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Review

# Is implantation of autologous chondrocytes superior to microfracture for articular-cartilage defects of the knee? A systematic review of 5-year follow-up data

Yuyan Na[a,1], Yuting Shi[b,1], Wanlin Liu[c], Yanbo Jia[a], Lingyue Kong[a], Ting Zhang[a], Changxu Han[a,**], Yizhong Ren[a,*]

[a] Department of Arthroscopy and Sports Medicine, The Second Affiliated Hospital of Inner Mongolia Medical University, Huimin District, Hohhot, 010000, Inner Mongolia Autonomous Region, China
[b] Cardiac Function Department, Cadre Health Care Center, Inner Mongolia Autonomous Region People's Hospital, Saihan District, Hohhot, 010000, Inner Mongolia Autonomous Region, China
[c] Department of Pediatric Orthopedics, The Second Affiliated Hospital of Inner Mongolia Medical University, Huimin District, Hohhot, 010000, Inner Mongolia Autonomous Region, China

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ABSTRACT

*Background:* Autologous chondrocyte implantation (ACI) and microfracture are two of the main surgical treatment options for articular cartilage lesions of the knee. Consensus regarding the best clinical options to repair knee cartilage lesions is lacking. We undertook a systematic review to clarify the clinical efficacy of ACI and microfracture at minimum mean 5-year follow-up.

*Methods:* A literature search was conducted using the MEDLINE, Embase and Cochrane Library databases up to August 2018. Only comparative clinical studies of ACI and microfracture for the treatment of articular cartilage lesions of the knee with level I/II evidence were included. Clinical outcomes and the prevalence of treatment failure from each study were extracted and compared. The methodological quality of the included studies was analyzed by means of the PEDro scale.

*Results:* Five comparative studies (three randomized controlled trials and two prospective cohort studies) met our eligibility criteria. ACI and microfracture elicited significant improvement in clinical outcomes after 5 years. However, better clinical results with significant differences were found with modified versions of ACI (ACI with a modified collagen membrane [ACI-C] or matrix-applied chondrocyte implantation [MACI]) than with microfracture as determined by the Knee Injury and Osteoarthritis Outcome Score, activities of daily living assessment, Tegner Activity Scale score, and the International Knee Documentation Committee objective and subjective scores. No significant difference was observed in the treatment failure rate between these two methods within a particular study.

*Conclusions:* Currently, the best-available evidence suggests that some clinical outcomes of articular cartilage lesions of the knee treated with modified versions of ACI (ACI-C or MACI) can significantly improve patient outcomes at the mid-term follow-up of 5 years compared with those obtained using microfracture.

## 1. Introduction

Lesions of articular cartilage have a high prevalence. Curl and colleagues reported that 63% of patients had cartilage injuries in a retrospective study of 31,516 knee arthroscopies [1]. Widuchowski and coworkers found that 60% of patients who suffered from knee pain had defects of articular cartilage in a retrospective study of 25,124 knee arthroscopies [2]. Injury to articular cartilage can cause chronic pain, recurrent effusions, and joint dysfunction [3]. Despite worldwide efforts, no procedure can reproducibly regenerate normal hyaline cartilage due to its poor intrinsic regenerative capacity [4,5].

Different surgical treatments have been described for symptomatic

* Corresponding author. No.1 Yingfang Road, Huimin District, Hohhot, 010000, Inner Mongolia Autonomous Region, China.
** Corresponding author. No.1 Yingfang Road, Huimin District, Hohhot, 010000, Inner Mongolia Autonomous Region, China.
*E-mail addresses:* namedical@sina.com (Y. Na), 768088139@qq.com (Y. Shi), 15024979153@163.com (W. Liu), 870032574@qq.com (Y. Jia), 15591868680@163.com (L. Kong), 364522490@qq.com (T. Zhang), 671025003@qq.com (C. Han), 18004876325@163.com (Y. Ren).
[1] These authors contributed equally to this work.

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full-thickness chondral defects, such as stimulation of bone marrow through microfracture, regenerative approaches through implantation of cultured autologous chondrocytes, transplantation of autologous osteochondral tissue, and simple arthroscopic debridement [6]. Among the available treatments, ACI and microfracture are the cartilage-repair methods used most frequently.

ACI was first described by Brittberg and colleagues in 1994. ACI is used more frequently for larger lesions and is a three-stage procedure [7,8]: (i) acquisition of normal cartilage tissue during arthroscopy, (ii) culture of chondrocytes in the laboratory and (iii) transplantation of cultured chondrocytes into the defect for development into hyaline-like cartilage.

Microfracture was first described by Steadman and colleagues [9] and involves debridement of the defect and perforation on the subchondral bone [9]. Multipotent mesenchymal stem cells, platelets, and growth factors are recruited to produce fibrocartilage filling from the condyle to the defect through perforation. This method has the advantages of a minimally invasive approach, low costs, and technical simplicity [10,11].

Despite several studies and systematic reviews focusing on the treatment comparison between ACI and microfracture for articular cartilage lesions of the knee, consensus on the best treatment strategy is absent due to a lack of high-quality evidence and long-term research. In some studies, microfracture has been rated as the first-line option with good short-term clinical outcomes, especially for smaller lesions of articular cartilage [9,12–14]. However, recent studies have demonstrated that clinical outcomes may worsen $\geq 5$ years after microfracture, especially for larger articular cartilage lesions of the knee [13,15,16].

Saris and colleagues [17] showed the safety of matrix-applied chondrocyte implantation (MACI) and clinically better outcomes of MACI *versus* microfracture for symptomatic cartilage defects of the knee $\geq 3\ cm^2$. Knutsen carried out a multicenter randomized trial comparing the two methods with long-term follow-up at 14–15 years [18]. They found no significant differences with respect to the clinical functional score between the two methods.

In consideration of the lack of clarity surrounding the treatment options based on the studies mentioned above, we undertook a systematic review. We aimed to identify high-quality studies (level of evidence (LoE): I and II) with a minimum mean follow-up of 5 years. In this way, we aim to provide an update on the most appropriate treatment option for articular cartilage defects of the knee.

## 2. Methods

### 2.1. Search strategy

This study was reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR (assessing the methodological quality of systematic reviews) guidelines. A literature search was conducted in the MEDLINE, Embase and Cochrane Library databases on 20 August 2018. The following key words were used for searches: “microfracture”, “chondrocyte”, and “knee”. In addition, a manual search of the references of the included studies was performed to ensure that no eligible studies were missed.

### 2.2. Inclusion and exclusion criteria for studies

The inclusion criteria were (i) comparative clinical studies (randomized controlled trials [RCTs] and prospective comparative studies) of ACI and microfracture for articular cartilage lesions of the knee, (ii) studies with LoE I and II, (iii) studies with follow-up of 5 years, (iv) studies with full text available, and (v) studies published in English.

The exclusion criteria were (i) studies that included pediatric and adolescent populations (younger than 16 years) and (ii) studies that reported 5-year results were included only for consecutive studies with multiple follow-up periods.

### 2.3. Quality assessment

The methodological quality of the included studies was assessed using the Physiotherapy Evidence Database (PEDro) scale. A “yes” is equivalent to one point on the scale and is only assigned if the criteria are specifically stated within the text. A “no” is assigned to categories not specifically stated within the text. Using the PEDro scale for assessment, the articles with more “yes” scores are of higher quality given the scale of the assessment. The modified Coleman Methodology Score was also utilized to quantify the degree of possible bias. Each included study was scored for ten criteria to give a total score between 0 and 100. A higher score represents a better study design that largely avoids the influence of different biases and confounding factors. In that case, the analysis would be performed independently by two evaluators and disagreements resolved by discussion and consensus.

### 2.4. Data collection

The following data were collected from each included study by two independent reviewers: first author, publication year, sample size of each group, mean age, LoE, and follow-up period.

The following clinical outcome measures were collected and compared: the Tegner Activity Scale (TAS) score, Lysholm Knee Scoring Scale (LKSS), visual analog scale (VAS) pain score, International Knee Documentation Committee (IKDC) subjective score, Knee Injury and Osteoarthritis Outcome Score (KOOS), Hospital for Special Surgery (HSS) score and the Short Form (SF)-36 physical component score. The characteristics of cartilage defects (size, site, and grade of lesion) were extracted, as well as the prevalence of treatment failure.

The reviewers were not blinded to information on authors, journal of publication, or source of financial support. The quality of the methodology was evaluated for each study. Disagreements were discussed and resolved by referencing the original article.

## 3. Results

Because of the heterogeneity of the studies included in this review, a meta-analysis was not carried out, and data are summarized and expressed in tables as presented in the original articles.

### 3.1. Search results

The literature search in MEDLINE, Embase and the Cochrane Library yielded 679 articles, and 551 potentially relevant articles were identified after duplicates had been removed. After screening the titles and abstracts, 514 records were eliminated, thereby leaving 37 studies for further review. Two studies included the same cohort of patients at 5 years and 14.5 years postoperatively, and the longer-term follow-up of 14.5 years was excluded according to the criteria of the present study.

After application of inclusion and exclusion criteria, five comparative studies [19–23] (three RCTs and two prospective cohort studies) were identified in this systematic review. A PRIMSA flow diagram is presented in Fig. 1.

### 3.2. Patient demographics and characteristics of cartilage defects

Detailed information regarding the included studies (first author, publication year, sample size of each group, mean age, sex, cartilage-defect characteristics, LoE) is presented in Table 1.

The five articles included in this systematic review involved 448 patients, and there was a predominance of male patients in all studies. The mean age of patients ranged from 25.1 years to 35.0 years. Three studies utilized periosteum-based ACI (ACI-P), one study employed ACI with a modified collagen membrane (ACI-C), and one study utilized matrix-based ACI (MACI). The included studies involved 214 patients

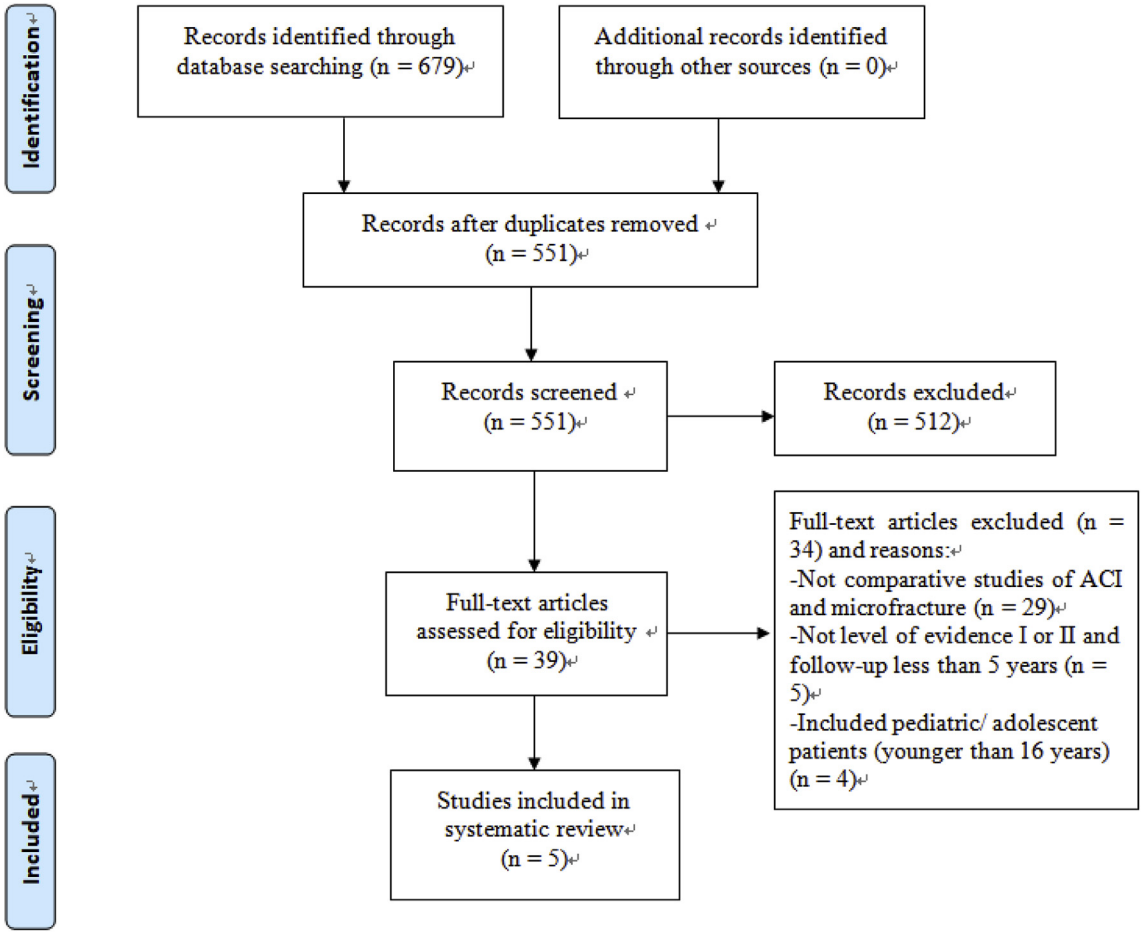


**Fig. 1.** PRISMA flowchart of literature search.

treated by ACI, with lesion sizes ranging from 1.5 $cm^2$ to 5.1 $cm^2$, and 234 patients treated with microfracture, with lesion sizes ranging from 1.0 $cm^2$ to 4.9 $cm^2$. Most lesions were found on the medial femoral condyle. Cartilage lesions were classified by Outerbridge grade or International Cartilage Repair Society (ICRS) grade. Typically, lesions were Outerbridge grade III/IV or ICRS grade III/IV, although 4% of lesions in the study by Knutsen et al. were graded as Outerbridge grade II.

### 3.3. Quality assessment

The methodological quality of the included studies was assessed by the PEDro scale and the modified Coleman score (Table 2). Each of the studies received scores of at least 6. Given the scores as assessed by the

**Table 1**
Patient demographics and characteristics of cartilage defects.

| Author (year) | Treatment | No. of patients | Mean age of patients (years) | Male:female ratio | Defect characteristics | | | LoE |
|---|---|---|---|---|---|---|---|---|
| | | | | | size, mean (SD), $cm^2$ | Lesion site, n | Lesion grade, n (%) | |
| Knutsen 2007 | ACI-P | 40 | 33.3 | 48M:32F | 5.1 | MFC: 34; LFC: 6 | Outerbridge grade III or IV, 96; grade II, 4 | I |
| | MF | 40 | 31.1 | | 4.5 | MFC: 36; LFC: 4 | | |
| Kon 2009 | ACI-C | 40 | 29.0 | 60M:20F | 2.2 (0.75) | MFC: 26; LFC: 12; T: 2 | grade III or IV (not specified) | II |
| | MF | 40 | 30.6 | | 2.5 (0.79) | MFC: 28; LFC: 10; T: 2 | | |
| Vanlauwe 2011 | ACI-P | 51 | 33.9 | 76M:42F | 3.5 | FC: 51 | ICRS grade III,18; grade IV, 82 | I |
| | MF | 61 | 33.9 | | 2.3 | FC: 51 | ICRS grade III,26; grade IV, 74 | |
| Lim 2012 | ACI-P | 18 | 25.1 | 27M:20F | 2.84 | MFC: 13; LFC: 5 | Modified Outerbridge grade III or IV | II |
| | MF | 30 | 32.9 | | 2.77 | MFC: 23; LFC: 7 | | |
| brittberg 2018 | MACI | 65 | 35.0 | 82M:46F | 5.1 (3) | MFC: 48; LFC: 13; T: 4 | Outerbridge Grade III, 29; Grade IV, 71 | I |
| | MF | 63 | 34.0 | | 4.9 (2) | MFC: 44; LFC: 15; T: 4 | Outerbridge Grade III, 19; Grade IV, 81 | |

ACI, autologous chondrocyte implantation; MF, microfracture.
MFC, medial femoral condyle; LFC, lateral femoral condyle; FC, femoral condyle; T, trochlea.
LoE, Level of evidence; ICRS: International Cartilage Repair Society.

**Table 2**
Quality assessment of included studies.

| Author | I | II | III | IV | V | VI | VII | VIII | IX | X | XI | Total score | Coleman Score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Knutsen et al. | Y | Y | N | Y | N | N | N | Y | Y | Y | Y | 7 | 90 |
| Kon et al. | Y | N | N | Y | N | N | N | Y | Y | Y | Y | 6 | 83 |
| Vanlauwe et al. | Y | Y | Y | Y | Y | N | N | Y | Y | Y | Y | 9 | 89 |
| Lim et al. | Y | Y | Y | Y | Y | N | Y | N | Y | Y | Y | 9 | 84 |
| Brittberg et al. | Y | Y | Y | Y | Y | N | N | Y | Y | Y | Y | 9 | 89 |

I = Eligibility criteria specified; II = Random allocation of subjects; III = Concealed allocation of subjects.
IV = Groups similar at baseline; V = Subject blinding; VI = Therapist blinding; VII = Assessor blinding.
VIII = Outcome measures obtained from > 85% of subjects; IX = Treatment received or gave intention to treat.
X = Between-group statistical comparison; XI = Within-group statistical comparison; Y = Yes; N = No.

**Table 3**
Summary of clinical-outcome measures.

| Author (year) | Follow-up, mean | Clinical-outcome measures |
|---|---|---|
| Knutsen 2007 | 5 y | TAS: Improvement in activity level after 5 years for ACI (P = 0.007) and MF (P = 0.002).<br>LKSS: Significant improvement from baseline for ACI and MF after 2 (P < 0.003, P < 0.001, respectively) and 5 years (P < 0.05 for both).<br>VAS: Significant reduction in pain from baseline for ACI and MF after 2 (P < 0.001 both) and 5 years (P < 0.05 for both).<br>SF-36 physical function: Greater improvement from baseline for MF compared with ACI after 2 years (P = 0.01) but not after 5 years (P = 0.054) |
| Kon 2009 | 5 y | TAS: Improvement in activity level for ACI and MF after 2 (P < 0.001 for both) and 5 years (P < 0.001 for both), whereas it worsened for MF at 5-year follow-up.<br>IKDC: Significant improvement for the IKDC subjective and objective scores from before surgery for ACI (P < 0.001 for both) and MF (P < 0.001 for both) after 5 years, but a higher improvement in the IKDC subjective score (P = 0.003) and objective score (P < 0.001) was observed for ACI at 5-year follow-up |
| Vanlauwe 2011 | 5 y | KOOS: The mean change from baseline in KOOS was not different between CCI (18.84 ± 3.58) and MF (13.21 ± 5.63) after 5 years (P = 0.116). |
| Lim 2012 | 5.7 y | TAS: Improvement in activity level after 5 years for ACI (P < 0.001) and MF (P < 0.001).<br>LKSS: Significant improvement from before surgery for ACI (P < 0.001) and MF (P < 0.001) after 5 years.<br>HSS: Significant improvement from before surgery for ACI (P < 0.001) and MF (P < 0.001) after 5 years. |
| Brittberg 2018 | 5 y | KOOS: Improvement in MACI over MF with regard to the co-primary endpoint of KOOS pain and function scores (P = 0.022). Improvements in activities of daily living remained significantly longer (P = 0.007) in MACI. Significantly better improvements from baseline to year-5 were observed for MACI for the modified Cincinnati Knee Rating System score (P = 0.035), 12-Item Short Form Health Survey (SF-12) physical dimension (P = 0.025), and the EuroQol 5 Dimensions Visual Analog Scale (EQ-5D VAS) score (P = 0.043). |

ACI, autologous chondrocyte implantation; MF, microfracture.
VAS, visual analog scale; SF-36, Short-form 36; HSS, Hospital For Special Surgery.
IKDC, International Knee Documentation Committee; KOOS, Knee Injury and Osteoarthritis Outcome Score; TAS, Tegner Activity Scale; LKSS, Lysholm Knee Scoring Scale.

PEDro scale, all included studies are of moderate-to-high quality. All level of evidence I studies presented a high modified Coleman score (≥89), while the Coleman score in the level of evidence II studies was lower.

### 3.4. Measures of clinical outcome

Measures of clinical outcome are presented in Table 3, which shows direct comparisons between the ACI and microfracture. Superior clinical outcomes were observed in modified ACI techniques ACI-C and MACI but not ACI-P when compared to microfracture.

The study by Brittberg and colleagues noted an improvement using MACI compared with microfracture with regard to the coprimary endpoint of pain and function using the KOOS, and it was clinically and statistically significant (P = 0.022). Additionally, improvements in the activities of daily living (ADL) remained significant when MACI was employed compared with when microfracture was used (P = 0.007). Brittberg and coworkers also observed significantly better improvements from baseline to year 5 favoring MACI using the modified Cincinnati Knee Rating System score (P = 0.035), the physical dimension of the 12-item Short Form Health Survey (SF-12) (P = 0.025), and the EuroQol 5 Dimensions Visual Analog Scale score (P = 0.043). After a 5-year follow-up, although there was a significant improvement compared to baseline in the TAS score, LKSS, VAS pain assessment, SF-36 questionnaire, IKDC subjective score, and HSS score in both the MACI and microfracture groups, a significant difference between the two methods was not observed. Additionally, Brittberg and coworkers suggested that symptomatic cartilage defects in the knee ≥3 $cm^2$ treated by MACI were clinically and significantly improved at 5 years compared to those after microfracture treatment.

Kon and colleagues suggested that the ACI and microfracture groups showed significant improvement in IKDC subjective and objective scores as well as sporting activity (evaluated using the TAS score) from before surgery to the 5-year follow-up. When comparing the two procedures, greater improvements in the IKDC subjective score (P = 0.003) and objective score (P < 0.001) were observed for ACI-C at the 5-year follow-up. Additionally, a return to sporting activity was delayed in the microfracture group at the 5-year follow-up.

Knutsen and colleagues found that the ACI and microfracture groups had improved LKSS, TAS score, and SF-36 physical functioning score and decreased VAS pain scores at the 5-year follow-up, but neither method improved patient outcome at a significantly different rate than the other. Knutsen and coworkers suggested that being under 30 years of age resulted in a better clinical outcome than that for older patients after a 5-year (P = 0.013) follow-up for both treatment methods.

Lim and colleagues reported that the ACI and microfracture groups experienced improvements in the TAS score, LKSS, and HSS score from before surgery to the 5-year follow-up. Likewise, neither group improved outcome to a significantly greater extent.

In the study by Vanlauwe and coworkers, the ACI and microfracture groups experienced improvements in overall KOOS from before surgery to the 5-year follow-up, but the mean change from baseline in overall scores was not significantly different between the two groups (P = 0.116). Vanlauwe and colleagues suggested that in patients with

**Table 4**
Prevalence of treatment failure.

| Author (year) | Treatment | Failure | Definition of failure |
|---|---|---|---|
| Knutsen 2007 | ACI-P | 9/40 (22.5%) | Reoperation because of symptoms due to a lack of healing of the treated defect |
| | MF | 9/40 (22.5%) | |
| Kon 2009 | ACI-C | 0/40 (0) | Reoperation because of symptoms due to primary defects |
| | MF | 1/40 (2.5%) | |
| Vanlauwe 2011 | ACI-P | 7/51 (13.7%) | Reintervention affecting > 20% of the index lesion |
| | MF | 10/61(16.4%) | |
| Lim 2012 | ACI-P | 2/18 (11.1%) | Reoperation owing to recurrent knee pain, limitation of motion, and persistent articular effusion |
| | MF | 3/30 (10.0%) | |
| Brittberg 2018 | MACI | 1/65 (1.5%) | After week-24, the result was identical or worse than at baseline, < 10% improvement in the KOOS pain subscale, physician-diagnosed failure excluding all other potential causes, and the physician deciding that surgical retreatment was indicated |
| | MF | 3/63 (4.8%) | |

ACI, autologous chondrocyte implantation; MF, microfracture.
KOOS, Knee Injury and Osteoarthritis Outcome Score.

symptom onset < 3 years, the overall KOOS (P = 0.026) showed a statistically significant and clinically relevant difference in improvement when using ACI compared to that using microfracture at the 5-year follow-up.

### 3.5. Treatment failure

"Treatment failure", defined as a need for reoperation for the original cartilage defect, was reported in some of the included studies. Brittberg and colleagues defined "treatment failure" as a result that was identical or worse than that at baseline; a < 10% improvement in the KOOS pain subscale; physician-diagnosed failure excluding all other potential causes; or the physician deciding that surgical retreatment was needed. Among the ACI groups, the reported failure rates were 22.5%, 0%, 13.7%, 11.1%, and 1.5%, and the corresponding reported failure rates among the microfracture groups was 22.5%, 2.5%, 16.4%, 10.0% and 4.8%, respectively (Table 4). No significant difference was observed in the prevalence of treatment failure between ACI and microfracture within a particular study. Vanlauwe and coworkers found that male patients had a lower prevalence of failure than female patients did in the ACI group (P = 0.007) and microfracture group (P = 0.010).

## 4. Discussion

Different surgical options have been proposed to treat articular cartilage defects of the knee, but their indications and results are controversial. Some surgeons may make their treatment decisions based on their preference instead of on evidence-based medicine.

Our systematic review was based on data from five high-quality RCTs of two methods used for the treatment of articular cartilage defects: ACI and microfracture. In our systematic review, both methods elicited significant improvement in clinical outcomes from before surgery to the 5-year follow-up. Nevertheless, superior clinical results were found with modified ACI (ACI-C orMACI) compared with those obtained using microfracture as assessed using the KOOS pain and function scores, ADL assessment, TAS score, and IKDC objective and subjective scores at a mid-term follow-up of 5 years. No significant difference was observed in the prevalence of treatment failure between the two treatment methods within a particular study.

Some scholars have suggested an influence of the site and size of the defect, as well as the sex and age of the patient, on clinical outcomes [24–28]. Microfracture had less favorable results if it was used to treat patellofemoral lesions, and ACI may be a better option for trochlear defects, as determined in the study by Kreuz and coworkers [25]. In our systematic review, only 12 patients had lesions on the femoral trochlea, and all remaining patients had lesions on the weightbearing surface of the medial or lateral femoral condyle, which hampered the comparison between lesions on the femoral trochlea and medial or lateral femoral condyle.

Bekkers and coworkers carried out a systematic review of four relevant LoE-1 studies. They concluded that lesions > 2.5 $cm^2$ should be treated with osteochondral autologous transplantation or ACI and that smaller lesions (< 2.5 $cm^2$) could be treated with microfracture. Mithoefer and colleagues [10,31] undertook a systematic review of the clinical efficacy of microfracture for articular cartilage defects of the knee and demonstrated better functional knee scores in lesions < 4 $cm^2$. Although two studies included in our systematic review treated patients with a mean lesion size > 4 $cm^2$, patients who underwent ACI did not have a lower failure rate at the 5-year follow-up (or even at the 14–15-year follow-up) than that of patients who underwent microfracture. However, in terms of clinical outcomes, one study included in our systematic review demonstrated that articular cartilage defects of the knee ≥ 3 $cm^2$ treated with MACI were clinically and significantly improved at 5 years compared with those treated by microfracture. Therefore, we suggest that clinically relevant articular cartilage defects of the knee ≥ 3 $cm^2$ should be treated cautiously with microfracture.

Apart from the site and size of the defect, age can also influence clinical outcomes [29–32]. Bekkers and coworkers demonstrated better clinical outcomes in patients under 30 years of age regardless of the treatment strategy. Additionally, microfracture and ACI seemed to be more effective in younger patients. In our systematic review, the age of patients between the two groups was not significantly different, which did not allow us to make comparisons of treatment choices based on age. In addition, Vanlauwe and colleagues found that male patients had a lower prevalence of treatment failure than female patients did in both the ACI group (P = 0.007) and microfracture group (P = 0.010).

ACI-P involves the use of an autologous periosteal patch, which has two main limitations: a risk of uneven distribution of cells and postoperative complications (e.g., periosteal hypertrophy) [33,34]. ACI-C involves the use of a bioabsorbable collagen membrane (type I/III) cover instead of an autologous periosteal membrane, and compared to ACI-P, ACI-C has demonstrated superior long-term clinical outcome and fewer complications, such as hypertrophy [35–37]. MACI was developed to address safety and efficacy concerns and to ensure the consistency of the product. MACI involves the use of a template with elastic properties so that it can conform to differently shaped defects and allows easy introduction into the joint *via* mini-arthrotomy or arthroscopy [38,39]. Modified ACI (ACI-C and MACI) also be superior to ACI-P in terms of treatment failure rates according to our results (ranging from 11.1% to 22.5% for ACI-P, 0% for ACI-C, and 1.5% for MACI), which is similar to the review by Oussedik et al., with failure rates ranging from 7% to 26% for ACI-P, 9%–13% for ACI-C, and 10% for MACI.

In our systematic review, one study each used ACI-P, ACI-C, and MACI. Superior clinical outcomes were demonstrated with ACI-C (KOOS pain and function scores, ADL) and MACI (TAS score, IKDC objective and subjective scores) from before surgery to the 5-year follow-up compared with those obtained using microfracture. However, with regard to ACI-P, we did not observe a statistically significant difference when compared with microfracture at the 5-year follow-up. Zeifang and coworkers found no significant difference between MACI and ACI-P with respect to the IKDC score, TAS score, or SF-36 score at the 12- and 24-month follow-up [40], but we found superior clinical outcomes in studies using ACI-C or MACI compared with those using ACI-P.

Oussedik and coworkers and Devitt and colleagues compared the efficacy of ACI and microfracture for articular cartilage lesions of the knee in a systematic review with follow-up from 6 months to 10 years of

included studies [41,42]. When considering the efficacy of treatment of cartilage injury, it is important not to focus solely on short-term outcomes but to also examine mid-term and long-term results. Kraeutler and coworkers undertook a systematic review of studies with a 5-year follow-up that was similar in design to our systematic review [43]. However, a new study that showed significant improvement using ACI compared with that obtained using microfracture in terms of KOOS pain and function scores and ADL was not included by Kraeutler and colleagues. Additionally, two of the five studies included in our systematic review using second-generation or third-generation ACI showed superior clinical outcomes. Hence, a modified version of ACI may have better mid-term clinical outcomes than those elicited by microfracture, which was not reported by Kraeutler et al.

Our systematic review had three main limitations. First, due to the lack of a consistent definition of "treatment failure" or "heterogeneity" (e.g., different generations of ACI, lesion size and male:female ratio) of the included studies, reliable survival analyses could not be carried out. Second, even though our systematic review reported promising mid-term results for ACI-C and MACI, the results for long-term follow-up are absent. The prevalence of treatment failure increased with time, and a significant difference was detected between both methods after a 14–15-year follow-up compared with that at the 5-year follow-up by Knutsen and coworkers, which emphasized the importance of long-term follow-up. Finally, a lack of standardized measures of clinical outcome, pain scores, definitions of treatment failure, and follow-up periods did not allow for pooling and comparison of the data.

## 5. Conclusion

Our systematic review of five comparative studies (three RCTs and two prospective cohort studies) compared the efficacy of two repair methods of articular cartilage defects, ACI and microfracture, at a mid-term follow-up period. Our results suggested that both methods can elicit significant improvement in clinical outcomes after 5 years. However, better clinical results with significant differences in KOOS pain and function scores, ADL assessments, TAS score, and IKDC objective and subjective scores were found in the groups treated with modified versions of ACI (ACI-C or MACI) than in those treated with microfracture. It is essential that future studies with longer term follow-up as well as a well-designed control group that was not treated with surgery be followed to determine the efficacy of modified ACI treatment.

## Ethical approval

Not applicable.

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## Author contribution

CH, YR, and YN conceived of and designed the study, performed the analysis, interpreted the results. YJ and LK performed the literature search and data extraction. YN and YS wrote the manuscript. WL and TZ revised the manuscript.

## Conflicts of interest

The authors declare that they have no competing interests.

## Research registration number

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## Guarantor

Yizhong Ren.

## Level of evidence

II.

## Provenance and peer review

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## Consent for publication

All authors have read the final manuscript and approved it for publication.

## Data statement

The data in our article is available.

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## Abbreviations

ACI: Autologous chondrocyte implantation; ACI-C: Second-generation ACI; MACI: Matrix-applied chondrocyte implantation; LoE: Level of evidence; RCTs: Randomized controlled trials; PEDro: Physiotherapy Evidence Database; TAS: Tegner Activity Scale; LKSS: Lysholm Knee Scoring Scale; VAS: Visual analog scale; IKDC: International Knee Documentation Committee; KOOS: Knee Injury and Osteoarthritis Outcome Score; HSS: Hospital for Special Surgery; SF: Short Form; ACI-P: First-generation ACI; ICRS: International Cartilage Repair Society; ADL: Activities of daily living.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.06.007.

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