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Meta-Analysis

Clinical effectiveness of various treatments for cartilage defects compared with microfracture: a network meta-analysis of randomized controlled trials

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ABSTRACT

Background: Advancements have been made in the realm of cartilage-regenerative techniques in the past decades. However, their comparative advantage has not yet been fully studied.
Objectives: To comparatively analyze the functional, radiological and histological outcomes, and complications of various procedures available for the treatment of cartilage defects.
Data sources: PubMed, Embase, Web of Science, Cochrane, and Scopus.
Study eligibility criteria, participants, and interventions: Randomized controlled trials reporting functional, radiological, histological outcomes, or complications of various methods were utilized in the management of cartilage defects. Patients with cartilage defects. Treatment methods include microfracture (MFX), autologous chondrocyte implantation (ACI), osteochondral allograft/autograft transplantation (OAT), mosaicplasty, or acellular implants.
Study appraisal and synthesis methods: Cochrane's Confidence in Network meta-analysis approach. Network meta-analysis was conducted in Stata. Random effects model was used for forest plots.
Results: Three thousand one hundred ninety-three patients from 54 randomized controlled trials were included in the analysis. The mean age of included patients was 37.9 (±9.46) years. MFX-I was used as a constant comparator. Among the restorative methods, OAT-II offered significantly better functional outcome at 5 years (weighted mean difference [WMD] = 16.00, 95% confidence interval [CI] [11.66, 20.34], $P < .001$) and 10 years (WMD = 16.00, 95% CI [10.42, 21.58], $P < .001$), while OAT-I offered significantly better pain relief (WMD = −1.74, 95% CI [−3.45, −0.02], $P = .042$), and retained hyaline histology (odds ratio = 8.12, 95% CI [4.17, 12.07], $P = .001$) at 1 year with least-reported adverse events and failures. Among the regenerative methods, MFX-III (WMD = −10.0, 95% CI [−13.07, −6.93], $P = .008$) offered significantly better functional outcomes at 5 years, while ACI-III (odds ratio = 0.89, 95% CI

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[0.03, 1.76], $P = .032$) demonstrated significantly better radiological outcomes at 2 years.
Limitations: Heterogeneity in reporting of diverse functional outcome measures.
Conclusions and implications of key findings: Compared with MFX-I, OAT-II demonstrated significantly better long-term functional outcome (10 years), while ACI-III and MFX-III demonstrated significantly better functional outcomes only till midterm (5 years), and there is a paucity of long-term data on these treatment methods.
Systematic review registration number: CRD42022338329.

Introduction

Knee arthroscopy is one of the most common surgical procedures in the field of orthopedic surgery. Approximately 1 million arthroscopic surgeries are being performed every year in the United States alone.[1] In around 60% of these patients undergoing arthroscopic knee evaluation, evidence of substantial articular cartilage damage has been reported.[2] Traditionally, microfracture (MFX) and debridement have been the most commonly performed procedures for such cartilage defects, and still constitute over 98% of the interventions performed for these pathologies.[3] However, there is sufficient evidence that the results of MFX gradually deteriorate over time and these procedures have limited ability to regenerate hyaline cartilage.[3]

Advancements have been made in the realm of cartilage-regenerative techniques in the past decades.[4] While cellular and acellular adjuncts have been employed to stimulate cartilage regeneration over the microfractured tissue bed,[5] autologous cartilage implantation (ACI) of different generations has emerged as excellent modalities to stimulate chondrogenesis.[6] Lesions smaller than 1 cm^2 in low-demand individuals are typically managed by MFX; ACI can facilitate cartilage replacement in lesions larger than 4 cm^2.[7] In addition, osteochondral allografts or autografts may directly be transplanted onto the deficient articular surfaces, which provide immediate cover to the cartilage-deficient surfaces with hyaline graft architecture.[8] The comparative efficacy of these modern treatment modalities is still largely unknown, owing to the paucity of high-quality, multi-arm studies.[9] A large volume of the current clinical guidelines and practice algorithms has been based on level-IV and level-V evidence.[9]

Network meta-analysis (NMA) is considered as an extension of pairwise meta-analysis, that provides pairwise comparisons among diverse treatment methods within a network, even if the treatment options have not previously been compared head-to-head in the individual studies.[9-13] The current meta-analysis available in the literature has compared one of the treatment methods with the other, while an overall comparison of all the treatment methods is lacking.[14-16] The purpose of this study is to comparatively analyze the different cartilage restoration and regeneration techniques, based on their functional, radiological, and histological outcomes and their complications; and provide the best recommendations on their relative efficacy. The efficacy of the diverse surgical interventions has been compared using NMA with MFX as the common comparator.

Materials and methods

PROSPERO (International Prospective Register of Systematic Reviews) registration (CRD42022338329) was obtained for the study. Preferred Reporting Items for Systematic Review and Meta-analysis for NMA guidelines[17] was followed for the conduction and reporting of the study.

Search strategy

PubMed, EMBASE, Medline, Cochrane, and Scopus electronic databases were used for literature searches. The search was performed by 3 reviewers independently on June 15, 2023. The search strategy was built using the Medical SubHeadings (MeSH) terms and corresponding keywords for knee cartilage defects and their different treatment methods with related complications employing different boolean operators as required. The model search strategy is described in Supplementary Material Table 1 following the Peer Review of Electronic Search Strategies guidelines.[18] We employed English language restriction on the results obtained.

The following Patient, Intervention, Comparator, Outcome, Time frame, and Study type (PICOTS) criteria were used for the inclusion of studies:

Population: Patients with cartilage defects.

Intervention: Treatment methods, including MFX, ACI, osteochondral allograft/autograft transplantation (OAT), mosaicplasty, or acellular implants.

Comparator: MFX.

Outcome: Functional, radiological, histological outcome, or complications.

Time frame: Inception to June 2022.

Study type: Randomized controlled trials (RCTs).

Prospective nonrandomized studies, retrospective studies, studies without comparator groups, and preclinical or animal model studies were excluded. Disagreement on decisions during the article selection was resolved through discussions among the authors. Deduplication of the articles screened from electronic databases was done using the citation manager—Zotero. References of the articles included in the study were screened manually to identify the studies missed during the primary search.

Extraction of data

Cochrane Consumers and Communication Group recommendations were followed for data extraction from the included studies. The following were extracted, and a master chart was prepared:

Study characteristics: Author name, country, publication year, and number of patients in the study.

Baseline characteristics: Age for the individual treatment arms, gender proportions, cartilage defect size, interventions analyzed, and duration of follow-up.

Functional outcomes: Visual Analog Scale (VAS) score for pain, Western Ontario McMaster Universities Osteoarthritis Index (WOMAC) score, Tegner score, Lysholm score, International Knee Documentation Committee (IKDC) score, Cincinnati score, and Knee Osteoarthritis Outcome Scale (KOOS) score.

Radiological outcomes: Magnetic resonance observation of cartilage repair tissue (MOCART) score and successful defect-filling (more than or equal to two-thirds of the defect).

Histological outcomes: Demonstration of hyaline architecture in histology.

Complications: Adverse events and failures (patient requiring revision surgeries).

Data extraction was done independently by 2 reviewers. The different cartilage regeneration and repair techniques were classified into broad groups and further subgroups. We expected heterogeneity in the duration of follow-up in the analysis of outcome measures, so we analyzed individual outcomes at short-term (1, 2 years), intermediate-term (5 years), and long-term (≥10 years) based on the available data at individual time points for the outcome concerned. Apart from the statistical significance, individual outcomes were also interpreted based on the minimum clinically important difference (MCID). The following MCID values for the outcomes concerned were fixed as a priori: VAS (1.5), WOMAC (10), Tegner score (10), Lysholm score (13), IKDC score (9), Cincinnati score (10), and KOOS score (10).[19,20]

The risk of bias in the included studies was analyzed by RoB2 tool from the Cochrane group.[21] Studies with a high risk of bias were decided to be excluded from the study.

Statistical analysis

The relative effects of various treatment methods used in the management of cartilage defects have been used for NMA. Bias in outcome reporting of pairwise meta-analyses has been reduced by employing a multivariate meta-analytic strategy.[22] Stata (16.1, Stata Corp LLC) was employed for the analysis. The outcome adjusted for the number of studies and number of subjects involved in the individual arms was used to plot a network map. The difference between the direct effect estimates obtained by head-to-head comparisons and the effect estimates that arrived indirect information for the outcomes was used to assess the global inconsistency in the network. If a treatment belonged to a closed loop of evidence in the network (both direct and indirect effects available), their difference was calculated along with their 95% confidence intervals (CIs) and *P*-values. The *P*-values estimated the likelihood of conflict to be attributable to chance. *P*-value $< .05$ was considered suggestive of inconsistency and the inconsistency model of NMA was utilized and the inconsistency was further explored with sensitivity analysis using the network side-split method.[23] If $P > .05$, a consistency model of NMA was used.

Forest plot using the pooled log odds ratio (OR) or weighted mean difference (WMD) was used for reporting events and continuous outcomes, respectively, along with their 95% CIs for the individual arms in the network to demonstrate their effect on the outcome analyzed compared with a constant comparator. We also described an individual pairwise comparison within the network. Random effects model of analysis using the common variance approach has been employed because of the heterogenicity in the involved treatment arms.[24] Funnel plots for the outcomes in the included studies have been employed for assessing the publication bias. Confidence in Network Meta-Analysis (CINeMA) approach[25] using CINeMA app (Campbell Collaboration and Cochrane)[26] has been employed to analyze the confidence of the evidence generated.

Results

Nine thousand four hundred sixteen articles were shortlisted for initial screening. Deduplication resulted in 3584 articles. Title and abstract screening excluded 3231 articles. Three hundred and fifty-three articles qualified for full-text review and 54 eligible RCTs[27–80] with 3193 included patients qualified for inclusion in the study. Preferred Reporting Items for Systematic Review and Meta-analysis flow diagram for the inclusion of studies is shown in Figure 1.

Included studies reported at least one of the outcomes of interest comparing the treatment methods employed in cartilage defect management. The baseline characteristics of the studies included in the network are presented in Table 1. Germany ($n = 8$) and Norway ($n = 6$) were the leading countries conducting the highest number of RCTs in the field followed by the United States ($n = 5$). The network plot has been presented in Supplementary Material Figure 2. The network had 36 possible pairwise comparisons, among which 14 had direct evidence data. The network had 52 2-armed studies and 2 multi-armed studies. We did not find significant variability among the characteristics of the included patients in the network concerning age and gender proportions. The mean age of the patients included in the trials was 37.9 ($\pm$ 9.46) years. The follow-up of the included trials ranged between 1 and 15 years.

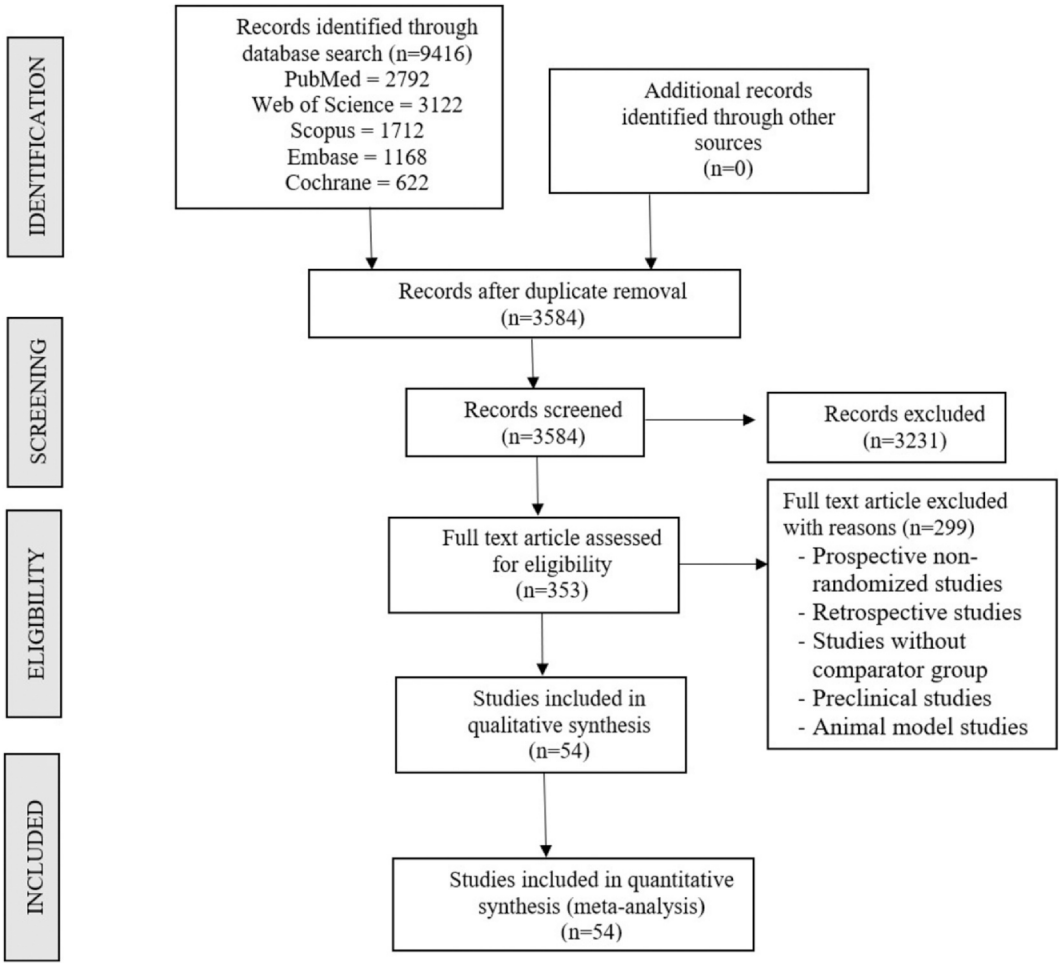

Fig. 1. PRISMA flow diagram of selection of studies included in the analysis. PRISMA, Preferred Reporting Items for Systematic Review and Meta-analysis.

Quality assessment

None of the included studies showed a high risk of bias to warrant exclusion from the study. The risk of bias of the pairwise comparisons is presented in Supplementary Material Figure 3. We did not find any significant publication bias using the funnel plot for most of the outcome measures analyzed. When publication bias was noted, we adjusted using the "trim and fill" method to identify the missing studies and their effects on the overall estimate. We did not find any significant impact of the missing studies on the overall outcomes, as shown in Supplementary Material Figure 4.

Classification of interventions

Various treatment modalities used across the included RCTs were classified into 3 technique-based categories, namely cartilage regeneration, cartilage restoration, and cartilage substitution category. These categories can be divided into 4 broad groups, namely the MFX group, ACI group, OAT group, and implant group. These groups were further divided into different generations based on the advancement of the corresponding surgical techniques. Some hybrid techniques combining one or more of the below-said treatment modalities have also been described.

Cartilage regeneration category

1. MFX group

- *First-generation MFX (MFX-I):* Traditional MFX technique.
- *Second-generation MFX (MFX-II):* MFX-I combined with acellular additives such as platelet-rich plasma (PRP), hyaluronic acid (HA), collagen, and procedures such as autologous matrix-induced chondrogenesis.

Table 1
Characteristics of included studies in the network meta-analysis.

Study ID	Author	Year	Country	Study design	Sample size	Intervention	Treatment code	Mean age	Female	Mean defect size	Follow-up (months)	Funding status
1	A Barie	2020	Germany	RCT	7	ACI-P	ACI-I	28.8	0	4	120	NA
1	A Barie	2020	Germany	RCT	9	MACI	ACI-III	30.4	5	4.2	120	NA
2	A Clave	2016	France	RCT	24	Cartipatch	ACI-III	29.2	10	3.2	24	Govt-funded
2	A Clave	2016	France	RCT	23	Mosaicplasty	OAT-II	28.3	5	3.6	24	Govt-funded
3	A Volz	2017	Germany	RCT	34	AMIC	MFX-II	40	7	3.9	60	Industry-funded
3	A Volz	2017	Germany	RCT	13	Microfracture	MFX-I	36.5	3	2.9	60	Industry-funded
4	AAB de Queiroz	2018	Brazil	RCT	19	OAT	OAT-I	38.6	NA	2.3	24	Nonfunded
4	AAB de Queiroz	2018	Brazil	RCT	19	Cartiva	IMPLANT	33.6	NA	2.4	24	Nonfunded
5	P Niemeyer	2019	Germany	RCT	52	MACI	ACI-III	36	19	2.7	24	Industry-funded
5	P Niemeyer	2019	Germany	RCT	50	Microfracture	MFX-I	37	22	2.4	24	Industry-funded
6	V Fossum	2019	Norway	RCT	21	ACI-C	ACI-II	37.2	7	4.9	24	NA
6	V Fossum	2019	Norway	RCT	20	AMIC	MFX-II	38.3	12	5.2	24	NA
7	CR Gooding	2006	UK	RCT	33	ACI-P	ACI-I	30.5	17	4.5	24	NA
7	CR Gooding	2006	UK	RCT	35	ACI-C	ACI-II	30.5	18	4.5	24	NA
8	W Bartlett	2005	UK	RCT	44	ACI-C	ACI-II	33.7	18	6	12	NA
8	W Bartlett	2005	UK	RCT	47	MACI	ACI-III	33.4	19	6.1	12	NA
9	S Ulstein	2014	Norway	RCT	11	Microfracture	MFX-I	31.7	11	2.6	120	Govt-funded
9	S Ulstein	2014	Norway	RCT	14	OAT	OAT-I	32.7	NA	3	120	Govt-funded
10	G Bentley	2003	UK	RCT	58	ACI-C	ACI-II	30.9	43	4.4	19	NA
10	G Bentley	2003	UK	RCT	42	Mosaicplasty	OAT-II	31.6	NA	3.9	19	NA
11	G Bentley	2012	UK	RCT	58	ACI-C	ACI-II	30.9	42	4.4	120	NA
11	G Bentley	2012	UK	RCT	42	Mosaicplasty	OAT-II	31.6	NA	3.9	120	NA
12	P Visna	2004	Czech Republic	RCT	25	Autologous chondrograft transplantation	ACI-III	29.4	7	4	12	NA
12	P Visna	2004	Czech Republic	RCT	25	Microfracture	MFX-I	32.2	9	3.3	12	NA
13	DV Assche	2010	Belgium	RCT	33	ACI-P	ACI-I	34	11	2.5	24	Industry-funded
13	DV Assche	2010	Belgium	RCT	34	Microfracture	MFX-I	34	10	2.3	24	Industry-funded
14	K Saw	2013	USA	RCT	24	Microfracture with HA	MFX-II	42	17	NA	18	Govt-funded
14	K Saw	2013	USA	RCT	25	Microfracture with PBSC	MFX-III	38	15	NA	18	Govt-funded
15	S Anders	2013	Germany	RCT	22	AMIC	MFX-II	41	17	3.7	24	Industry-funded
15	S Anders	2013	Germany	RCT	8	Microfracture	MFX-I	38	15	3.5	24	Industry-funded
16	GW Lee	2013	Republic of Korea	RCT	25	Microfracture	MFX-I	46	10	3	24	Nonfunded
16	GW Lee	2013	Republic of Korea	RCT	24	Microfracture with PRP	MFX-II	46	10	3	24	Nonfunded
17	M Brittberg	2018	Sweden	RCT	65	MACI	ACI-III	38	23	5.1	60	Industry-funded
17	M Brittberg	2018	Sweden	RCT	63	Microfracture	MFX-I	34	20	4.9	60	Industry-funded
18	H Lim	2012	South Korea	RCT	30	Microfracture	MFX-I	32.9	12	2.7	60	NA
18	H Lim	2012	South Korea	RCT	22	OAT	OAT-I	30.4	10	2.7	60	NA
18	H Lim	2012	South Korea	RCT	18	ACI-P	ACI-I	25.1	8	2.8	60	NA
19	G Knutsen	2007	Norway	RCT	40	ACI-P	ACI-I	33.3	NA	5	60	Govt-funded
19	G Knutsen	2007	Norway	RCT	40	Microfracture	MFX-I	31.1	NA	5	60	Govt-funded
20	G Knutsen	2016	Norway	RCT	40	ACI-P	ACI-I	33.3	NA	5	180	Govt-funded
20	G Knutsen	2016	Norway	RCT	40	Microfracture	MFX-I	31.1	NA	5	180	Govt-funded
21	F Zeifang	2010	Germany	RCT	11	ACI-C	ACI-II	29.1	5	4.3	24	Govt-funded
21	F Zeifang	2010	Germany	RCT	10	ACI-P	ACI-I	29.5	0	4.1	24	Govt-funded
22	Y Liu	2021	Taiwan	RCT	10	Kartigen	ACI-III	54.8	5	2.9	24	Industry-funded

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Table 1 (*continued*)

Study ID	Author	Year	Country	Study design	Sample size	Intervention	Treatment code	Mean age	Female	Mean defect size	Follow-up (months)	Funding status
22	Y Liu	2021	Taiwan	RCT	5	Microfracture	MFX-I	67.8	3	1	24	Industry-funded
23	K Yoon	2020	Republic of Korea	RCT	20	ACI-CCP	ACI-III	41.5	6	3.5	12	Govt-funded
23	K Yoon	2020	Republic of Korea	RCT	10	Microfracture	MFX-I	47.2	7	2.5	12	Govt-funded
24	E Kon	2017	Italy	RCT	51	Collagen HA	IMPLANT	34	15	3.4	24	Industry-funded
24	E Kon	2017	Italy	RCT	49	Microfracture	MFX-I	35.2	18	3.5	24	Industry-funded
25	J Vanlauwe	2011	Belgium	RCT	51	ACI-P	ACI-I	33.9	22	2.6	60	Industry-funded
25	J Vanlauwe	2011	Belgium	RCT	61	Microfracture	MFX-I	33.9	20	2.4	60	Industry-funded
26	WD Stanish	2013	Canada	RCT	41	Microfracture with BST-CarGel	MFX-II	35.1	18	NA	12	Industry-funded
26	WD Stanish	2013	Canada	RCT	39	Microfracture	MFX-I	37.2	14	NA	12	Industry-funded
27	E Basad	2010	Germany	RCT	40	MACI	ACI-III	33	15	7	24	NA
27	E Basad	2010	Germany	RCT	20	Microfracture	MFX-I	37.5	3	7	24	NA
28	E Solheim	2017	Norway	RCT	20	Microfracture	MFX-I	35	6	4	180	NA
28	E Solheim	2017	Norway	RCT	20	Mosaicplasty	OAT-II	31	6	4	180	NA
29	S Bisicchia	2019	Italy	RCT	20	Microfracture with SVF	MFX-III	49.8	8	3.2	12	Nonfunded
29	S Bisicchia	2019	Italy	RCT	20	Microfracture	MFX-I	46.1	7	3.1	12	Nonfunded
30	DBF Saris	2014	Netherlands	RCT	72	MACI	ACI-III	34.8	27	4.9	24	Industry-funded
30	DBF Saris	2014	Netherlands	RCT	72	Microfracture	MFX-I	32.9	24	4.7	24	Industry-funded
31	DBF Saris	2008	Netherlands	RCT	57	ACI-P	ACI-I	33.9	22	2.6	12	Industry-funded
31	DBF Saris	2008	Netherlands	RCT	61	Microfracture	MFX-I	33.9	20	2.4	12	Industry-funded
32	DBF Saris	2009	Netherlands	RCT	57	ACI-P	ACI-I	33.9	22	2.6	36	Industry-funded
32	DBF Saris	2009	Netherlands	RCT	61	Microfracture	MFX-I	33.9	20	2.4	36	Industry-funded
33	Z Qiao	2020	China	RCT	10	Microfracture	MFX-I	62.3	7	4	12	Govt-funded
33	Z Qiao	2020	China	RCT	10	Microfracture with HA	MFX-II	59.7	5	4	12	Govt-funded
33	Z Qiao	2020	China	RCT	10	Microfracture with MSC	MFX-III	62	7	4	12	Govt-funded
34	PD Nguyen	2016	Vietnam	RCT	15	Microfracture with SVF	MFX-III	58.6	12	NA	18	Industry-funded
34	PD Nguyen	2016	Vietnam	RCT	15	Microfracture	MFX-I	58.2	12	NA	18	Industry-funded
35	S Zaffagnini	2020	Italy	RCT	20	Mosaicplasty	OAT-II	28.7	5	2	144	Industry-funded
35	S Zaffagnini	2020	Italy	RCT	23	MACI	ACI-III	29.1	5	2	144	Industry-funded
36	H Lim	2021	Republic of Korea	RCT	43	Microfracture with MSC	MFX-III	55.3	28	4.9	60	Industry-funded
36	H Lim	2021	Republic of Korea	RCT	46	Microfracture	MFX-I	54.4	30	4	60	Industry-funded
37	M Venosa	2022	Italy	RCT	19	Microfracture with PRP	MFX-II	56.4	7	1	12	NA
37	M Venosa	2022	Italy	RCT	19	Microfracture with MSC	MFX-III	55.8	10	1	12	NA
38	MS Shive	2014	Canada	RCT	34	Microfracture with BST-CarGel	MFX-II	34.3	12	2.4	60	Industry-funded
38	MS Shive	2014	Canada	RCT	26	Microfracture	MFX-I	40.1	12	2	60	Industry-funded
39	Y Koh	2015	Republic of Korea	RCT	40	Microfracture with MSC	MFX-III	39.1	24	4.8	24	NA
39	Y Koh	2015	Republic of Korea	RCT	40	Microfracture	MFX-I	38.4	26	4.6	24	NA
40	G Knutsen	2004	Norway	RCT	40	ACI-P	ACI-I	33	16	5.1	24	Govt-funded
40	G Knutsen	2004	Norway	RCT	40	Microfracture	MFX-I	31.1	16	4.5	24	Govt-funded
41	MS Kim	2017	South Korea	RCT	14	Microfracture	MFX-I	55.7	0	2.9	12	Industry-funded
41	MS Kim	2017	South Korea	RCT	14	Microfracture with collagen	MFX-II	55.4	1	3.6	12	Industry-funded
42	MS Kim	2019	South Korea	RCT	48	Microfracture	MFX-I	51.7	9	4.6	24	Industry-funded
42	MS Kim	2019	South Korea	RCT	52	Microfracture with collagen	MFX-II	48.9	12	3.9	24	Industry-funded

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Table 1 (*continued*)

Study ID	Author	Year	Country	Study design	Sample size	Intervention	Treatment code	Mean age	Female	Mean defect size	Follow-up (months)	Funding status
43	MS Kane	2018	USA	RCT	21	Neocart	ACI-III	41.4	2	2.2	60	Industry-funded
43	MS Kane	2018	USA	RCT	9	Microfracture	MFX-I	38.8	3	1.7	60	Industry-funded
44	C Ibarra	2021	USA	RCT	24	MACI	ACI-III	33.7	7	1.9	72	Govt-funded
44	C Ibarra	2021	USA	RCT	24	Microfracture	MFX-I	35.8	10	1.7	72	Govt-funded
45	U Horas	2003	Germany	RCT	20	ACI-P	ACI-I	31.4	12	3.8	24	NA
45	U Horas	2003	Germany	RCT	20	OAT	OAT-I	35.4	5	3.6	24	NA
46	Y Hashimoto	2019	Japan	RCT	7	Microfracture with MSC	MFX-III	42.6	4	3	12	Govt-funded
46	Y Hashimoto	2019	Japan	RCT	4	Microfracture	MFX-I	46.3	0	4.4	12	Govt-funded
47	R Gudas	2006	Lithuania	RCT	28	OAT	OAT-I	24.6	10	2.8	36	NA
47	R Gudas	2006	Lithuania	RCT	29	Microfracture	MFX-I	24.3	12	2.7	36	NA
48	R Gudas	2012	Lithuania	RCT	28	OAT	OAT-I	24.6	10	2.7	120	Nonfunded
48	R Gudas	2012	Lithuania	RCT	29	Microfracture	MFX-I	24.3	12	2.8	120	Nonfunded
49	R Gudas	2005	Lithuania	RCT	29	Microfracture	MFX-I	24.3	12	2.8	36	NA
49	R Gudas	2005	Lithuania	RCT	28	OAT	OAT-I	24.6	10	2.7	36	NA
50	J Glasbrenner	2020	Germany	RCT	12	Microfracture	MFX-I	36.7	3	1.7	12	Industry-funded
50	J Glasbrenner	2020	Germany	RCT	12	Microfracture with BMAC	MFX-III	47.9	6	1.7	12	Industry-funded
51	U Dasar	2016	Turkey	RCT	20	Microfracture	MFX-I	36.4	15	3.5	24	NA
51	U Dasar	2016	Turkey	RCT	20	Carbon fiber rod	IMPLANT	38.5	15	4	24	NA
52	DC Crawford	2012	USA	RCT	21	NeoCart	ACI-III	41	2	2.8	24	Industry-funded
52	DC Crawford	2012	USA	RCT	9	Microfracture	MFX-I	39	3	2.5	24	Industry-funded
53	BJ Cole	2011	USA	RCT	9	Microfracture	MFX-I	33	4	3.4	24	Industry-funded
53	BJ Cole	2011	USA	RCT	20	MACI	ACI-III	32.7	6	2.7	24	Industry-funded
54	JY Chung	2013	South Korea	RCT	24	Microfracture with BMAC	MFX-III	47.4	10	1.3	24	Govt-funded
54	JY Chung	2013	South Korea	RCT	12	Microfracture	MFX-I	44.3	10	1.5	24	Govt-funded

Abbreviations: ACI, autologous chondrocyte implantation; ACI-C, ACI with collagen cover; ACI-CCP, autologous chondrocyte implantation-cultured chondrocyte pellet; ACI-P, ACI with periosteal cover; AMIC, autologous matrix-induced chondrogenesis; BMAC, bone marrow aspiration concentrate; HA, hyaluronic acid; MACI, matrix-induced autologous chondrocyte implantation; MFX, microfracture; MSC, mesenchymal stromal cell; NA, not available; OAT, osteochondral allograft/autograft transfer; PBSC, peripheral blood stem cell; PRP, platelet-rich plasma; RCT, randomized controlled trial; SVF, stromal vascular fraction; UK, United Kingdom; USA, United States of America.
Each row depicts the individual comparator arm in the studies included.

- *Third-generation MFX (MFX-III):* MFX-I combined with cellular additives such as mesenchymal stromal cells (MSCs), bone marrow aspiration concentrate, peripheral blood stem cells, and stromal vascular fraction.

2. ACI group

- *First-generation ACI (ACI-I)*: Traditional ACI covered with periosteum.
- *Second-generation ACI (ACI-II)*: ACI covered with a collagen membrane.
- *Third-generation ACI (ACI-III):* ACI using matrix-induced autologous chondrocyte implantation (MACI) techniques as in Cartipatch, Kartigen, or Neocart.

Cartilage restoration category

OAT group

- *First-generation OAT (OAT-I):* Autologous or allogeneic osteochondral transfer techniques.
- *Second-generation OAT (OAT-II):* Multiple autologous or allogeneic osteochondral transfer techniques as in mosaicplasty.

Cartilage substitution category

Implants

Acellular implants such as carbon fiber rods, collagen HA hydrogels, and synthetic acellular cartilage analogs such as Cartiva.

Network analysis results

We performed a pooled NMA using a frequentist approach to every outcome of interest. Among all the treatment arms in the network, MFX-I had high data strength as compared with all the other comparators (as shown in the network plots in the Supplementary Material Fig. 2). Therefore, MFX-I is taken as the constant comparator and all the outcomes have been reported in comparison with the performance of MFX-I. All the included studies with the OAT group in their treatment arm have performed only autologous transfer. The outcomes have been analyzed in terms of pain, functional outcomes, radiological outcomes, histological outcomes, adverse effects, and failures.

Pain

Inference from the VAS score is taken into consideration for pain outcomes. VAS score was reported at 1 year in 15 studies[27,29,33,34,41,50-53,55,57,58,62,75,78] involving 805 patients, at 2 years in 11 studies[27,33,36,41,51,53,55,57,58,62,65] involving 729 patients, and at 5 years in 3 studies[35,53,60] involving 297 patients. Figure 2 shows the pooled forest plot of the VAS score outcome, subgrouped based on the aforementioned follow-up time points. OAT-I revealed a statistical and clinical significance in the VAS score improvement at 1 year (WMD = −1.74, 95% CI [−3.45, −0.02], $P = .042$) in comparison with MFX-I. The highest data point available for the VAS score was 5 years. The data for the 5-year VAS score were not available for MFX-II, ACI-II, OAT-I, and the Implant arm. It is to be noted that the VAS score was not at all reported for OAT-II.

Functional outcomes

The functional outcomes were reported using *WOMAC score, Tegner score, Lysholm score, IKDC score, KOOS score, and Cincinnati score.* Figures 2 and 3 show the pooled forest plot of various scores. The individual pairwise comparison forest plot of the treatment arms is presented in Supplementary Material Figure 3. WOMAC score was reported at 5 years in 2 studies[60,69] involving 149 patients. Tegner score was reported at 1 year in 7 studies[28,48,49,52,57,76,80] involving 303 patients, at 2 years in 6 studies[28,44,48,49,57,80] involving 282 patients, at 5 years in 3 studies[49,53,59] involving 198 patients, and at 10 years in 3 studies[28,44,79] involving 116 patients. Lysholm score was reported at 1 year in 14 studies[28,30,33,40,41,48,49,53,55,62,70,76,78,80] involving 614 patients, at 2 years in 12 studies[28,30,33,35,41,48,49,53,55,58,62,80] involving 631 patients, at 5 years in 5 studies[49,53,54,59,70] involving 318 patients, and at 10 years in 4 studies[28,54,70,72] involving 161 patients. IKDC score was reported at 1 year in 19 studies[28,33,37-39,42,47,49-52,57,58,61,68,75,76,78,80] involving 753 patients, at 2 years in 17 studies[28,33,35–39,42,48–51,57,58,61,65,68,80] involving 904 patients, and at 5 years in 4 studies[35,49,50,60] involving 295 patients. KOOS score was reported at 1 year in 8 studies[41,51,52,63,67,74,75,78] involving 569 patients, and at 2 years in 4 studies[41,51,63,67] involving 361 patients. Cincinnati score was reported at 1 year in 4 studies[27,29,40,77] involving 208 patients, and at 2 years in 5 studies[27,35,43,65,77] involving 417 patients. The consolidated list of evidence strength is given in Table 3.

The functional outcomes reported at 1-, 2-, 5-, and 10-year data points using the above-said scores have been clubbed together for the sake of understanding, respecting the limitation that this approach possesses, and considering the heterogenicity in reporting of functional outcomes in the included studies.

One-year functional outcomes

OAT-I (WMD = 3.33, 95% CI [0.06, 6.60], $P = .045$) demonstrated a statistically significant improvement compared with MFX-I based on the Tegner score that is below the MCID cutoff for the score concerned. Although ACI-III (WMD = 9.18, 95% CI [4.05, 14.31], $P = .032$) and OAT-II (WMD = 13.0, 95% CI [5.13, 20.87], $P = .019$) had significantly improved outcomes based on Lysholm

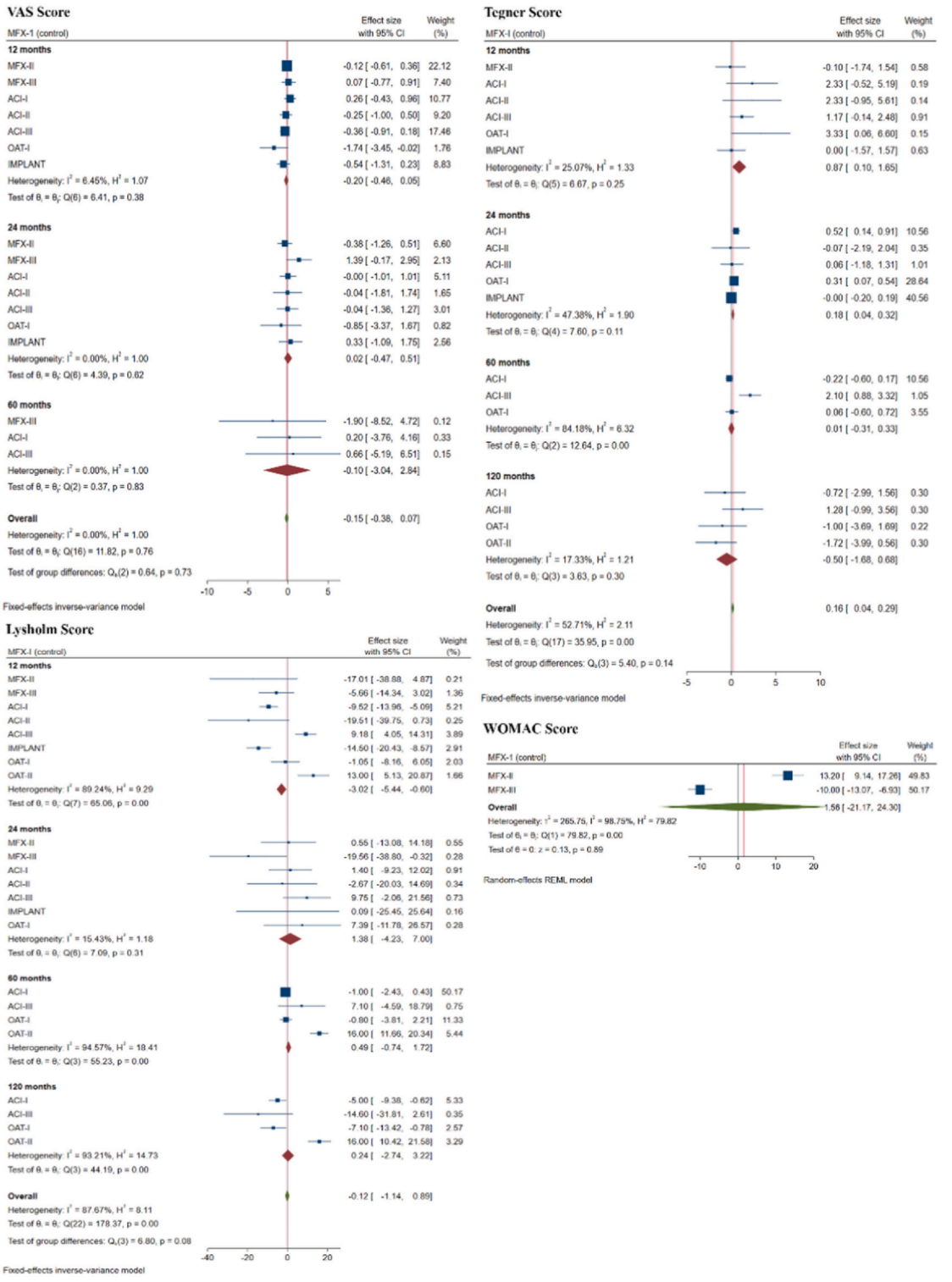

Fig. 2. Forest plot comparing the interventions for the functional outcomes analyzed across the included studies in the network. ACI, autologous chondrocyte implantation; CI, confidence interval; MFX, microfracture; OAT, osteochondral allograft/autograft transplantation; REML, restricted maximum likelihood; VAS, Visual Analog Scale; WOMAC, Western Ontario McMaster Universities Osteoarthritis Index.

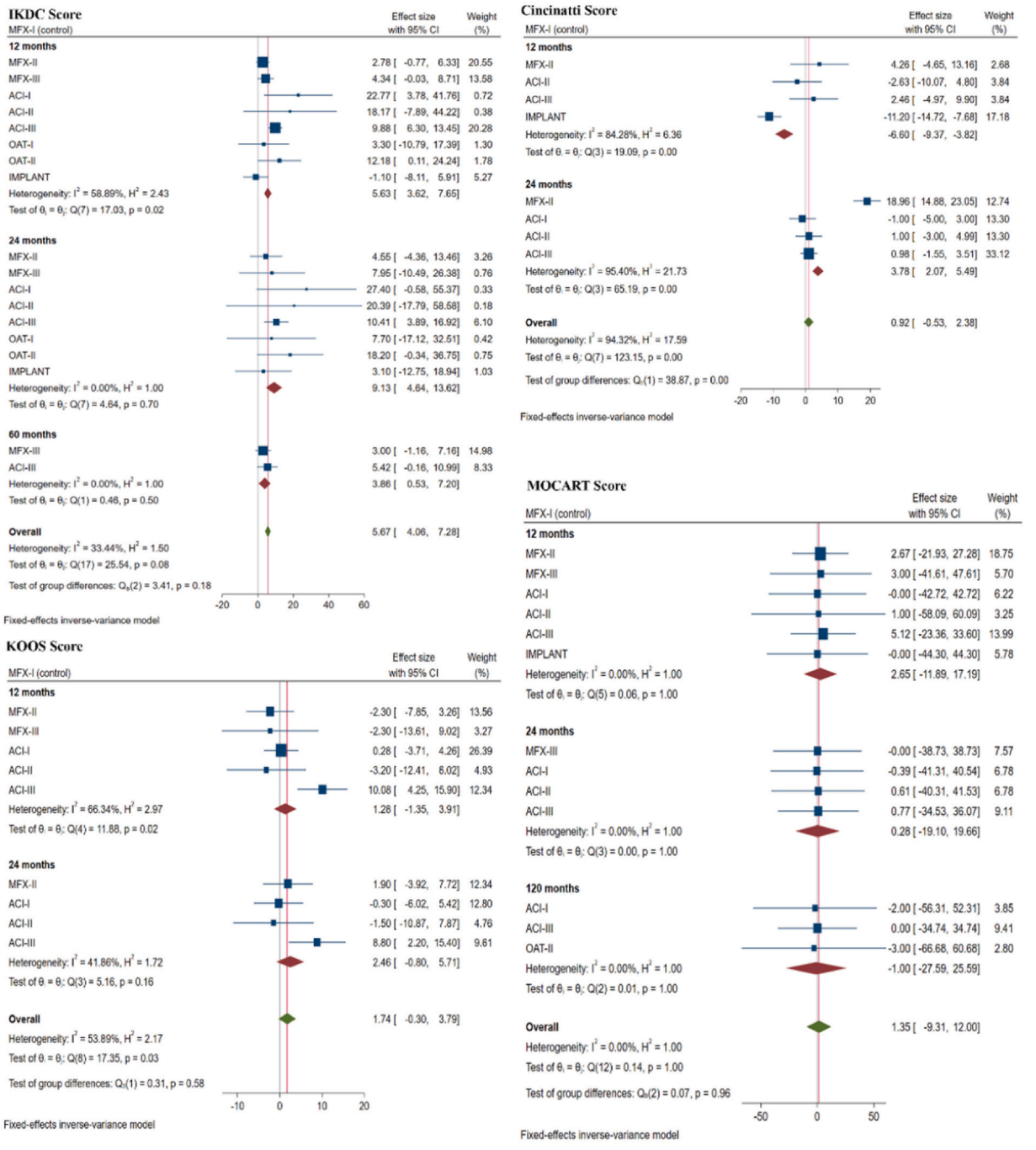

Fig. 3. Forest plot comparing the interventions for the functional and radiological outcomes analyzed across the included studies in the network. ACI, autologous chondrocyte implantation; CI, confidence interval; IKDC, International Knee Documentation Committee; KOOS, Knee Osteoarthritis Outcome Scale; MFX, microfracture; MOCART, magnetic resonance observation of cartilage repair tissue; OAT, osteochondral allograft/autograft transplantation.

score, only OAT-II demonstrated clinical significance. We also noted a significant deterioration in ACI-I (WMD = −9.52, 95% CI [−13.96, −5.90], $P = .022$) and implant (WMD = −14.50, 95% CI [−20.43, −8.57], $P = .001$) treatment arms based on Lysholm score. However, implants showed a clinically significant deterioration in the Lysholm score. In comparison with MFX-I, we noted significant statistical and clinical improvement in ACI-I (WMD = 22.77, 95% CI [3.78, 41.76], $P = .003$), ACI-III (WMD = 9.88, 95% CI [6.30, 13.45], $P = .013$), and OAT-II (WMD = 12.18, 95% CI [0.11, 24.24], $P = .042$) treatment arms at 1 year based on IKDC score. Based on the KOOS score compared with MFX-I, we noted significant statistical and clinical improvement in the ACI-III group

(WMD = 10.08, 95% CI [4.25, 15.90], $P = .001$) at 1 year. Significant statistical and clinical deterioration in the implant arm (WMD = −11.20, 95% CI [−14.72, −7.68], $P = .003$) was noted at 1 year based on the Cincinnati score.

Two. -year functional outcome

At 2 years, based on the IKDC score, only ACI-III (WMD = 10.41, 95% CI [3.89, 16.92], $P = .003$) demonstrated statistical and clinical significance. Based on the KOOS score compared with MFX-I, we noted only statistically significant improvement in the ACI-III group (WMD = 8.80, 95% CI [2.20, 15.40], $P = .001$) without clinical importance. The MFX-II (WMD = 18.96, 95% CI [14.88, 23.05], $P = .001$) demonstrated statistical and clinical significance based on the Cincinnati score at 2 years.

Five. -year and 10-year functional outcomes

Significant statistical and clinical improvement in the overall WOMAC scores with MFX-III compared with MFX-I (WMD = −10.0, 95% CI [−13.07, −6.93], $P = .008$) and a significant statistical and clinical deterioration in the overall WOMAC scores with MFX-II compared with MFX-I (WMD = 13.20, 95% CI [9.14, 17.26], $P = .004$) has been reported. ACI-III (WMD = 2.10, 95% CI [0.88, 3.32], $P = .023$) performed significantly better than MFX-I based on the Tegner score without clinical significance. At 5 years (WMD = 16.00, 95% CI [11.66, 20.34], $P < .001$) and 10-year (WMD = 16.00, 95% CI [10.42, 21.58], $P < .001$) follow-up, we noted OAT-II to demonstrate continued significant statistical and clinical improvement based on the Lysholm score.

The highest data point available for any functional outcome was 10 years. It is to be noted that ACI-II and Implant arm did not have functional outcomes reported at 5 or 10 years. The MFX-II and MFX-III arms did not have functional outcomes reported at 10 years. Based on the available data, at 1-year ACI-III ($P = .001$), OAT-II ($P = .019$) resulted in significantly increased functional outcomes. At 2 years, ACI-III ($P = .001$) and MFX-II ($P = .001$) resulted in significantly increased functional outcomes. At 5 years, OAT-II ($P < .001$), MFX-II ($P = .004$), MFX-III ($P = .008$), and ACI-III ($P = .023$) resulted in significantly increased functional outcomes. At 10 years, OAT-II ($P < .001$) resulted in significantly increased functional outcomes. The implant arm ($P = .003$) showed significant statistical and clinical deterioration of functional outcomes at 1 year.

Radiological outcomes

The MOCART score and defect-filling (more than two-thirds) have been used to report the radiological outcomes in the included studies. MOCART score was reported at 1 year in 9 studies[40,47,49,51,52,55,63,78,80] involving 460 patients, at 2 years in 4 studies[49,56,63,80] involving 251 patients, and at 10 years in 3 studies[28,49,79] involving 107 patients. Defect-filling was reported at 1 year in

Table 2
Risk of bias for all the pairwise comparisons for the functional outcome from the network assessed with the CINeMA approach.

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reasons for downgrading
DIRECT EVIDENCE									
ACI-I:ACI-II	1	Some Concerns	Low risk	No concerns	Some Concerns	No concerns	Some Concerns	High	nil
ACI-I:ACI-III	1	Some Concerns	Low risk	No concerns	Some Concerns	No concerns	No concerns	High	nil
ACI-I:MFX-I	5	Some Concerns	Low risk	No concerns	No concerns	No concerns	Some Concerns	High	nil
ACI-I:OAT-I	1	Some Concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	nil
ACI-II:ACI-III	1	Some Concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Within-study bias, Imprecision
ACI-II:MFX-II	1	Some Concerns	Low risk	No concerns	Some Concerns	No concerns	No concerns	High	nil
ACI-II:OAT-II	1	Some Concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	nil
ACI-III:MFX-I	2	Some Concerns	Low risk	No concerns	Some Concerns	No concerns	No concerns	High	nil
ACI-III:OAT-II	1	Some Concerns	Low risk	No concerns	Some Concerns	No concerns	No concerns	High	nil
IMPLANT:MFX-I	1	Some Concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Within-study bias, Imprecision
MFX-I:MFX-II	4	Some Concerns	Low risk	No concerns	Some Concerns	No concerns	No concerns	High	nil
MFX-I:MFX-III	1	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	High	nil
MFX-I:OAT-I	4	Some Concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	nil
MFX-I:OAT-II	1	Some Concerns	Low risk	No concerns	Some Concerns	Some Concerns	Some Concerns	High	nil

(*continued on next page*)

Table 2 (*continued*)

INDIRECT EVIDENCE									
ACI-I:IMPLANT	0	Some Concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Within-study bias, Imprecision
ACI-I:MFX-II	0	Some Concerns	Low risk	No concerns	Some Concerns	Some Concerns	No concerns	High	nil
ACI-I:MFX-III	0	Some Concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Within-study bias, Imprecision
ACI-I:OAT-II	0	Some Concerns	Low risk	No concerns	Some Concerns	Some Concerns	No concerns	High	nil
ACI-II:IMPLANT	0	Some Concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Within-study bias, Imprecision
ACI-II:MFX-I	0	Some Concerns	Low risk	No concerns	Some Concerns	No concerns	No concerns	High	nil
ACI-II:MFX-III	0	Some Concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Within-study bias, Imprecision
ACI-II:OAT-I	0	Some Concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Within-study bias, Imprecision
ACI-III:IMPLANT	0	Some Concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Within-study bias, Imprecision
ACI-III:MFX-II	0	Some Concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Within-study bias, Imprecision
ACI-III:MFX-III	0	Some Concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Within-study bias, Imprecision
ACI-III:OAT-I	0	Some Concerns	Low risk	No concerns	Some Concerns	Some Concerns	No concerns	High	nil
IMPLANT:MFX-II	0	Some Concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Within-study bias, Imprecision
IMPLANT:MFX-III	0	Some Concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Within-study bias, Imprecision
IMPLANT:OAT-I	0	Some Concerns	Low risk	No concerns	Some Concerns	Some Concerns	No concerns	High	nil
IMPLANT:OAT-II	0	Some Concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Within-study bias, Imprecision
MFX-II:MFX-III	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	High	nil
MFX-II:OAT-I	0	Some Concerns	Low risk	No concerns	Some Concerns	No concerns	No concerns	High	nil
MFX-II:OAT-II	0	Some Concerns	Low risk	No concerns	Some Concerns	No concerns	No concerns	High	nil
MFX-III:OAT-I	0	No concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	High	nil
MFX-III:OAT-II	0	Some Concerns	Low risk	No concerns	Major concerns	No concerns	No concerns	Moderate	Within-study bias, Imprecision
OAT-I:OAT-II	0	Some Concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	nil

Abbreviations: ACI, autologous chondrocyte implantation; CINeMA, Confidence in Network Meta-Analysis; MFX, microfracture; OAT, osteochondral autograft/allograft transfer.

18 studies[27,30,38,42,44,45,47,51,52,57,59,61,68,69,71,77,78,80] involving 868 patients, and at 2 years in 11 studies[27,28,30,36,38,42,56,57,65,69,77] involving 626 patients.

None of the compared interventions demonstrated significant improvement in the MOCART score at all the analyzed time points as shown in Figure 3. Compared with MFX-I, ACI-III (OR = 1.10, 95% CI [0.05, 2.14], $P = .043$) and OAT-I (OR = 1.07, 95% CI [0.32, 1.82], $P = .003$) demonstrated statistically significant improvement at 1 year based on defect-filling. At 2 years, we noted continued significant improvement in the ACI-III (OR = 0.89, 95% CI [0.03, 1.76], $P = .032$) group, as compared with MFX-I. It is to be noted that OAT-II had no data reported on radiological outcomes at 1, 2, and 5 years, OAT-I had no data reported on radiological outcomes at 2, 5, and 10 years, MFX-II, MFX-III, ACI-III, and implant arm had no data reported on radiological outcomes at 5 and 10 years, and MFX-I, ACI-I, and ACI-II had no data reported on radiological outcomes at 5 years.

Histological outcome

The histological outcome was reported at 1 year in 5 studies[29,31,43,45,55] involving 868 patients. Figure 4 shows the pooled forest plot of the successful hyaline histology at 1 year. Compared with MFX-I, we noted OAT-I (OR = 8.12, 95% CI [4.17, 12.07], $P = .001$)

Table 3
Strength of evidence of the individual reported outcomes.

Outcome category	Outcome	Follow-up	Number of studies	Population strength
Pain	VAS score	1 year	15 studies	805 patients
		2 years	11 studies	729 patients
		5 years	3 studies	297 patients
Functional outcome	WOMAC score	5 years	2 studies	149 patients
	Tegner score	1 year	7 studies	303 patients
		2 years	6 studies	282 patients
		5 years	3 studies	198 patients
		10 years	3 studies	116 Patients
	Lysholm score	1 year	14 studies	614 patients
		2 years	12 studies	631 patients
		5 years	5 studies	318 patients
		10 years	4 studies	161 patients
	IKDC score	1 year	19 studies	753 patients
		2 years	17 studies	904 patients
		5 years	4 studies	295 patients
	KOOS score	1 year	8 studies	569 patients
		2 years	4 studies	361 patients
	Cincinnati score	1 year	4 studies	208 patients
		2 years	5 studies	417 patients
Radiological outcome	MOCART score	1 year	9 studies	460 patients
		2 years	4 studies	251 patients
		10 years	3 studies	107 patients
	Defect-filling	1 year	18 studies	868 patients
		2 years	11 studies	626 patients
Histological outcome	Hyaline histology	1 year	5 studies	868 patients
Complications	Adverse events	1 year	36 studies	2173 patients
	Failures	1 year	36 studies	1377 patients

Abbreviations: IKDC, International Knee Documentation Committee; KOOS, Knee Osteoarthritis Outcome Scale; MOCART, magnetic resonance observation of cartilage repair tissue; VAS, Visual Analog Scale; WOMAC, Western Ontario McMaster Universities Osteoarthritis Index.

to demonstrate successful hyaline histology on follow-up. MFX-II, MFX-III, OAT-II, and the implant arm had no data reported with regard to their histological outcomes.

Complications

Adverse events

The adverse events following the compared interventions were reported in 36 studies[27–31,33,35,37–41,43,44–47,50,51,60–71,74,75,77,78,80] involving 2173 patients. Figure 4 shows the pooled forest plot of the reported complications for the analyzed interventions. In comparison with MFX-I, there was no statistically significant difference in the reported rates of adverse events, except OAT-I (OR = −1.03, 95% CI [−1.98, −0.08], $P = .032$), which demonstrated significantly reduced rates of adverse events. The individual pairwise comparison forest plot of the treatment arms is presented in Supplementary Material Figure 3.

Failures

The need for subsequent procedures following the interventions was considered as treatment failure, and the same was reported in 36 studies[27–29,32,35,40–43,45,46,49,51,53–55,59,70,72,74,77,79] involving 1377 patients. Figure 4 shows the pooled forest plot of the failure events for the reported interventions. In comparison with MFX-I, there was no statistically significant difference in the failure events among the diverse interventions analyzed, except OAT-I (OR = −1.53, 95% CI [−2.52, −0.54], $P = .002$), which demonstrated a significantly reduced rate of reported failures (as compared with MFX-I). The individual pairwise comparison forest plot of the treatment arms is presented in Supplementary Material Figure 3.

Sensitivity and subgroup analysis

We did not observe significant heterogeneity across various outcomes analyzed in the network as shown by the heterogeneity values in the corresponding individual forest plots of pairwise comparisons in Supplementary Material Figure 5. We subgrouped and analyzed the studies based on the follow-up time point to avoid heterogeneity in the reported outcomes.

Consistency

We did not observe any significant evidence of global inconsistency, which could have affected the transitivity of the network results. The consistency analysis was performed for the individual outcomes analyzed and presented the chi-square values in the corresponding pairwise comparison forest plots. We noted the indirect pooled estimates to have wider CI compared with direct

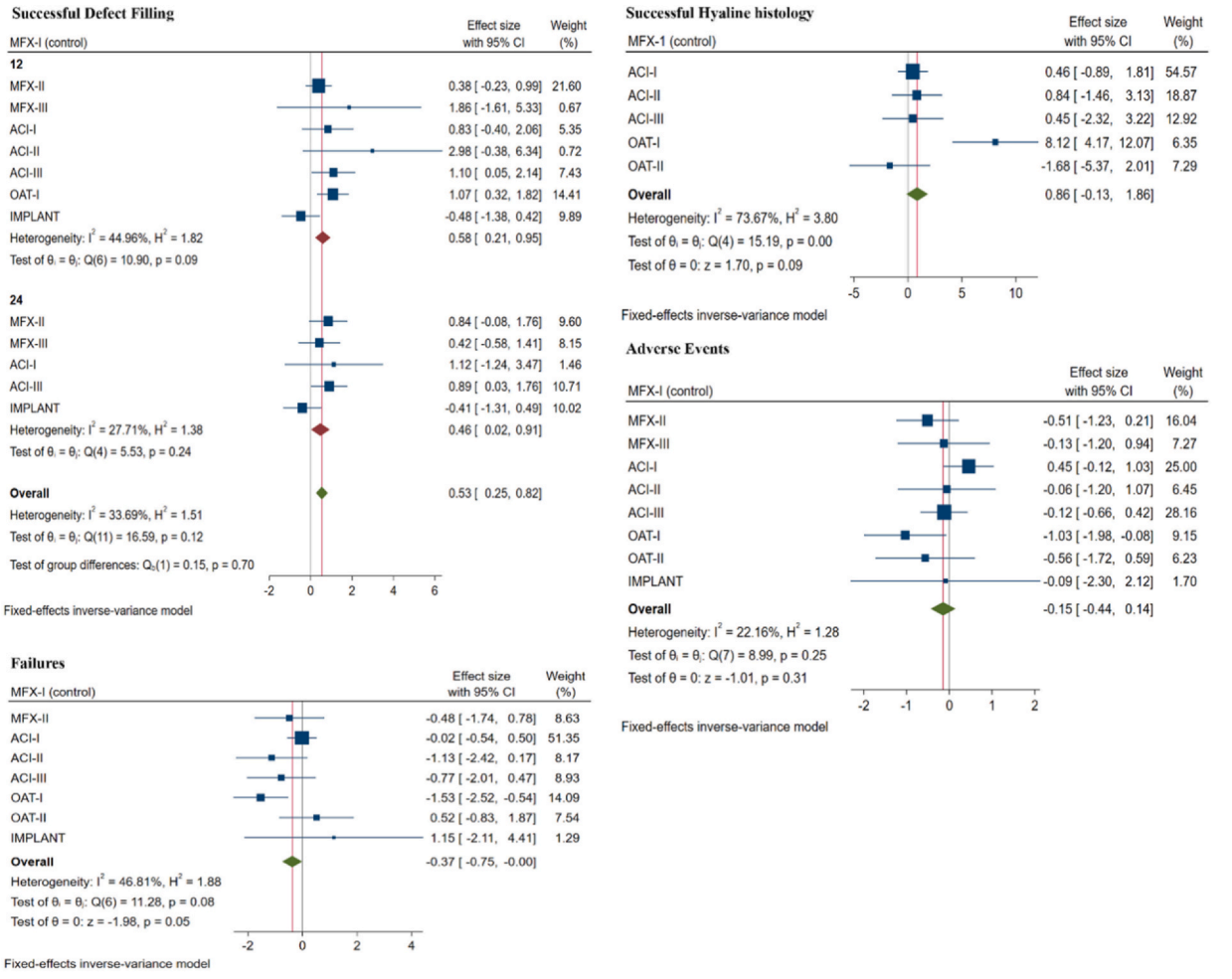

Fig. 4. Forest plot comparing the radiological, histological outcomes, and complications of interventions analyzed across the included studies in the network. ACI, autologous chondrocyte implantation; CI, confidence interval; MFX, microfracture; OAT, osteochondral allograft/autograft transplantation.

estimates, in some of the paired networks analyzed, without any evidence of systematic differences concerning the potential effect modifiers. We considered these apparent inconsistencies to be the effect of true differences between the direct and indirect estimates, and the indirect estimates to reflect a more precise estimate as they were from a network with a larger number of studies.

Confidence in evidence

Upon grading the paired comparisons in the network using the CINeMA approach, a "high" confidence was noted across most of the paired comparisons as shown in Table 2. However, some of the comparison pairs demonstrated "moderate" confidence. Lack of precision was the common reason that downgraded the quality of evidence in the indirect estimates due to wider CIs extending on both sides of the axes. We also noted some concerns due to the identified within-study bias from selective reporting of some of the outcome measures of interest.

Discussion

With the improved understanding of cartilage biology and advancement in surgical techniques, many different cartilage restoration, regeneration, and substitution techniques have been developed over the years.[81] A generalized classification system of these techniques would help in easy understanding of the techniques and will ease the communication among researchers and clinicians. The classification system that we have proposed is simple and based on the mechanism of cartilage repair—regeneration, restoration, or substitution.

The key observations in our results include the following: there is a paucity of long-term functional, radiological, and histological outcomes and complications of various procedures analyzed. All our results are in comparison with that of MFX-I. From the data

available, OAT-II showed significantly better functional outcomes at 10 years of follow-up. At 5 years of follow-up, MFX-III, ACI-III, and OAT-II showed significantly better functional outcomes. At 2 years of follow-up, ACI-III and MFX-II showed significantly better functional outcomes. At 1 year, OAT-II and ACI-III showed significantly better functional outcomes. Radiological outcomes were not significantly different for all interventions when compared with MFX-I concerning the MOCART score. Concerning radiological defect-filling of more than two-thirds, OAT-I at 1 year and ACI-III at 2 years showed significantly better results. Histological outcomes were reported by only a limited number of studies at 1 year. OAT-I being a cartilage restoration procedure, understandably showed significantly better results at 1 year. Complications were not significantly different among the analyzed procedures. Only ACI-I and implant arm (cartilage substitution category) showed a significant fall in functional outcomes even at 1-year follow-up.

Articular cartilage lesions of the knee are challenging clinical entities because of the limited ability of the chondral tissues to heal and the inevitable progression of these untreated lesions to osteoarthritis.[2] The endogenous repair mechanism of articular cartilage is inefficient, which is attributed to the poor penetration of regenerative cells into the defective area.[11] The concept of the MFX technique was initially put forth by Steadman et al,[82] wherein subchondral MFX was demonstrated to result in marrow stimulation, migration of mesenchymal stromal cells (MSC), and growth factors; and replacement of hyaline articular surface with fibrocartilage. It is still the gold-standard treatment for small cartilaginous defects; and offers the benefits of being a minimally invasive, single-staged, cost-effective approach in the management of cartilaginous defects with excellent short-term clinical outcomes.[8] The concerns for suboptimal fibrocartilaginous restoration and unacceptable long-term outcomes following MFX have paved the way for diverse cartilage restoration techniques such as mosaicplasty/OATS and cartilage regeneration techniques such as ACI.[5] Recently, the UK National Institute for Health and Care Excellence has recommended clearly in favor of ACI and chondral restoration modalities over traditional MFX techniques.[83] It has been hypothesized that the unsatisfactory outcomes with traditional MFX can be attributed to the inadequate concentrations of MSC and growth factors released from subchondral marrow tissue to the defect area. To circumvent this problem, researchers have supplemented MFX with intra-articular injectable adjuvants such as PRP, HA, and MSC.[56] In addition, techniques for augmentation of defects with scaffolds or polymer-based implants may aid in enabling the entrapment of marrow elements within the cartilage defect, and thereby, facilitate effective cartilage regeneration.[84,85] Such biological augmentation modalities, popularly described as “microfracture-plus” techniques, have demonstrated favorable short- and long-term benefits.[5] The current NMA comprehensively analyzed the existing literature on chondral injuries of the knee; and comparatively evaluated the clinical, radiological, and histological outcomes of all these treatment modalities. As discussed above, there was low heterogeneity or inconsistency and “high confidence” concerning the reporting and paired comparisons of the functional outcome measures. Thus, the quality of evidence on this subject in the current literature is good.

Among cartilage regeneration interventions, ACI-III demonstrated the best short-term (1 and 2 years) and mid-term (5 years) results. On a similar note, the use of acellular adjuvants (such as PRP, HA, collagen, and autologous matrix-induced chondrogenesis) following MFX also seems to improve outcomes during the early (Cincinnati score at 1 and 2 years) and late (WOMAC score at 5 years) follow-up time points.

In a previous NMA by Riboh et al,[9] MFX and advanced cartilage regeneration modalities demonstrated similar functional outcomes and failure rates at 2 years; nevertheless, the regenerative procedures resulted in ameliorated repair tissues and mitigated reoperation rates at 5 or 10 years. In a systematic review of RCTs, Karpinski et al[6] showed that MACI was a safe and valid single-staged technique to induce cartilage repair in small- to medium-sized articular defects. Gou et al,[86] based on a systematic review comparing ACI and MFX, demonstrated significant benefits in activities of daily living, improved quality of life, and pain relief at 2 and 5 years. Na et al[87] in a previous meta-analysis have included 5 articles comparing ACI and MFX and have concluded that ACI with collagen membrane and MACI (ACI-II and ACI-III, respectively) have demonstrated better results when compared with MFX. Karpinski et al similarly compared 5 studies involving ACI and MFX and recommended MACI for small-to-medium defects of the knee. Both these studies, similar to our study, highlighted the paucity of long-term data on histological and radiological outcomes in cartilage regeneration techniques.[6,87]

Among the cartilage restoration interventions, OAT-I provides the best short-term (at 1 and 2 years) pain relief. At 1 and 2 years, OAT-I also results in good WOMAC and Tegner scores. This is consistent with the fact that OAT-I directly replaces the articular surface and therefore, provides the quickest relief from symptomatology. There is not much evidence regarding the long-term functional outcome following this intervention. So longer-term benefits of this modality, in comparison with treatment options in the cartilage regeneration category, are still unclear. OAT-II (mosaicplasty) has shown significantly better functional outcomes concerning Lysholm score till 10 years of follow-up. There is still a paucity of data (both early and late) regarding other functional, radiological, and histological outcomes following mosaicplasty.

In a NMA comparing diverse cartilage repair modalities with MFX, Zamborsky et al[88] showed that cartilage restoration techniques had substantially improved the quality of repair tissue, reduced failure, and quicker return-to-activity rates. In a systematic review by Han et al,[89] the OAT group had earlier return to play, ameliorated functional outcome (Lysholm, Tegner, and International Cartilage Regeneration and joint preservation Society) scores, and reduced failure rates than the MFX procedure. In another meta-analysis by Pareek et al,[90] OAT achieved higher-activity status with lower failure rates, as compared with MFX while treating lesions larger than 3 cm^2. However, there was no statistically significant difference in lesions smaller than 3 cm^2. Nevertheless, both these studies emphasized the paucity of high-quality data on long-term outcomes following the OAT procedure.

None of the described interventions has significantly increased reported rates of adverse events, complications, or failures, as compared with MFX. In general, OAT-I seems to be the safest procedure, with the lowest prevalence of adverse events and failure rates (defined as the need for subsequent, revision surgeries). In a recent systematic review by Arshi et al,[5] it was concluded that the administration of biological adjuvants following MFX (microfracture-plus technique) was a safe approach for marrow stimulation to treat chondral deficiencies. However, they emphasized the need for higher-quality evidence to make definitive conclusions.

The type of procedure that a surgeon chooses depends on several factors such as the physiological status of the patient, defect size, affordability, technical demand of procedures, and resource limitations. From the available literature, for smaller- to medium-sized defects, autologous OAT-II seems to be a promising option with improved long-term functional outcomes. The allogeneic osteochondral graft can be used for larger-sized defects. Other options such as ACI-III and MFX-III can also be tried in larger defects depending on the resource availability.

Though our study is one of the most comprehensively performed reviews of the existing literature on this subject, there are certain limitations. The long-term data on histological and radiological outcomes following cartilage repair techniques are limited. There is substantial paucity as well as heterogeneity in the reporting on the diverse functional outcome measures following cartilage repair techniques (especially in OAT-I, -II, and implants) that prevented uniform comparison of events. We also did not analyze the outcomes subcategorized based on defect sizes and location. The classification that we provided does not include the recently developed techniques that have not been employed in RCTs. Including those techniques would make the classification only exhaustive. Without RCTs, the results of those techniques cannot be interpreted with confidence.

Conclusion

All procedures analyzed were found to be safe and have comparable complication and failure rates as the traditional MFX-I technique. There is a substantial paucity of long-term data in the literature regarding histological, radiological, and functional outcome measures of various interventions at said time points. From the available data, ACI-III, OAT-II, and MFX-III offered significantly better functional outcomes at 5 years. OAT-II is found to have a significantly better 10-year functional outcome.

Ethics approval

This is a systematic review and individual patient consent form does not apply to this study type.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jcjp.2023.100163.

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