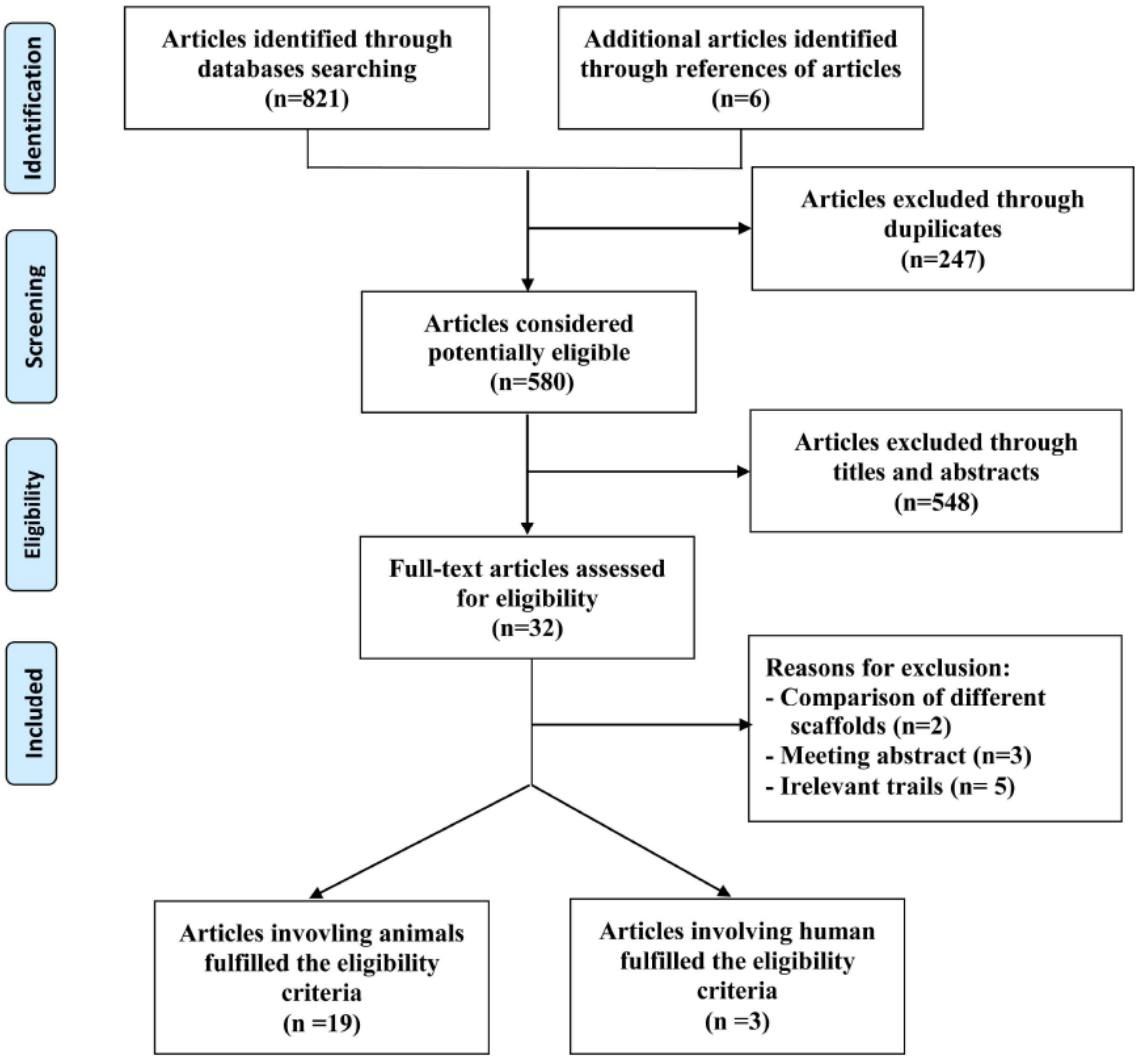

Fig. (1). The selection process for eligible studies included in the meta-analysis.

Table 1. Basic information of included studies involving animals.

Author	Year	NO. of Animals	Stem Cell	Groups	Other Supplements Used	Measurement	Conclusion
Gulotta [27]	2009	98 Lewis rats	BMSC	1. BMSC+fibrin sealant carrier 2. Fibrin sealant carrier 3. Control	Fibrin sealant carrier	Biomechanical testing and histomorphometric analysis in 2 and 4 weeks	BMSCs has shown modest improvements in the healing of tendon grafts in bone tunnels.
Shen [38]	2012	14 rabbits	TSPC	1. Scaffold control 2. Scaffold+TSPC	Knitted silk–collagen sponge + collagen gel containing PBS	PCR, histological and immunohistochemistry assessment and biomechnical testing	TSPCs exhibited fast proliferation on the knitted silk-collagen sponge scaffold and the transcript levels of the tendon-related genes were increased with proliferation.
Yokoya [24]	2012	68 Japanese white rabbits	BMSC	1. Control 2. Polyglycolic acid (PGA) group 3. PGA+BMSC group	PGA sheet	Histochemical, immunohistochemical analysis and mechanical test in 4, 8 and 16 weeks	1. BMSCs had a good capacity to regenerate tendon-bone insertion, including the production of type I collagen. 2. The mechanical properties in the regenerated tendon were unsatisfactory.
Cheng [41]	2014	55 Lewis rats	TSPC	1. TSPC+fibrin glue carrier 2. TSG-6 silenced TSPC 3. Control	Fibrin glue carrier	Biomechanical testing in 4 weeks	TSG-6 mediates the function of TDSCs to improve the structure and the attachment strength of the healing tendon-bone interface
Mora [36]	2014	50 Sprague-Dawley rats	ADSC	1. Suture 2. Suture+carrier 3. Suture+carrier+ ADSCs	Collagen carrier	Biomechanical testing and Histological study in 1, 2 and 4 weeks.	1. No differences in biomechanical properties of the rotator cuff in animal model. 2. Absorbed energy and mechanical deformation data may indicate that the changes in the inflammatory pattern lead to a more elastic and less scarred healing.
Chen [42]	2015	120 Sprague-Dawley rats	ADSC	1. Control 1. ADSC treatment	No	Histological analysis and biomechanical test in 1,2,3 and 4 weeks.	Pathology and telescopic strength analyses showed significant recovery in the supraspinatus tendon.
Lipner [29]	2015	64 Male Sprague-Dawley rats	ADSC	1. Negative control group; 2. Acellular scaffold; 3. Cellular scaffold; 4. Cellular BMP2 scaffold	PLGA nanofibers	Histology, bone & scar tissue morphology, mechanical test in 4 and 8 weeks	1. Regenerative strategies can be overwhelmed by the natural scar-mediated response. 2. BMP2 is not an effective growth factor for improving tendon-to-bone healing. 3. Scaffolding material may negatively affect healing.
Park [30]	2015	30 Male New Zeald White rabbits	UCB-MSC	1. Injected with 0.1 ml of human UCB-MSCs; 2. Injected with 0.1 ml of hyaluronic acid; 3. Control group injected with 0.1 ml of normal saline	Hyaluronic acid	Gross morphology, histological examination and motor analysis in 4 weeks	1. UCB-MSC injection resulted in the partial healing of full-thickness rotator cuff tendon tears in a rabbit model. 2. Histology revealed that UCB-MSC induced regeneration of rotator cuff tendon tears and that the regenerated tissue was predominantly composed of type I collagens. 3. Motion analysis showed better walking capacity after MSC injection.

Table (1) contd….

Author	Year	NO. of Animals	Stem Cell	Groups	Other Supplements Used	Measurement	Conclusion
Pilar [37]	2015	41 Sprague-Dawley rats	BMSC	1. Control 2. Collagen I membrane 1. Collagen I membrane+BMSCs	Collagen I membrane	Boimechanical testing and gross inspection	1. The introduction of MSCs in the type I collagen membrane placed at the site of the surgically created defects resulted in the production of mechanically superior tissue 2. Improved SP tendon strength and stiffness at 3 months after treatment in comparison with the use of an acellular collagen membrane or sutures
Degen [31]	2016	52 Athymic rats	BMSC	1. Fibrin glue carrier containing BMSC; 2. Control group 1 with fibrin glue carrier; 3. Control group 2 intact rotator cuff	Fibrin Glue carrier	Stem cell viability, histomorphometric analysis and moimechanical test in 2 and 4 weeks	Rotator cuff repair augmentation with purified human BMSC improved early histologic appearance and biomechanical strength of the repair at 2 weeks, but no significant differences between groups at 4 weeks.
Gao [26]	2016	72 Male Sprague-Dawley rats	BMSC	1. Fibrin glue carrier with BMSC; 2. Fibrin glue carrier with shRNA-TOB1 transduced BMSC; 3. Fibrin glue carrier plus miR-218-transduced BMSC; 4. Control group	Fibrin glue carrier ShRNA-TOB1-transduced BMSC; MiR-218-transduced BMSC	Boimechanical test, histology analysis, cell proliferation, gene expression and Western blot in 4 and 8 weeks.	TOB1 deficiency enhanced the effect of MSCs on tendon-bone healing in a rat rotator cuff repair model and demonstrated that expression of TOB1 may be regulated by miR-218.
Omi [39]	2016	39 Lewis rats	BMSC	1. No augmentation 2. Composite of multilayer tendon slices (COMP) 3. BMSC+COMP	Composite of multilayer tendon slices	Boimechanical testing, histological analysis and cell migration.	1. Stronger tendon-to-bone healing was found in BMSCs treatment combined with a multilayer xenograft tendon scaffold 2. Transplanted BMSCs migrated widely in the fibrous tissue, including to the tendon-to-bone interface, and contributed to the initial healing process after surgery.
Peach [25]	2016	66 Male Sprague-Dawley rats	BMSC	1. Positive control group native supraspinatus; 2. Negative control group; 3. Repair and PCL/PNEA-mPh electrospun matrix; 4. Repair PCL/PNEA-mPh electrospun matrix and BMSC	PCL/PNEA-mPh electrospun matrix	Histological analysis and mechanical testing analysis 4 weeks and 8 weeks.	1. Combine an electrospun scaffold mimicking the tissue microenvironment and BMSC delivery using the rat RC augmentation model. 2. Matrix augmentation and the delivery of BMSCs increased biomechanics resulting in tissue morphology that closely resembled intact tendon indicating accelerated tendon remodeling as compared to other repair groups.
Sevivas[15]	2016	44 Wistar-Han rats	BMSC	1. Positive control group; 2. Negative control group; 3. Single local injection; 4. Multiple local injection; 5. Single systemic injection; 6. Multiple systemic injection	No	Histological analysis: fatty degeneration and muscle weight/body weight at 8 and 16 weeks.	1. Therapeutic intervention with BMSC secretome injection starting immediately after the occurrence of a 2-tendon massive rotator cuff tear, in a rat model, can decrease the muscle degeneration associated with this lesion. 2. The positive effects could be safely obtained with either systemic application or local injection.

Table (1) contd…

Author	Year	NO. of Animals	Stem Cell	Groups	Other Supplements Used	Measurement	Conclusion
Güleçyüz [32]	2018	112 Female Inbred Lewis rats	BMSC	1. Control group only received repair; 2. Received repair with injection myocytes; 3. Received repair with injection BMSC	No	Supraspinatus mass and histology in 4 weeks and 8 weeks	The supraspinatus mass of the degenerated muscle to a certain extent improved with BMSC and myocyte in comparison to the control groups.
Kwon [33]	2018	32 Male New Zeal White rabbits	UCB-MSC	1. Control group injected normal saline; 2. Injected PDRN; 3. Injected UCB-MSCs; 4. Injected UCB-MSCs and PDRN	PDRN	Gross morphology examination, histology and motion analysis in 4 weeks	1. No significant difference is in gross morphologic change of the tendon tear between UCB-MSC only and the combination with PDRN injection in a rabbit model of chronic RCT. 2. Coinjection of UCB-MSC and PDRN was more effective than the injection of UCB-MSCs alone in histological and motion analyses.
Rothrauff [34]	2018	110 Male Lewis rats	ADSC	1. Positive control group; 2. Negative control group; 3. Repair augmented with fibrin; 4. Repair augmented with GelMA; 5. Repair augmented with fibrin + ADSC; 6. Repair augmented with GelMA + ADSC; 7. Repair augmented with fibrin + ADSC + TGF-β3; 8. Repair augmented with GelMA + ADSCs + TGF-β3	GelMA; Fibrin; TGF-β3	Bone morphometry, histology and mechanical test	1. ADSC mitigated bone loss at the proximal humeral epiphysis in chronic as opposed to acute tears in a rodent model. 2. Repairs augmented with GelMA constructs also failed more frequently at the tendon-to-bone interface. 3. No experimental intervention significantly improved the histologic appearance or structural properties in the acute or chronic conditions.
Wang [35]	2018	62 Male Sprague-Dawley rats	BMSC	1. Positive control group (normal rats implanted with nontreated stem cells); 2. Blank (model rats implanted with nontreated stem cells); 3. Negative control (model rats implanted with irrelevant plasmid-transfected stem cells); 4. Pc-DNA PDGF-B (model rats implanted with Pc-DNA PDGF-B-transfected stem cells); 5. Short hairpin PDGF-B (shPDGF-B; model rats implanted with shPDGF-B-transfected stem cells)	Pc-DNA PDGF-B-transfected stem cells; Short hairpin PDGF-B-transfected stem cells.	Cell proliferation, histology,biomechanical testing, gene expression and Western blot in 4 weeks and 8 weeks	1. Overexpression of PDGF-B acts to enhance the positive effect of BMSCs with regard to the tendon-bone healing process in a rat rotator cuff injury repair model. 2. Present a theoretical basis for an improved application of PDGF-B and BMSC in relation to improving the tendon-bone healing.
Liu [40]	2018	42 mixed-Breed dogs	BMSC	1. Control (only suture repair) 1. TFBC 2. TFBC+BMSC cell sheet	Tendon-fibrocartilage-bone composite	Histomorphometric analysis and biomechnical analysis in 6 weeks	Engineered TFBC and BMSCs on the enthesis healing by histological appearance and mechanical strength.

Abbreviation: ADSC: Adipose-derived stem cell; ASES: American shoulder and elbow surgeons score; BMP2: Bone morphogenetic protein 2; BMSC: Bone marrow stem cell; TSPC:Tendon stem progenitor cell; BMAC: bone marrow aspirate concentrate; GelMA: gel-methacrylic anhydride; PCL: Polycaprolactone; PDGF: Platelet-derived growth factor; PDRN: Polydeoxyribonucleotides; PNEA-mPh: Polyphosphazene poly[(ethyl alanato) 1(p-methyl phenoxy)1] phosphazene; PLGA: Poly (lactic-co-glycolic acid) PRP: Platelet rich plasma; RC: Rotator cuff; SPADI: Shoulder pain and disability index; TOB1: Transducer of ERBB2,1; TGF-β: Transforming growth factor beta; UCB-MSC: Umbilical cord blood-derived mesenchymal stem cell; VAS: visual analog scale score.

Table 2. Basic information of included studies involving human.

Author	Year	NO. of Animals	Stem Cell	Groups	Other Supplements Used	Measurement	Conclusion
Kim [21]	2017	12 human	TSPC	1. Negative control preoperation group; 2. 3 weeks postoperation; 3. 3 months postoperation	BMAC PRP	Function of shoulders in 3 weeks and 3 months	TSPCs provide a mechanistic basis for the therapeutic benefits of BMAC–PRP for rotator cuff tendon tear.
Jo [44]	2018	18 human	ADSC	1. Low dose; 2. Mid-dose; 3. High-dose; 4. Negative control group baseline	No	The SPADI at 6 weeks; clinical, radiological, and arthroscopic in 1, 3 and 6 months	Intratendinous injection of ADSC is feasible, safe, and capable of regenerating tendon defect and results in the improvement of function and pain of shoulder in patient with rotator cuff disease.
Kim [43]	2018	24 human	BMSC	1. Experimental group BMAC-PRP injection; 2. Negative control group rotator cuff exercise	BMAC; PRP	ASES and VAS score in 3 weeks and 3 months.	1. BMAC-PRP improved pain and shoulder function in patients with partial tear of the rotator cuff tendon. 2. Tear size decreased after BMAC-PRP injection although this decrement did not show any significant difference compared to the control group.

Abbreviation: ADSC: Adipose-derived stem cell; ASES: American shoulder and elbow surgeons score; BMSC: Bone marrow stem cell; TSPC: Tendon stem progenitor cell; BMAC: bone marrow aspirate concentrate; GelMA: gel-methacrylic anhydride; PRP: Platelet rich plasma; VAS: visual analog scale score.

characteristics of the selected studies and demographic data of participants are listed in Table **1** and Table **2**. All included studies were rated as high-quality in the risk of bias assessment.

3.3. Biomechanical Test

The biomechanical test was conducted to examine the effect of stem cells in the tendon tissue repair regarding outcomes of interest including stiffness, ultimate load, and ultimate strain.

3.3.1. Stiffness

Results assessing rotator cuff stiffness extracted from 10 datasets in 9 studies [26, 27, 29, 31, 35-39] demonstrated that the stem cell group exhibited no significant difference in stiffness compared to the control group (SMD = 0.06, 95% CI: -0.56 to 0.68) at 2 weeks; similarly, the stiffness in the stem cell group had no significant difference compared to the control group at 4 weeks (SMD = 0.13, 95% CI: -0.45 to 0.71) as well as at 8 weeks (SMD = 0.81, 95% CI: -0.54 to 2.16) and 12 weeks (SMD = 1.91, 95% CI: -0.22 to 4.04) (Fig. **2**).

3.3.2. Ultimate Load & Ultimate Stress to Failure

A total of 13 datasets involving the ultimate load results were extracted from 12 studies [24, 26, 27, 29, 31, 35-40, 42]. The pooled outcomes revealed that the ultimate load at short follow-up (1, 2 or 3 weeks) showed no significanct difference between the two groups (SMD = 0.00, 95% CI: -0.80 to 0.80; SMD = 0.49, 95% CI: -0.03 to 1.02; SMD = 0.00, 95% CI: -0.80 to 0.80, respectively). However, at longer follow-up (4, 6, 8, and 16 weeks), the ultimate load in the stem cell group was significantly higher than that in the control group (SMD = 0.80, 95% CI: 0.20 to 1.40; SMD = 2.17, 95% CI: 1.47 to 2.86; SMD = 1.50, 95% CI: 0.14 to 2.87; SMD = 8.93, 95% CI: 5.24 to 12.63, respectively) (Fig. **3**).

A total of 6 studies [25, 27, 29, 38, 40, 41] assessing the ultimate stress demonstrated that ultimate stress in the stem cell group was significantly higher than that in the control group at 4 weeks (SMD = 0.63, 95% CI: 0.15 to 1.11) as well as at 6 weeks (SMD = 2.17, 95% CI: 1.49 to 2.85), 8 weeks (SMD = 0.95, 95% CI: 0.42 to 1.47), and 12 weeks (SMD = 1.67, 95% CI: 1.03 to 2.31), except at 2 weeks (SMD = -0.30, 95% CI: -0.81 to 0.21) (Fig. **4**).

3.4. Muscle weight

Seven datasets for the assessment of muscle weight extracted from two studies [15, 32] suggested that at 8 weeks, the stem cell group had a significantly higher muscle weight than that in the control group (SMD = 1.90, 95% CI: 0.90 to 3.72), while no significant differences were detected at 16 weeks (SMD = 1.34, 95% CI: -0.24 to 2.93) (Fig. **5**).

3.5. Trabecular Thickness Using Micro-Computed Tomography (Micro-CT)

Only 2 studies [29, 34] and 1 study [29] assessed the trabecular thickness at 4 and 8 weeks, respectively, confirming that there were no significant difference in the two groups (SMD = -0.39, 95% CI: -1.16 to 0.39; SMD = 0.23, 95% CI: -0.39 to 0.86, respectively) (Fig. **6**).

3.6. Walking Distance, Time, and Speed

A total of 2 studies [30, 33] assessing the rotator cuff rehabilitation by walking-related data were considered. The walking distance in the stem cell group was significantly longer than that in the control group (SMD = 8.36, 95% CI: 0.74 to 15.98). Similarly, compared with the control group, the stem cell group showed a longer walking time (SMD = 2.27, 95% CI: 0.97 to 3.57) as well as a higher walking speed (SMD = 3.01, 95% CI: 0.92 to 5.10) (Fig. **7**).

3.7. Visual Analog Scale Score (VAS)

The results of VAS score, performed and generated from 3 clinical studies [21, 43, 44] involving humans in the present meta-analysis, demonstrated that compared with the control group, shoulder pain in the stem cell group was significantly relieved at 1 month (SMD = -1.71, 95% CI: -3.11 to -0.31). Similar results were obtained at 3 months (SMD = -2.52, 95%CI: -4.37 to -0.66) as well as at 6 months (SMD = -7.35, 95% CI: -14.28 to -0.41) (Fig. **8**).

3.8. American Shoulder and Elbow Surgeons Score (ASES)

The results of ASES were generated from 2 clinical studies [21, 43] involving humans. There is no significant difference in the two groups at 3 weeks (SMD=0.27, 95% CI: -0.56 to 1.10). However, the stem cell group showed a relatively higher ASES score than that in the control group at 3 months (SMD = 1.45, 95% CI: 0.68 to 2.21) (Fig. **8**).

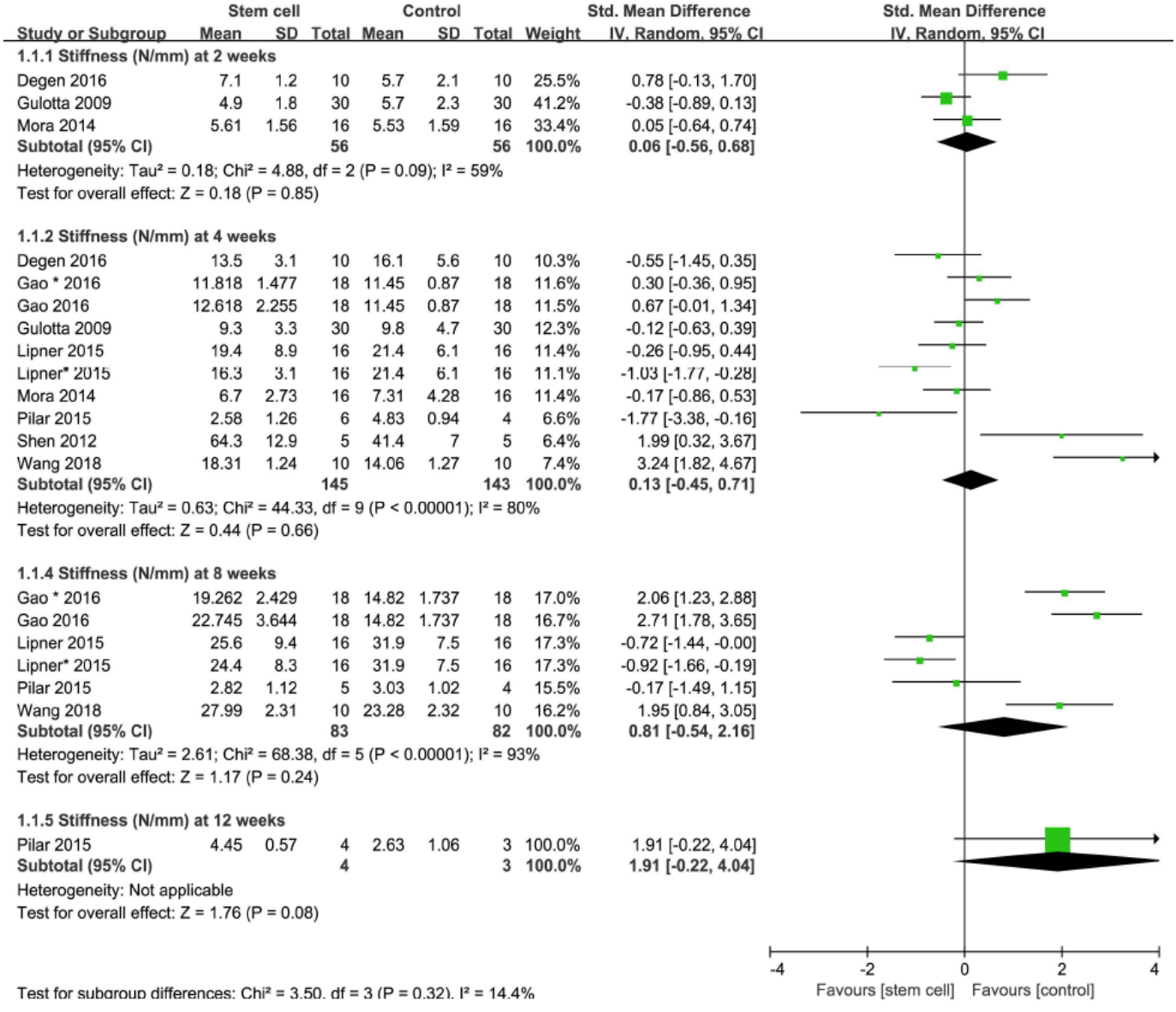

Fig. (2). Forest plot of the association between stem cell group and rotator cuff stiffness.

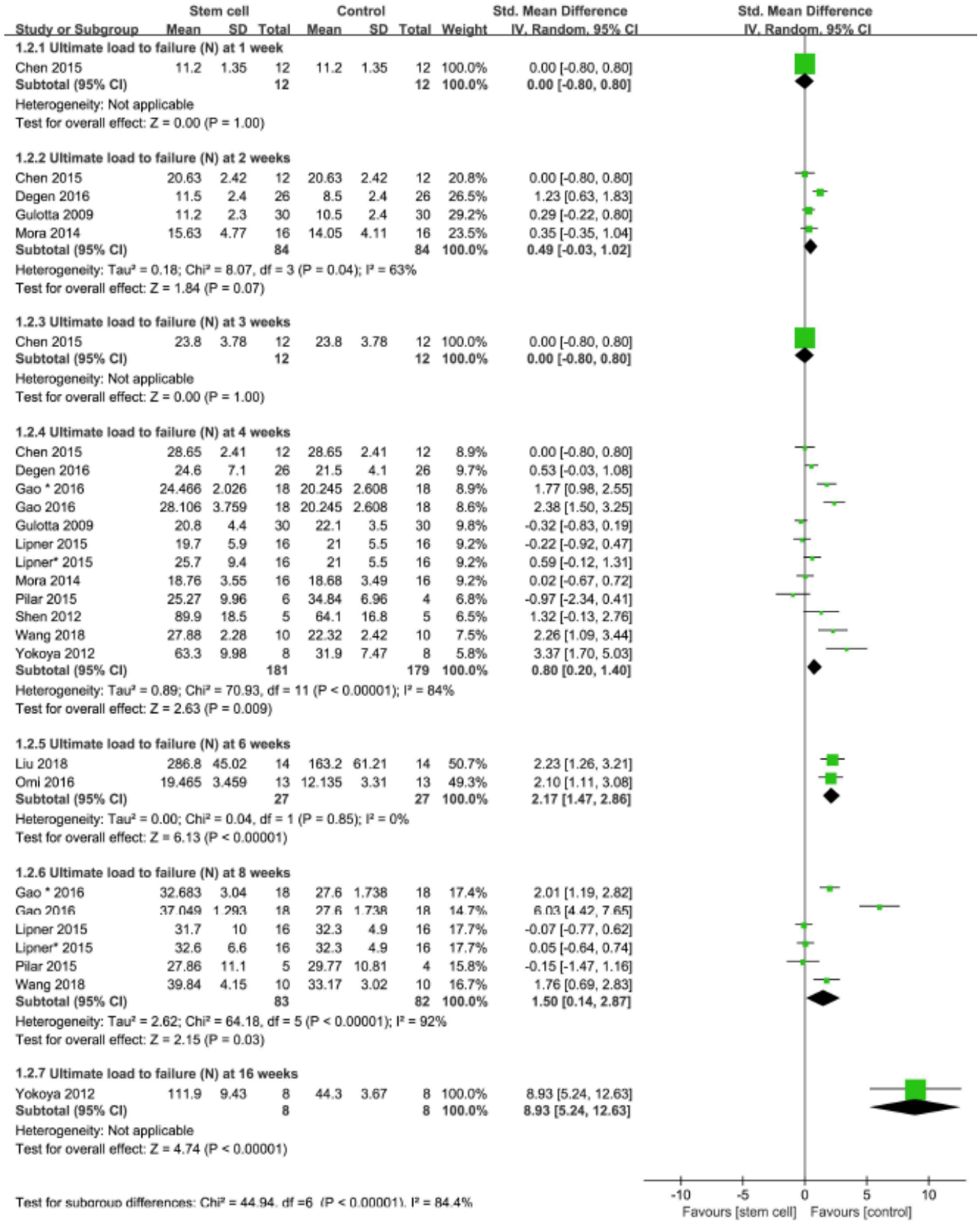

Fig. (3). Forest plot of the association between stem cell group and rotator cuff ultimate load.

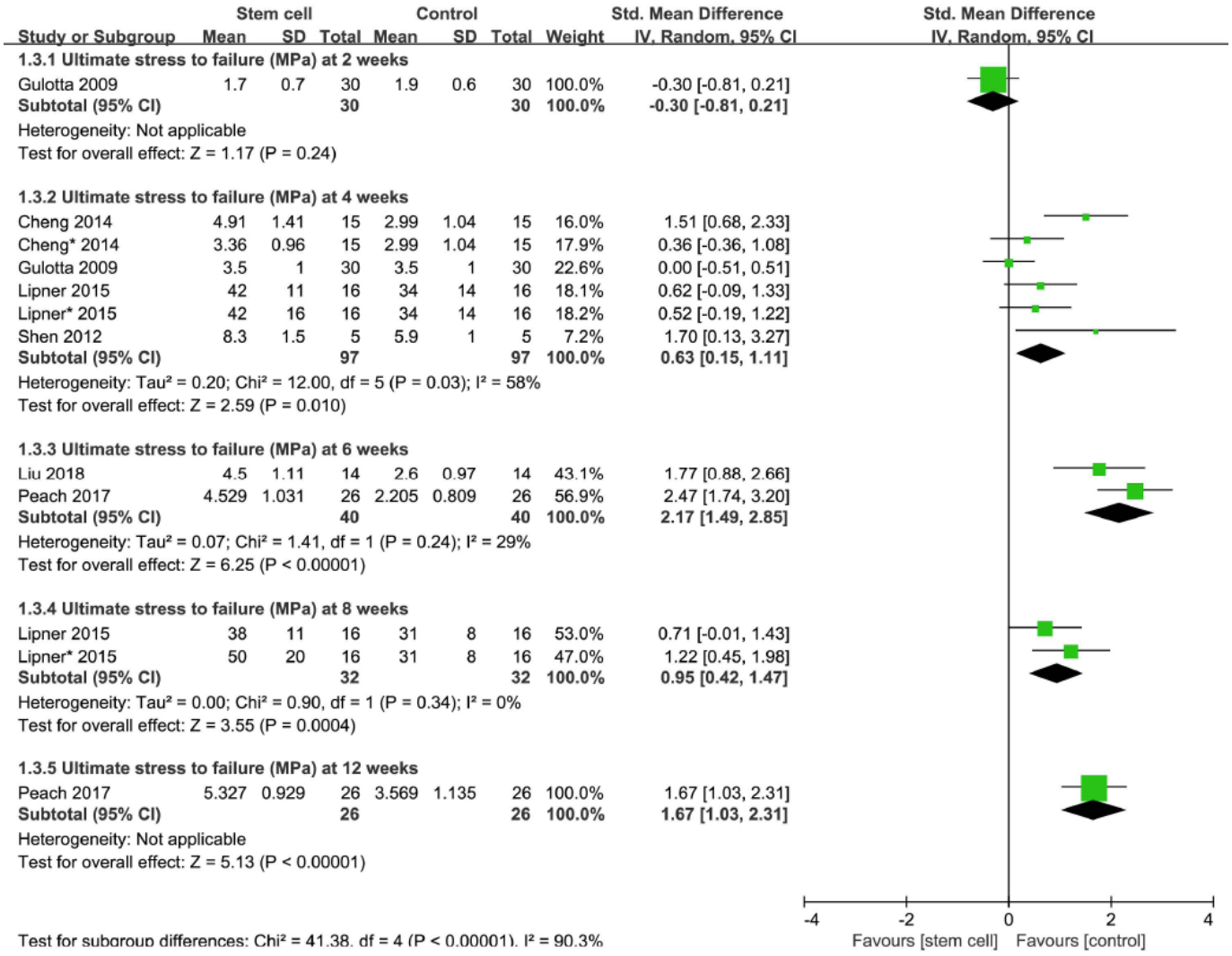

Fig. (4). Forest plot of the association between stem cell group and rotator cuff ultimate strain.

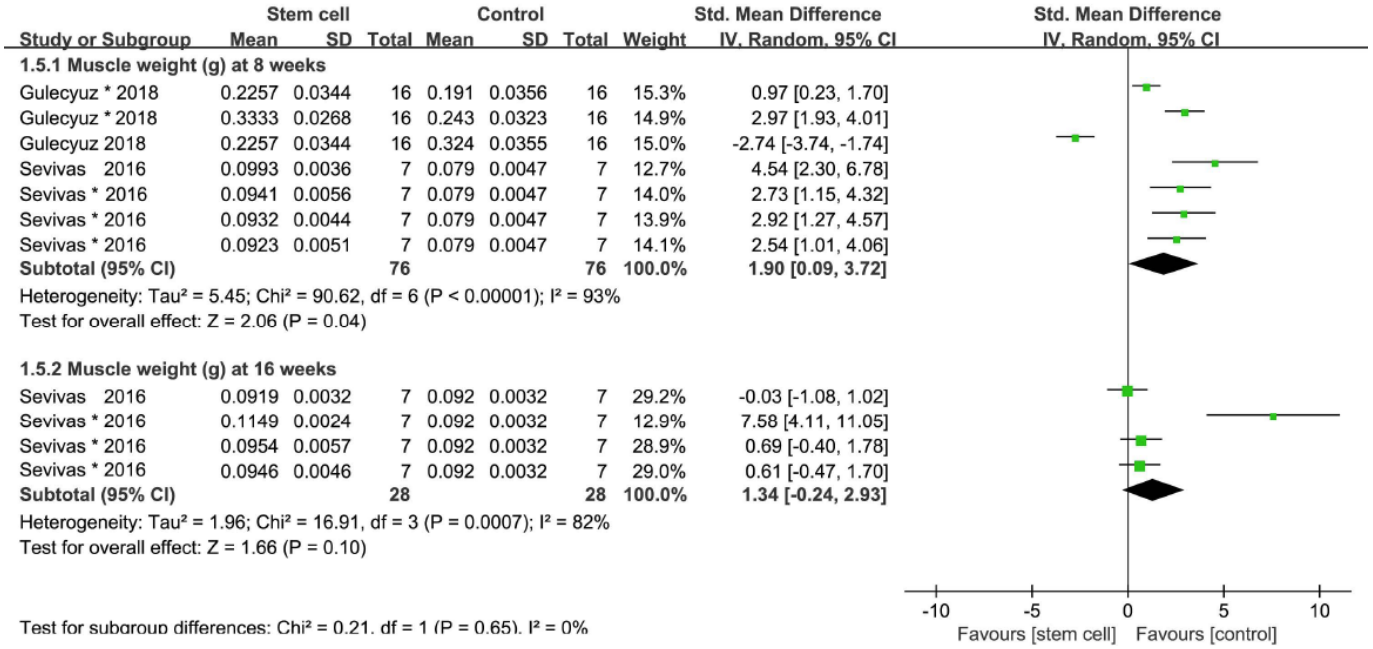

Fig. (5). Forest plot of the association between stem cell group and rotator cuff muscle weight at 8 and 16 weeks.

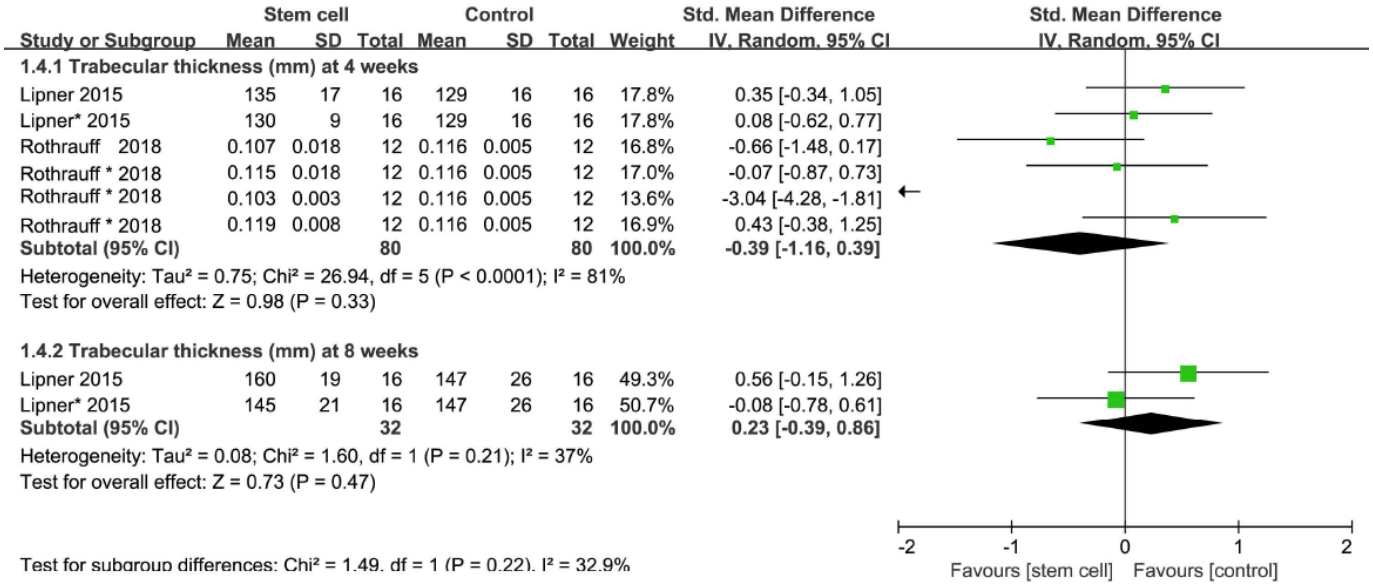

Fig. (6). Forest plot of the association between stem cell group and trabecular thickness score at 4 weeks and 8 weeks.

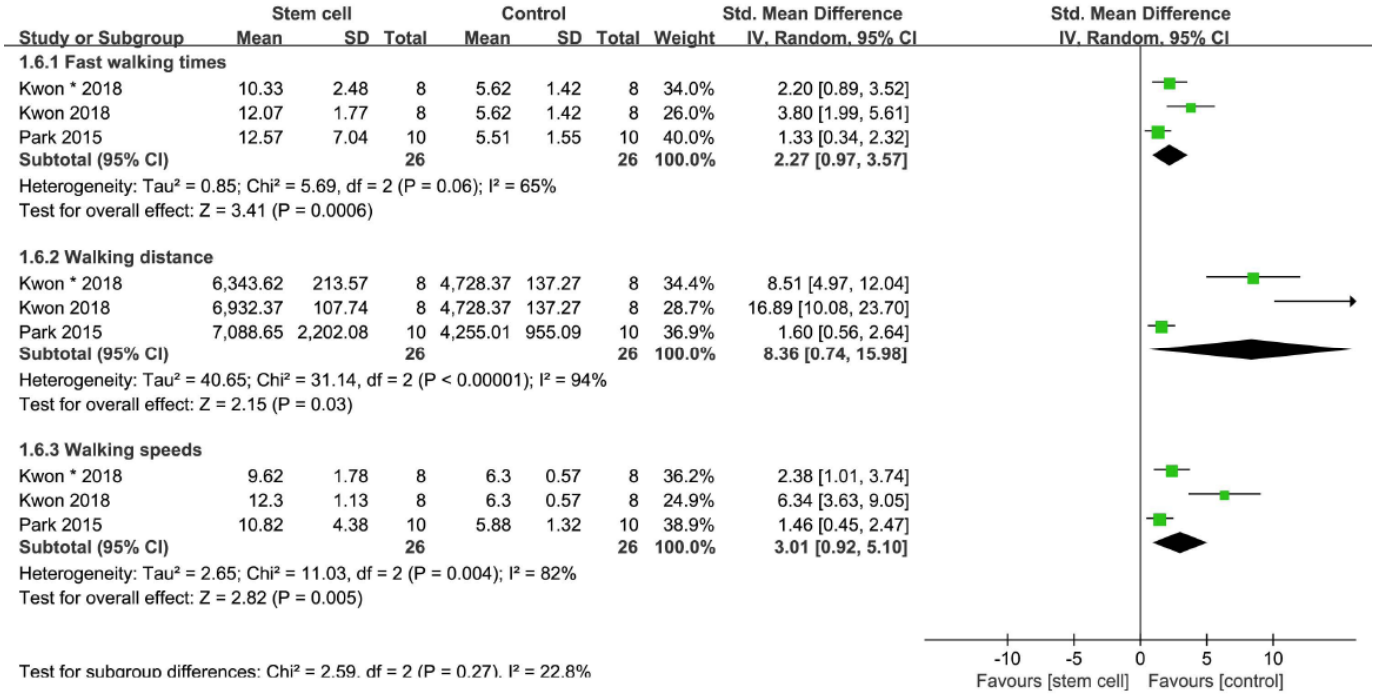

Fig. (7). Forest plot of the association between walking distance, fast walking time and walking speed.

4. DISCUSSION

Rotator cuff disorder is one of the most common diseases with about 21% in the general population who suffered pain and limitation of motion [2]. The most common age is between 40-59 years, posing a substantial socioeconomic burden [45]. Healing of the tendon-to-bone insertion is usually characterized by disorganized scar formation and a lack of a fibro-cartilaginous transition between the tendon and bone. Thus, re-rupture after surgical repair frequently occurred and reached a rate as high as 20-60% [46]. Recently, biological therapies using stem cells to boost rotator cuff healing has become a hot researched topic. Mesenchymal stem cells are multipotent fibroblast-like cells that are capable of differentiating into multiple cell types including osteoblasts, adipocytes, and chondrocytes [47]. Many studies have focused on the application of mesenchymal stem cell with or without augments of other complex treatments for rotator cuff repair. Our meta-analysis including 22 studies provided evidence that stem cells can improve the repair of the rotator cuff disorders by histological and biomechanical analyses.

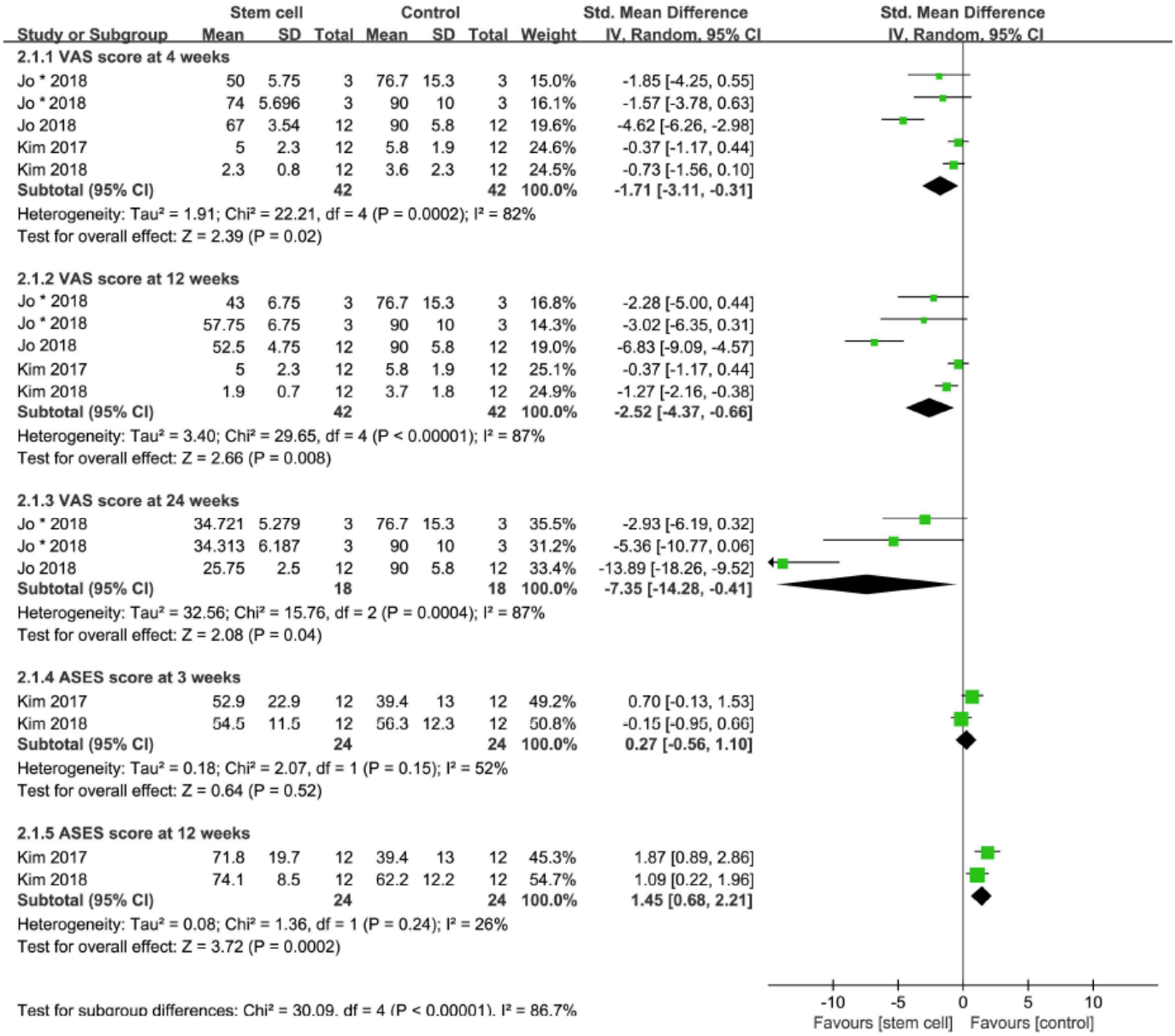

Fig. (8). Forest plot of the association between stem cell group and VAS score and ASES score.

Currently, stem cell therapy in combination with hard scaffold or hydrogel showed positive effects on rotator cuff healing. Stem cells have the ability to self-replicate through mitosis and reserve the capacity to differentiate into mature committed cells of various lineages [48-50] and have been applied to facilitate the regeneration of many different types of tissues such as bone, adipose, cartilage, ligament, and tendon [51-53].

The optimistic criteria for assessing rotator cuff repair are biomechanical evaluation and scoring. For the biomechanical test, the ultimate load and stiffness are available in 4 studies [26, 29, 31, 35]. Unfortunately, with regard to ultimate load and stiffness, the stem cell group was comparable to the control group. The reasons for the negative comparison might be: 1) Low number of implanted cells; 2) The implanted cells were not delivered to the interface between the healing tendon and bone [29].

Two main scoring systems, VAS and ASES score, were evaluated in the study. Our meta-analysis showed that ASES score in the stem cell group was higher than that in the control group at 3 months; however, no significant difference was detected between the two groups. In addition, stem cells-based therapy could relieve shoulder pain (VAS score) at 1, 3, and 6 months. Taken together, stem cell treatment for rotator cuff disease is safe and effective with evidence of relieved pain.

Motion analyzes including walking distance, fast walking time, and mean walking speed were conducted at different time points. Our results revealed that walking distance, time, and speed in the stem cell group were higher than those in the control group. Although these analyzes have still not proved to be as superior as mechanical testing, motion analyzes are potentially important parameters to assess the therapeutic effect of the rotator cuff tear [54-56].

For the clinical application of stem cells in patients, several major concerns need to be addressed. Currently, the two most researched and applied stem cells types for rotator cuff repair are BMSCs and ADSCs because of their relatively easier accessibility and abundant sources. However, these cells were frequently found to differentiate towards osteoblasts or adipocytes after *in vivo* transplantation and form ectopic ossified or adipose tissues, which even worsen the healing. Subsequently, the autologous application of some other adult stem cells, such as TSPCs, requires additional operation to harvest tendon biopsy that usually causes donor-site morbidity [57]. Regarding the application of embryonic stem cells and induced pluripotent stem cells, ethical concerns and safety problems with respect to tumorigenicity are expected to be overcome [58].

Nevertheless, this investigation is not without limitations and caveats. First, only 3 of the 22 included studies include human data, which are preferred for clinical decision making since it can avoid possible biases and confounding factors to the greatest extent. Second, by using a method of traditional meta-analysis, we could only pool some important outcomes of interest, some other results were impossible because of the insufficient data. Third, due to the small number of studies in the analysis, sensitivity analysis and publication bias (Egger' test or construction of funnel plot) was not conducted for secondary outcomes of interest. Fourth, the lack of some important characteristics in several studies poses a barrier to more detailed subgroup analysis. Last but not least, the results of several subgroup analyses showed higher heterogeneity, which may weaken the strength of our conclusion.

CONCLUSION

This meta-analysis of 22 studies demonstrates that stem cells improve the repair of rotator cuff injuries. Our further study will focus on the comparison between the improvements by different types of stem cells, then more articles must be included, and similar criterion must be found as a standard to compare between different articles. And other impact factors such as scaffold and growth factors can also be included in the comparison. Additional larger-scale and prospective studies are still needed to confirm our results.

LIST OF ABBREVIATIONS

ADSC	=	Adipose-derived stem cell
ASES	=	American shoulder and elbow surgeons score
BMAC	=	Bone marrow aspirate concentrate
BMP2	=	Bone morphogenetic protein 2
BMSC	=	Bone marrow-derived stem cell
CI	=	Confidence interval
GelMA	=	Gel-methacrylic anhydride
MicroCT	=	Microcomputed tomography
PCL	=	Polycaprolactone
PDGF	=	Platelet-derived growth factor
PDRN	=	Polydeoxyribonucleotides
PLGA	=	Poly (lactic-co-glycolic acid)
PNEA-mPh	=	Polyphosphazene poly [(ethyl alanato) 1 (p-methyl phenoxy) 1] phosphazene
PRISMA	=	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRP	=	Platelet rich plasma
SMD	=	Standardized mean difference
SPADI	=	Shoulder pain and disability index
TGF-β	=	Transforming growth factor beta
TOB 1	=	Transducer of ERBB2, 1
TSPC	=	Tendon stem/progenitor cell
UCB-MSC	=	Umbilical cord blood-derived mesenchymal stem cell
VAS	=	Visual analog scale score

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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