Archives of Orthopaedic and Trauma Surgery (2023) 143:71–79
https://doi.org/10.1007/s00402-021-03990-1

ORTHOPAEDIC SURGERY

Efficacy and safety of autologous chondrocyte implantation for osteochondral defects of the talus: a systematic review and meta-analysis

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Received: 4 February 2021 / Accepted: 31 May 2021 / Published online: 14 June 2021

Abstract

Introduction Studies have reported various effects of autologous chondrocyte implantation (ACI) on osteochondral defects of the talus. Therefore, to assess the effectiveness of ACI for osteochondral defects of the talus, we used the meta-analytic approach.

Materials and methods Electronic databases PubMed, Embase, and the Cochrane Library were systematically searched to identify eligible studies from their inception until November 2020. The random-effects model was used to calculate the incidence of success rate and American Orthopaedic Foot and Ankle Society (AOFAS) score for patients after ACI treatment. Subgroup analyses were also conducted based on age, technique, indication, size, and follow-up duration.

Results For the final meta-analysis, we selected 23 case series studies with a total of 458 patients with osteochondral defects of the talus. Overall, after ACI for patients with osteochondral defects of the talus, we noted that the incidence of success rate was 89% (95% confidence interval (95% CI) 85%–92%; $P<0.001$). Moreover, after ACI for patients with osteochondral defects of the talus, the AOFAS score was 86.33 (95% CI 83.33–89.33; $P<0.001$). Subgroup analysis showed that the AOFAS score after ACI is significantly different when stratified by the mean age of the patients ($P=0.006$).

Conclusions This study revealed that the use of ACI could provide a relatively high success rate and improve the AOFAS score for patients with osteochondral defects of the talus, which should be recommended in clinical practice.

Keywords Autologous chondrocyte · Implantation · Osteochondral defects · Talus · Meta-analysis

Introduction

Ankle sprains as a common joint injury and nearly 27,000 injuries per day occurred in the United States [1]. Moreover, nearly 70% of sprains and fractures involving the ankle could cause osteochondral lesions [2]. The entire body weight was supported, and stabilisation by the ankle and the small area of distribution caused the joint to be sensible to shearing stresses [3]. Osteochondral defects of the talus contained the lesion in the subchondral bone and its overlying cartilage, and mostly osteochondral defects of the talus occurred after an ankle fracture or lateral ankle ligament rupture [2, 4]. Moreover, osteochondral defects could progress to cystic lesion and induce deep ankle pain during activity, prolonged swelling, diminished range of motion, and synovitis [5, 6].

Recently, autologous chondrocyte implantation (ACI) is widely used to cover the anatomical defects for repairing osteochondral defects, which is based on two-time surgical procedures. The first procedure includes revision arthroscopy of the joint with the lesion area as well as a trephine of healthy cartilage tissue and then graft obtained by stimulating chondrocyte mitosis. The second procedure is conducted by implant matrix using arthroscopy or arthrotomy of the medial malleolus to expose the injury area [7, 8]. The effectiveness of ACI for patients with osteochondral defects of the talus has already been demonstrated, whereas, the treatment effectiveness was variable across studies [9–31]. Therefore, this systematic review and meta-analysis aimed to assess the

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effectiveness of ACI for patients with osteochondral defects of the talus.

Methods

Data sources, search strategy, and selection criteria

This systematic review and meta-analysis were performed and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement [32]. Studies that assessed the effectiveness of ACI for patients with osteochondral defects of the talus were eligible in our study. Electronic databases PubMed, Embase, and the Cochrane Library were systematically searched to identify eligible studies using the following search terms until November 2020: ("Chondrocytes" AND "Transplantation, Autologous" OR "autologous chondrocyte transplantation" OR "autologous chondrocyte implantation") AND ("Ankle" OR "Ankle Joint" OR "Ankle injuries" OR "Talus" OR "talus" OR "talar"). Furthermore, the reference lists of potentially relevant reviews and original articles were also manually searched to identify any new eligible study.

The literature search and study selection were independently performed by two reviewers, and the inconsistency was settled by a group discussion. Studies were included if they met the following criteria: (1) patients: osteochondral defects of the talus; (2) intervention: ACI; (3) outcome: success rate (defined as American Orthopedic Foot and Ankle Society (AOFAS) score > 80) and AOFAS score; and (4) study design: case series and observational and randomised controlled trials.

Data collection and quality assessment

The data collection and quality assessment were independently conducted by two reviewers, and any disagreement between reviewers was settled by discussion mutually until a consensus was reached. The items collected from each study included the first author's name, publication year, country, evidence level, sample size, age, number of males and females, technique, first-line or revision ACI, subchondral bone grafting, indication, size, follow-up, success rate, assessment tool, and reported outcomes. The modified Coleman methodology score was determined for each study to assess the study quality and the different types of detected bias [33].

Statistical analysis

After ACI, the success rate and AOFAS score were assigned as categorical and continuous data, respectively. Then, the random-effects model was used to calculate the pooled incidence of success rate and AOFAS score [34, 35]. After this, I^2 and Q statistics were applied to assess the heterogeneity across the included studies, and significant heterogeneity was defined as $I^2 > 50.0\%$ or $P < 0.10$ [36, 37]. Sensitivity analyses for success rate and AOFAS score were also performed to assess the impact of a single study on the overall conclusion [38]. Subgroup analyses for success rate and AOFAS score were also performed based on age, technique, indication, size, or follow-up duration, and the interaction *P* test was performed to assess the difference between subgroups [39]. Furthermore, Funnel plot, Egger, and Begg tests were performed to assess publication bias for success rate and AOFAS score [40, 41]. All reported *P* values are two-sided, and a significant difference was defined as $P < 0.05$. The STATA software (version 10.0; Stata Corporation, College Station, TX, USA) was used to perform all of the analyses in this study.

Results

Literature search

By initial electronic searches, a total of 786 articles were identified, and 381 studies were retained after exclusion of the duplicate articles. After this, 311 studies were removed because of irrelevant topics. The remaining 70 studies were retrieved for further full-text evaluations, and 47 studies were excluded because of osteochondral defects in knee ($n = 21$), no sufficient data ($n = 15$), and other interventions ($n = 11$). After reviewing the reference lists of relevant studies, three potentially included studies were found, and all of these studies were included in electronic searches. Therefore, the remaining 23 studies were selected for final meta-analysis [9–31] (Fig. 1).

Study characteristics

Table 1 shows the characteristics of the included studies and patients. All of the 23 included studies were designed as case series, and a total of 458 patients with osteochondral defects of the talus were recruited. The sample size ranged from 7 to 46, and the follow-up duration ranged from 12.0 to 154.8 months. For all of the included studies, the evidence level was IV. Six studies applied periosteum-covered ACI, and the remaining 17 studies applied matrix-associated ACI. All of the included studies had a level of evidence of IV. The mean modified Coleman methodology score was 48.1, and the score in each study ranged from 35 to 65, which suggested that all of the included studies were of low to moderate quality.

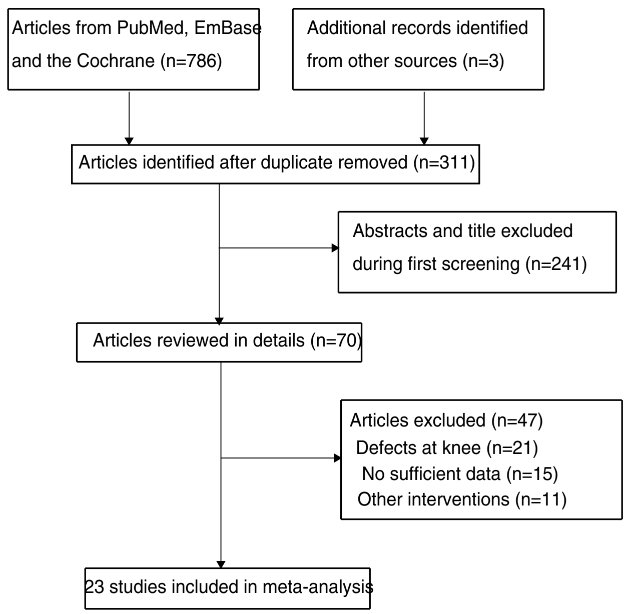

Fig. 1 The PRISMA flowchart for the literature search and study selection

Success rate

A total of 17 studies reported the incidence of success rate for patients after ACI. We noted that the pooled incidence for success rate was 89% (95% confidence interval (95%CI) 85%–92%; $P<0.001$; Fig. 2), and unimportant heterogeneity was detected across the included studies ($I^2=30.1\%$; $P=0.117$). Sensitivity analysis indicated that the incidence of success rate was robust after sequentially excluding individual study (Online Resource 1). Subgroup analysis indicated that the pooled incidence of success rate was > 80.0% in all subgroups, and age, technique, indication, size, or follow-up duration was not affecting the incidence of success rate (Table 2). Furthermore, a significant publication bias for success rate was found (P value for Egger: < 0.001; P value for Begg: 0.002; Online Resource 2), and the pooled incidence of success rate was not altered by adjusted using the trim and fill method [42].

AOFAS score

The AOFAS score for patients after ACI was reported in a total of 19 studies. We noted that the AOFAS score after ACI was 86.33 (95% CI 83.33–89.33; $P<0.001$; Fig. 3), and no evidence of heterogeneity was seen among the included studies ($I^2=0.0\%$; $P=0.603$). The pooled AOFAS score after ACI was stable after sequentially excluding single study (Online Resource 1). Subgroup analyses revealed that the pooled AOFAS score was lower when pooling studies for patients with chondral lesion (Table 2). Moreover, we noted that the AOFAS score could be affected after ACI for patients with osteochondral defects of the talus ($P=0.006$). There was no significant publication bias for the AOFAS score after ACI (P value for Egger: 0.794; P value for Begg: 0.069; Online Resource 2).

Adverse events

Ten out of the included studies reported complications after ACI [11–13, 15–18, 23–25, 28]. Six studies indicated no intraoperative or postoperative complications [11, 13, 15, 16, 24, 28]. Whittaker et al. reported one patient (10.0%) who presented with superficial infection of the ankle [12]. Schneider et al. reported two patients (10.0%) with anterior graft impingement, two patients (10.0%) with recurrent pain associated with hardware, and two patients (10.0%) who presented with clear failures combined with persistent pain and synovitis [18]. Lee et al. showed that the prevalence of nonunion and delayed unions of the osteotomy sites was 2.6% and 5.3%, respectively. Moreover, nine ankles (29.0%) sustained damaged medial malleolar cartilage [23]. Finally, Buda et al. reported three patients (15.0%) who presented with adhesions or joint effusion [25].

Discussion

The treatment effectiveness of ACI for patients with osteochondral defects of the talus has already been illustrated in numerous studies, while the effect was variable and not confirmed to date. This systematic review and meta-analysis was performed and assessed the effectiveness of ACI on the incidence of success rate and AOFAS score. A total of 458 patients with osteochondral defects of the talus were identified from 23 case series studies, and the characteristics of patients were broad across the included studies. We noted that the pooled success rate was high, and the AOFAS score was improved after ACI. Moreover, the AOFAS score after ACI for patients with osteochondral defects of the talus could be affected by age.

In a previous systematic review, 16 studies were identified and revealed that the ACI should be considered as a promising treatment for osteochondral and chondral defects of the talus [43]. Erickson et al. conducted a systematic review of 19 studies and found that there were no significant differences among the combination of open or arthroscopic matrix-associated ACI and periosteum-covered ACI for talar osteochondral lesions less than 2.5 cm^2 [44]. However, these two studies have just given the qualitative analysis for the included studies, and according to patients' characteristics, the quantitative analysis was not illustrated. Therefore, this systematic review and meta-analysis were performed to

Table 1 The baseline characteristics of identified studies and included patients

Study	Country	Evidence level	Sample size	Age (years)	Male/female	Technique	First-line or revision ACI	Subchondral bone grafting	Indication	Size (cm^2,mean or range)	Follow-up (months)	Success rate (%)	Assessment tool	Study quality
Giannini 2001 [9]	Italy	IV	8	28.0	4/4	P-ACI	First-line	NA	OCH	3.3	26.0	100.0	AOFAS	47
Dorotka 2004 [10]	Austria	IV	10	30.0	7/3	P-ACI	First-line	NA	CH	3.0	30.0	100.0	AOFAS	53
Giannini 2005 [11]	Italy	IV	16	30.5	11/9	M-ACI	First-line	NA	OCH	2.0	12.0	100.0	AOFAS	58
Whittaker 2005 [12]	UK	IV	10	42.0	7/3	P-ACI	Revision	NA	OCH	1.9	23.0	90.0	Modified Mazur, Schwartz Simon Score	65
Baums 2006 [13]	Germany	IV	12	29.7	5/7	P-ACI	Revision	Yes	CH/OCH	2.3	63.0	91.6	AOFAS, VAS	47
Caumo 2007 [14]	Italy	IV	41	35.2	30/11	M-ACI	First-line	Yes	CH	NA	12.0	92.8	AOFAS	53
Giannini 2008 [15]	Italy	IV	46	31.4	29/17	M-ACI	Both	NA	OCH	1.6	36.0	82.5	AOFAS	61
Giannini 2009 [16]	Italy	IV	10	25.8	5/5	P-ACI	First-line	NA	CH	3.1	120.0	90.0	AOFAS, MOCART	39
Nam 2009 [17]	USA	IV	11	33.0	5/6	P-ACI	Revision	NA	CH/OCH	2.1	38.0	81.2	Tegner, AOFAS; SSE, Finsen	41
Schneider 2009 [18]	Australia	IV	20	36.0	7/13	M-ACI	First-line	NA	OCH	2.3	21.1	85.0	AOFAS	57
Giza 2010 [19]	Australia	IV	10	40.2	5/5	M-ACI	Revision	NA	CH	1.3	24.0	50.0	AOFAS, SF-36	46
Lee 2010 [20]	Korea	IV	21	NA	NA	M-ACI	Revision	NA	OCH	1.4	12.0	95.2	AOFAS	49
Battaglia 2011 [21]	Italy	IV	20	35.0	14/6	M-ACI	First-line	Yes	OCH	NA	60.0	80.0	AOFAS	47

Table 1 (continued)

Study	Country	Evidence level	Sample size	Age (years)	Male/female	Technique	First-line or revision ACI	Subchondral bone grafting	Indication	Size (cm^2,mean or range)	Follow-up (months)	Success rate (%)	Assessment tool	Study quality
Haene 2012 [22]	Canada	IV	16	35.8	8/8	M-ACI	First-line	NA	OCH	> 1.5	49.2	62.5	AOFAS, SF-36, AAOS	37
Lee 2013 [23]	Korea	IV	38	35.0	33/5	M-ACI	First-line	NA	OCH	4.0	24.0	89.5	AOFAS	52
Kwak 2014 [24]	USA	IV	29	34.0	15/14	M-ACI	First-line	NA	OCH	2.0	70.0	96.6	AOFAS	48
Buda 2015 [25]	Italy	IV	40	31.4	25/15	M-ACI	First-line	Yes	OCH	1.7	48.0	100.0	AOFAS	53
Desando 2017 [26]	Italy	IV	7	31.2	4/3	M-ACI	First-line	NA	OCH	1.8	36.0	NA	AOFAS	35
Chan 2018 [27]	USA	IV	24	34.1	14/10	M-ACI	Both	NA	OCH	1.0–2.0	65.8	92.0	AOFAS	49
Pagliazzi 2018 [28]	Italy	IV	20	35.0	14/6	M-ACI	Revision	NA	OCH	> 1.5	87.2	90.0	AOFAS	41
Kreulen 2018 [29]	USA	IV	10	45.8	5/5	M-ACI	Revision	NA	OCH	1.3	84.0	100.0	SF-36, AOFAS	38
López-Alcorocho 2019 [30]	Spain	IV	24	31.0	14/10	M-ACI	First-line	NA	OCH	1.4	24.0	79.2	AOFAS	46
Lenz 2020 [31]	Australia	IV	15	36.0	4/11	M-ACI	First-line	NA	OCH	2.0	154.8	86.7	AOFAS, FAAM, VAS, MOCART	44

AAOS American Academy of Orthopaedic Surgeons, *ACI* autologous chondrocyte implantation, *AOFAS* American Orthopaedic Foot and Ankle Society, *CH* chondral, *FAAM* Foot and Ankle Activity Measurement, *M-ACI* matrix-associated autologous chondrocyte implantation, *MOCART* Magnetic Resonance Observation of Cartilage Repair Tissue, *NA* not available, *OCH* osteochondral, *P-ACI* periosteum-covered autologous chondrocyte implantation, *SSE* simplified symptomatology evaluation, *VAS* visual analogue scale

Fig. 2 Effect of ACI on the incidence of success rate

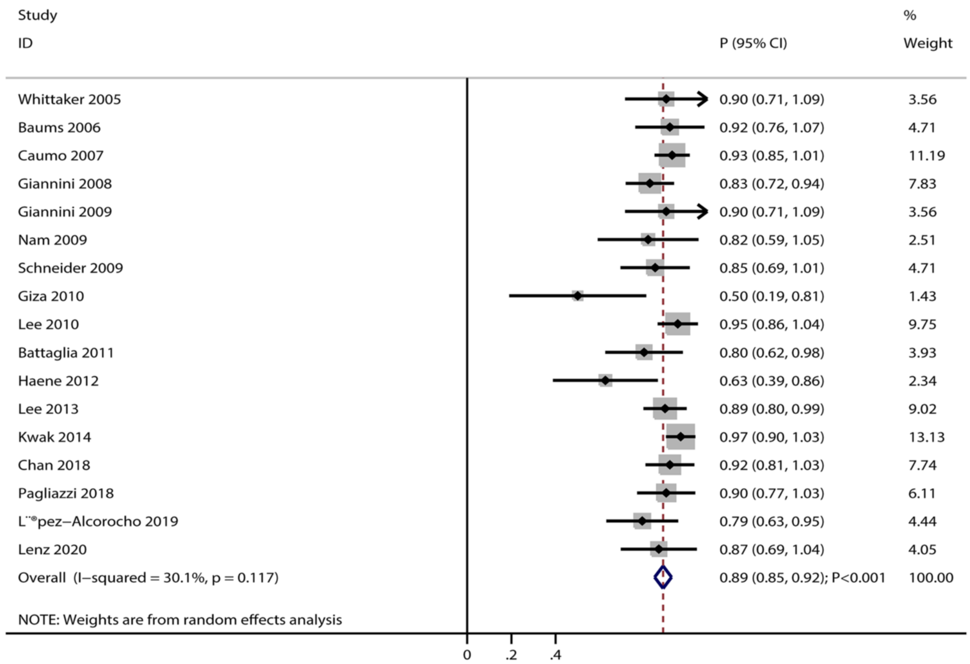

Table 2 Subgroup analyses for success rate and American Orthopaedic Foot and Ankle Society

Outcomes	Factors	Groups	Number of studies	Proportion or mean and 95% CI	*P* value	I^2 (%)	$P_{Q\ statistic}$	P value between subgroups
Success rate	Age (years)	≥ 35.0	9	0.86 (0.79–0.92)	< 0.001	37.0	0.123	0.277
		< 35.0	7	0.90 (0.85–0.95)	< 0.001	21.4	0.266	
	Technique	P-ACI	4	0.89 (0.80–0.98)	< 0.001	0.0	0.916	0.871
		M-ACI	13	0.88 (0.83–0.93)	< 0.001	46.3	0.034	
	Indication	OCH	12	0.89 (0.84–0.93)	< 0.001	29.1	0.160	0.975
		CH	3	0.83 (0.64–1.00)	< 0.001	70.7	0.033	
		Both	2	0.89 (0.76–1.00)	< 0.001	0.0	0.485	
	Size (cm^2)	≥ 2.0	7	0.92 (0.88–0.97)	< 0.001	0.0	0.675	0.468
		< 2.0	6	0.86 (0.78–0.94)	< 0.001	53.4	0.057	
	Follow-up (months)	≥ 36.0	10	0.88 (0.83–0.94)	< 0.001	29.0	0.178	0.987
		< 36.0	7	0.88 (0.82–0.95)	< 0.001	41.3	0.116	
AOFAS	Age (years)	≥ 35.0	8	80.15 (74.81–85.48)	< 0.001	0.0	0.494	0.006
		< 35.0	11	89.20 (85.57–92.84)	< 0.001	0.0	0.997	
	Technique	P-ACI	6	85.73 (79.31–92.15)	< 0.001	37.1	0.159	0.787
		M-ACI	13	85.96 (81.95–89.98)	< 0.001	0.0	0.798	
	Indication	OCH	14	87.66 (84.11–91.21)	< 0.001	0.0	0.818	0.101
		CH	3	79.60 (68.13–91.06)	< 0.001	25.7	0.260	
		Both	2	87.42 (79.67–95.17)	< 0.001	0.0	0.659	
	Size (cm^2)	≥ 2.0	10	88.52 (84.62–92.42)	< 0.001	0.0	0.993	0.196
		< 2.0	7	82.63 (75.08–90.18)	< 0.001	43.6	0.100	
	Follow-up (months)	≥ 36.0	11	87.83 (82.68–92.97)	< 0.001	0.0	1.000	0.483
		< 36.0	8	84.52 (78.66–90.39)	< 0.001	50.6	0.048	

AOFAS American Orthopaedic Foot and Ankle Society, *CH* chondral, *M-ACI* matrix-associated autologous chondrocyte implantation, *OCH* osteochondral, *P-ACI* periosteum-covered autologous chondrocyte implantation

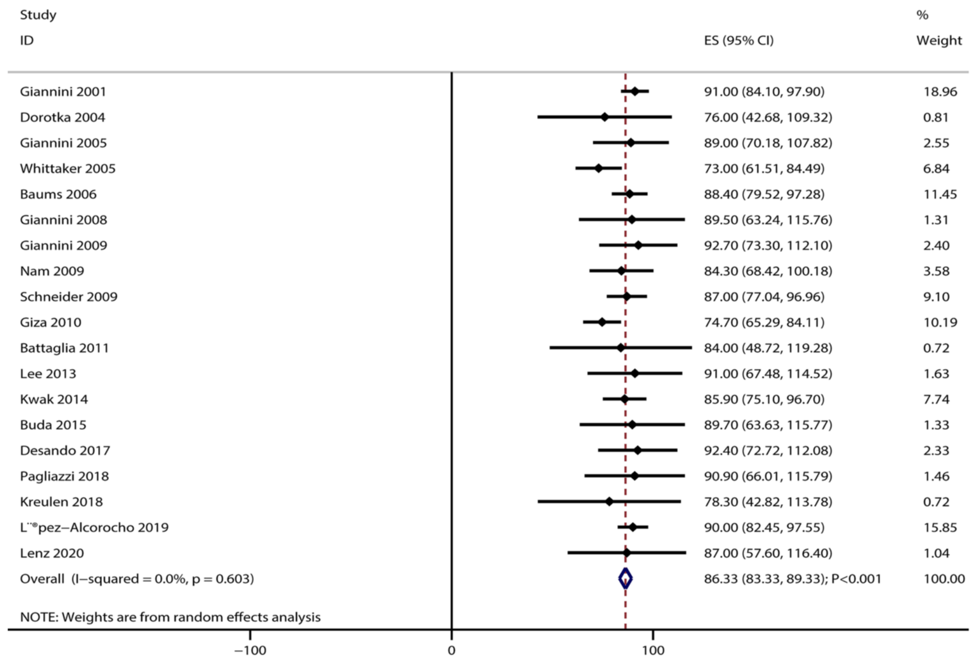

Fig. 3 Effect of ACI on AOFAS score

assess the treatment effectiveness of ACI on success rate and AOFAS score for patients with osteochondral defects of the talus.

The summary success rate for the effect of ACI was 89% (95% CI 85%–92%; $P<0.001$), and the success rate in each study ranged from 50 to 100%. In Giza et al.'s study, 10 patients with osteochondral defects of the talus were recruited and only five patients showed significant improvement in AOFAS score [19]. Five of the included studies presented 100% of success rate for patients treated with ACI [9–11, 25, 29]. Although subgroup analyses revealed that age, technique, indication, size, or follow-up duration did not affect the success rate for patients with osteochondral defects, we noted that the success rate was higher when the age of patients was < 35.0 years, patients were treated with periosteum-covered ACI, patients were with osteochondral defects, and the lesion size was ≥ 2.0 cm^2. These results suggested the ACI might give a superior effect on the success rate in patients with specific characteristics.

We noted that the pooled AOFAS score after ACI was 86.33 (95% CI 83.33–89.33) for patients with osteochondral defects of the talus, and the AOFAS score in the individual study ranged from 74.7 to 92.7. Subgroup analysis suggested the AOFAS score after ACI was high in the subgroups of the age of patients < 35.0 years, patients treated with matrix-associated ACI, patients with osteochondral defects, lesion size ≥ 2.0 cm^2, and follow-up duration ≥ 36.0 months. Moreover, after ACI, there was a significant difference in AOFAS score when stratified by age of patients. Studies have already revealed that patients' age could affect cartilage repair and the clinical outcome after ACI [15, 45], while this result was not consistent [46]. The potential reason for a beneficial effect of ACI on younger patients could be the restore ability of younger patients was stronger than elderly patients.

Several shortcomings of this study should be discussed. First, all of the included studies were designed as case series, and the evidence level was lower (IV). Second, in a smaller number of studies, the comparisons of various treatment strategies were reported [47], and in this study, the lack of controlled treatment strategies and the superiority or inferiority effects of ACI compared with other techniques were not addressed. Third, the analysis based on crude data and the potential role of other characteristics was not adjusted. Fourth, the background therapies including physical therapy, bracing, casting, and nonsteroidal anti-inflammatory medication were not mentioned, which could affect the treatment effectiveness of ACI. Fifth, the current study was not registered, and the transparency was restricted. Sixth, the AOFAS score is not a validated score, which could affect the treatment effects of ACI. Finally, inherent limitations for meta-analysis based on pooled data, including inevitable publication bias, and the restricted detail analyses.

Conclusions

The pooled success rate and AOFAS score after ACI for patients with osteochondral defects of the talus were 89% (95% CI 85%–92%) and 86.33 (95% CI 83.33–89.33), respectively. Moreover, the treatment effectiveness of ACI on the AOFAS score could be affected by age of patients. Further controlled compared studies should be conducted to compare the efficacy and safety of ACI with other techniques for patients with osteochondral defects of the talus.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00402-021-03990-1.

Acknowledgements Not applicable.

Author contributions Conceptualization: MH; methodology: MH, XL and XX; formal analysis and investigation: MH and XL; writing—original draft preparation: MH; writing—review and editing: XX.

Funding Not applicable.

Data availability All data generated or analysed during this study are included in this published article and its supplementary information files.

Code availability Not applicable.

Declarations

Conflicts of interest The authors have no conflicts of interest to declare that are relevant to the content of this article.

Ethics approval This study did not contain any participants' data and the ethics approval is not applicable.

Consent to participate This study did not contain any participants' data and the Consent to participate is not applicable.

Consent for publication Not applicable.

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