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Review

Scaffold-associated procedures are superior to microfracture in managing focal cartilage defects in the knee: A systematic review & meta-analysis

Sheena Seewoonarain, Divolka Ganesh, Edward Perera, Ravi Popat, Julian Jones, Kapil Sugand, Chinmay Gupte

MsK Lab, Dept of Medicine and Surgery, Sir Michael Uren Hub, Imperial College, London W12 0BZ, United Kingdom

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ABSTRACT

Background: Debate continues as to whether surgical treatment with chondral-regeneration devices is superior to microfracture for focal articular cartilage defects in the knee.
Purpose: To evaluate the superiority of scaffold-associated chondral-regeneration procedures over microfracture by assessing: (1) Patient-reported outcomes; (2) Intervention failure; (3) Histological quality of cartilage repair.
Study Design: A three-concept keyword search strategy was designed, in accordance with PRISMA guidelines: (i) knee (ii) microfracture (iii) scaffold. Four databases (Ovid Medline, Embase, CINAHL and Scopus) were searched for comparative clinical trials (Level I-III evidence). Critical appraisal used two Cochrane tools: the Risk of Bias tool (RoB2) for randomized control trials and the Risk of Bias in Non-randomized Studies-of Interventions (ROBINS-I). Study heterogeneity permitted qualitative analysis with the exception of three patient-reported scores, for which a meta-analysis was performed.
Results: Twenty-one studies were identified (1699 patients, age range 18–66 years): ten randomized control trials and eleven non-randomized study interventions. Meta-analyses of the International Knee Documentation Committee (IKDC), Knee Injury And Osteoarthritis Outcome Score (KOOS) for pain and activities of daily living, and Lysholm score demonstrated statistically significant improvement in outcomes for scaffold procedures compared to microfracture at two years. No statistical difference was seen at five years.
Conclusion: Despite the limitations of study heterogeneity, scaffold-associated procedures appear to be superior to MF in terms of patient-reported outcomes at two years though similar at five years. Future evaluation would benefit from studies using validated clinical scoring systems, reporting failure, adverse events and long-term clinical follow up to determine technique safety and superiority.
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E-mail addresses: Divolka.ganesh1@nhs.net (D. Ganesh), Edward.perera1@nhs.net (E. Perera), r.popat14@imperial.ac.uk (R. Popat), Julian.r.jones@imperial.ac.uk (J. Jones), Kapil.sugand04@imperial.ac.uk (K. Sugand), c.gupte00@imperial.ac.uk (C. Gupte)

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1. Introduction

Knee articular cartilage injury encompasses a range of chondral pathology from osteochondritis dissecans to chondral wear. Furthermore, hyaline cartilage is limited by a lack of regenerative capacity in the skeletally mature individual, such that any form of focal chondral defect (FCD) can progress to advanced cartilage destruction resulting in end-stage osteoarthritis (OA)[43].

In the United States (US), FCDs affect approximately 900,000 patients resulting in over 300,000 surgical procedures per annum [52]. Yet surgical management remains controversial as no agreed standard exists. Current techniques can be broadly divided into bone marrow stimulation (microfracture), cartilage replacement and cartilage regeneration.

1.1. Microfracture (MF)

MF, is a single stage arthroscopic procedure and considered first line surgery [15]. Arthroscopic awls are used to penetrate (microfracture) subchondral bone, releasing bone marrow mesenchymal stem cells (MSCs) to facilitate a fibrocartilaginous repair. MF is relatively low-cost, reproducible and less technically demanding than other techniques. Despite concerns that the fibrocartilaginous repair may degenerate over time, MF continues to be the most commonly used intervention accounting for 96% of arthroscopic cartilage surgery [54].

1.2. Scaffold-associated procedures

The use of autologous chondrocyte implantation (ACI) stimulates hyaline cartilage repair [15]. However, the cells must be harvested from tissue and osteochondral autografts may be limited by tissue availability, donor site morbidity, poor integration and a disparity between graft size and host defect. Subsequent cell based techniques evolved to incorporate three dimensional (3D) scaffolds, commonly referred to as third generation chondral regeneration. Scaffolds can be combined with cells and/or bioactive molecules to stimulate chondrogenesis in addition to providing a physical scaffold. Scaffolds are implanted either arthroscopically or via mini-arthrotomy in either single or two-stage procedures. Although studies suggest that scaffolds are set to replace cartilage replacement techniques (e.g. osteochondral allograft (OCA)) they are currently not licensed for general use in many countries, partly due to limited evidence, expense and lack of economic efficacy [10].

Several systematic reviews (SRs) have assessed randomized control trials (RCTs) of surgical knee cartilage repair techniques (SKCRT), including autologous chondrocyte implantation (ACI), osteochondral autograft transfer system (OATS), osteochondral allograft (OCA) and MF, and found that no single treatment had superior outcomes [32,12]. This finding was partially disputed by a recent SR reporting that MF had a higher failure rate, at follow up greater than 3 years, compared to other techniques when only considering Level 1 evidence [54], whereby trial conditions may not be transferable to clinical practice or all patient populations. These findings were partially supported by another SR when comparing MF and MF with augmented procedures to SKCRTs but only with regards to the KOOS Sport and KOOS QOL scoring system with an average follow up time of 3.5 years[1]. Additionally, the SRs neither accounted for the different interpretations of 'failure', nor reviewed grey literature which may have biased their findings. Clinical guidelines from both governmental and other professional bodies are based on all available literature, and all levels of evidence, in order to inform surgical practice.

Several SRs focused on directly comparing MF to all generations of ACI. Two SRs reported MF had poorer patient-reported five year outcomes than ACI [33,17] though one SR reported no significant difference [28]. Though previous SRs appraised all forms of ACI including the recent SRs by Zamborsky et al. [54] and Abraamyan et al. [1], shifting trends over the past decade have seen an increased use of 'newer generation ACI' phase out first generation ACI, whereby chondrocytes are seeded or loaded into a micro-environment created by a 3-dimensional scaffold or membrane to encourage cartilage regeneration. To our knowledge, no SR has compared MF to solely 3rdgeneration ACI i.e. scaffold-associated procedures.

2. Aims

The purpose of this SR was to evaluate the superiority of scaffold-associated procedures over MF to surgically treat human knee FCDs and inform clinical management. Superiority of the following outcomes were assessed: Patient-reported outcome measures; Failure rates and adverse events (AEs); Histological quality of cartilage repair.

3. Materials and methods

3.1. Search strategy

A comprehensive search strategy was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (PRISMA). Four databases were searched: MedLine (Ovid), Embase, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Scopus (appendix A). The strategy was based on a three concept search: (i) knee (ii) microfracture, and (iii) scaffold terminology. The search was last run 15th Sept 2021.

3.2. Inclusion and exclusion criteria

Comparative studies of the two interventions were included. Inclusion and exclusion criteria were developed prior to study selection (Table 1).

In order to appraise all available evidence, additional grey literature was explored: (i) Trove (trove.nla.gov.au) did not reveal any relevant literature, and (ii) Open Grey (opengrey.eu) revealed two theses regarding FCDs but not relevant to our SR. The NIHR SR registry, Prospero, revealed 13 ongoing SRs regarding various aspects of knee FCDs but none identical to this SR. Lastly, contemporary trial registries were searched for relevant clinical trials (n = 10) and additional data (Table 2).

3.3. Study selection

Following the search, studies were selected using a two-step screening process (Covidence SR software, Veritas Health Innovation). The first step of abstract screening was conducted by two reviewers (Cohen's Kappa inter-rater reliability 0.503). In the second step, two reviewers assessed the suitability of full text studies suitable using the pre-defined inclusion and exclusion criteria (Cohen's Kappa inter-rater reliability 0.8458; Table 1). During both steps, any conflict was resolved with a third reviewer. Corresponding authors of one non-English language full-text study and one bilingual abstract were contacted for study information [5,41]. No response was received.

Table 1
SR inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
Human studies	Animal studies In vitro studies
Comparative trial $\geq$ 5 patients in each group	Case reports/case series/systematic reviews Editorials/comments/surgical techniques/abstracts/letter
Must include microfracture AND scaffold associated procedure +/- other surgical technique (s)	Non-English language or English translation not available
Knee Joint	Patient < 18 years

Table 2
Trial registry search results for relevant clinical knee FCD trials listed by governing body. Abbreviations: World Health Organization (WHO), International Committee of Medical Journal Editors (ICMJE), International Standard Randomized Controlled Trial Number (ISRCTN), United Stated (US), National Institute for Health Research (NIHR). Data not stated (-).

Group	Trial Registry	Ongoing clinical trials	Clinical trials terminated or suspended
WHO and ICMJE	ISRCTN	1	-
US National Library of Medicine	ClinicalTrials	8	10
NIHR	Funding Award	1	-

3.4. Data extraction

Data extraction tables were manually compiled, for data regarding study information (author, year published, study type, funding), scaffold type, patient demographics, lesion data, clinical outcomes (patient scores, failure) and histology data. Data was spot checked by two other reviewers.

3.5. Critical appraisal

Final studies included randomized control trials (RCTs) and non-randomized study interventions (NRSIs). Therefore two Cochrane critical bias tools were used: (i) risk of bias (RoB 2) tool for RCTs and (ii) risk of bias in non-randomized studies (ROBINS-I) tool for NRSIs. Both tools use a set of 'signaling questions' to guide the appraiser to judge the risk of bias. The RoB 2 tool assesses risk across five domains and can be judged as low, high or some concerns. The ROBINS-I tool assesses risk across seven domains and the assigned risk can be low, moderate, serious, critical or no information [44,45]. Critical appraisal was carried out by two reviewers.

3.6. Presentation of results and statistical analyses

Outcome measures included patient related outcome scores, failure and adverse events, and histological study scores. Where possible, quantitative data analysis was used to address the hypothesis and outcome aims. A formal meta-analysis using both fixed and random effects models for summary estimated were used dependent on study heterogeneity. Continuous outcomes were reported as mean differences with 95% confidence intervals (CI) presented as forest plots with I [2] heterogeneity statistics (RevMan V5.3).

4. Results

The search strategy identified twenty-one studies for further analysis (Figure 1).

4.1. Critical appraisal of studies

Twenty-one studies were identified: ten (47.6%) randomized controls trials (RCTs) and eleven (52.4%) non-randomized study interventions (NRSIs: five prospective cohort studies, six retrospective cohort studies). Study quality was assessed with two Cochrane critical appraisal tools: RoB 2 for RCTS and ROBINS-I for NRSI [44,45]. Cochrane tools were selected, based on the related method of appraising risk factors, enabling both RCT and NRSI analysis in the same SR.

Study bias was presented as a traffic light plot and overall visualization plot (Figure 2). All studies displayed varying levels of risk, but none were excluded based on risk. 20% RCTs were deemed overall low risk and 20% deemed overall high risk. All NRSIs were deemed moderate risk. Reasons for high risk or serious risk are listed in appendix B.

Three studies had domains that were deemed high or serious risk (appendix B). [48], an extension study of [3], included a power analysis but underpowered their study [48,3]. Treatment centers with low recruitment rates were closed after two years despite the study endpoint being five years. Eleven studies in total used a power analysis (six RCTs, five NRSIs) yet Sofu et al. cited it as a requirement but did not perform it [42]. Saris et al. used a 90% power calculation compared to 80% across studies and generally accepted power for clinical trials [40]. Ibarra 2021 and Meza 2019 had a higher level of risk due to confounding of results with concomitant surgery [22,30].

The mean patient loss of follow-up was 11.63% (range 0–38.78%) amongst prospective studies (nine RCTs, five NRSIs). Anders et al. had the highest loss but did not specify reasons [3]. Eleven studies had patient drop-outs and five studies provided reasons. However, reasons included terms such as 'protocol violator,' 'patient choice' and 'unknown reason.'.

4.2. Study details

Study details are shown in Table 3 with further details of the scaffold chemistry and morphology provided in Appendix C. All studies were published within the past thirteen years. Volz et al. is an extension of the Anders et al. study; Brittberg et al is an extension of the Saris et al. study [48,3,8,40]. Both were included as outcome measures reported at different time

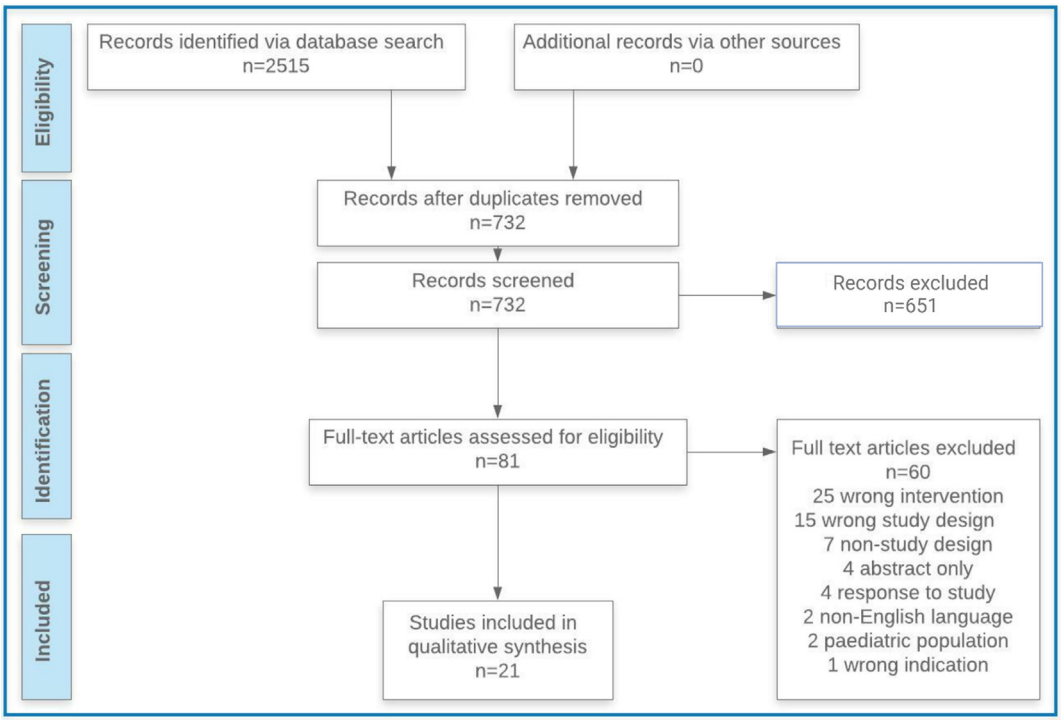

Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of the study review process. Full-texts articles included n = 21. Full-text articles excluded with reasons listed n = 60.

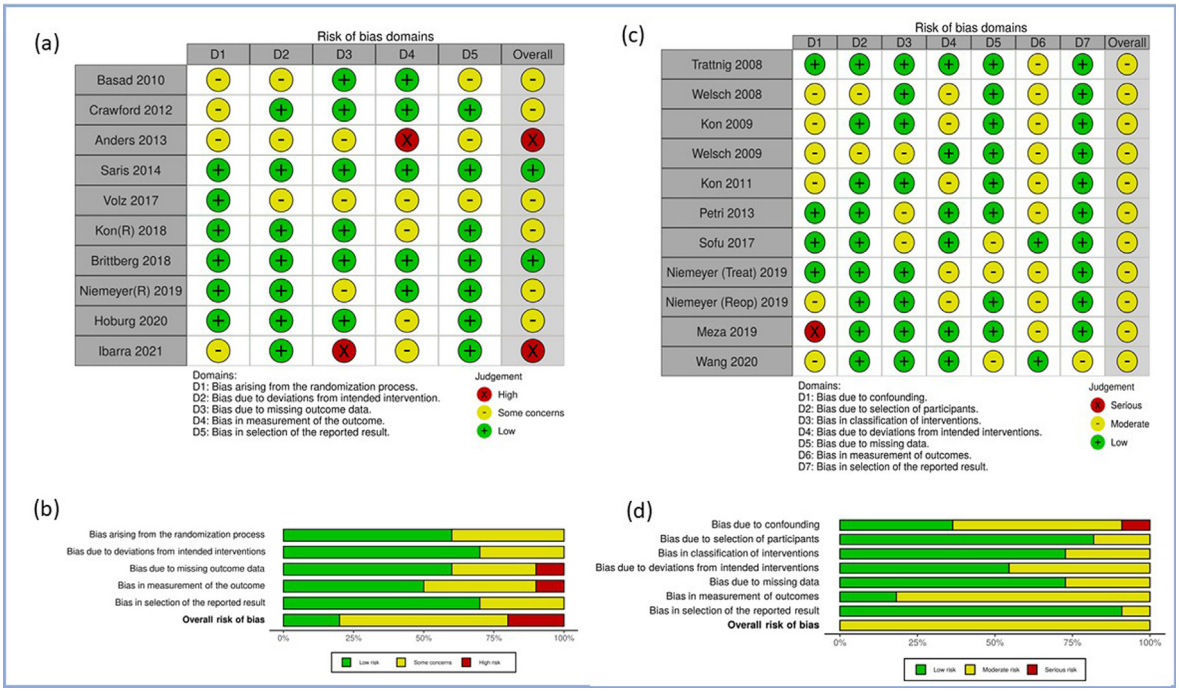

Figure 2. Cochrane risk of bias of studies. a. Risk of bias (RoB 2) tool for randomized control studies (RCT). Judgement across five domains for 8 RCTs b. Weighted summary plot of risk of bias (%) for RCTs c. Risk of bias for non-randomized studies of intervention (ROBIN-I). Judgement across seven domains for 12 NRSIs d. Weighted summary plot of risk of bias (%) for NRSIs.

points. Niemeyer [Reop] 2019 and Niemeyer [Treat] 2019 assessed different outcomes in the same patient population [35,36].

Participant details are shown in Table 6. In total 1,699 patients (study range 20–254) with an age range of 18–66 years were included. Participants in six studies had concomitant surgery, either ligament reconstruction or meniscal repair/resection (range 10–70.59%).

Eighteen studies provided information on the cartilage lesion characteristics with lesion size ranging from 1.7-4.99 cm^2 across studies (Appendix D). Thirteen studies stated lesion grade and of these, only Niemeyer [RCT] 2018 included patients with ICRS grade < III. Niemeyer [Treat] 2019 and Niemeyer [Reop] 2019 did not provide lesion data (Appendix D) [34,36,35].

4.3. Clinical outcome scores

A total of fourteen scoring systems were used (Figure 3). Studies may have used one or multiple scoring systems at the study endpoint or multiple time points; most commonly baseline, 12 months and 24 months. The most commonly used scoring systems were Knee Injury and Osteoarthritis Outcomes Score (KOOS), International Knee Documentation Committee (IKDC) and Lysholm (Figure 3).

Figures 4 and 5 summarize the meta-analysis of the clinical outcomes scores, suggesting better outcomes with scaffold procedures. The IKDC score is a single outcome score ranging from 0-100 with 100 being the best i.e. asymptomatic. From extracted data, four meta-analyses were performed, incorporating eight of the twenty-one studies (Figure 4a). Of the remaining thirteen studies, there was inadequate overlap in reporting of outcomes to perform quantitative analysis. A meta-analysis of six studies including 502 participants, compared the change in IKDC score between those undergoing MF and scaffold procedures. The analysis demonstrated a statistically significant improvement in IKDC scores in the scaffold group (MD = 5.48, 95% CI: 2.61 – 8.35, $p < 0.01$). All scores for studies were extracted at 24 months, except for Kon et al. [26], which was extracted at 60 months due to availability of data, although heterogeneity remained not to be important ($I^2 = 10\%$).

Two meta-analyses were performed comparing change in KOOS. Of the five patient-relevant subscales within KOOS, meta-analysis of KOOS pain and KOOS ADL were performed, based on reporting of outcomes (Figure 4b and 4c). For KOOS pain a meta-analysis of three studies, including 281 participants demonstrated a statistically significant improvement in the scaffold group (MD = 6.96, 95% CI: 2.74 – 11.18, $p < 0.01$, $I^2 = 10\%$). A statistically significant improvement in KOOS ADL score was demonstrated with MD of 8.80 (95% CI: 0.19 – 17.42, $p = 0.05$) in a meta-analysis of three studies including 276 participants. This was in favor of scaffold-associated procedures with moderate to substantial heterogeneity ($I^2 = 65\%$). A final analysis of three studies using the Lysholm score, included 138 participants, comparing scaffold-associated procedures to MF produced a MD of 12.42 (95% CI: 0.49 – 24.35, $p < 0.05$), with considerable heterogeneity ($I^2 = 75\%$)(Figure 4d).

Eight studies reported IKDC scores but had insufficient data to all be included in meta-analysis. Patient number ranged from 20-357 across time points (baseline-90 months). The highest patient number was at 24 months and comprised 23.2% of total participants across all studies. In all but one study, Meza et al [30], scaffold procedures resulted in a higher mean final score, suggesting a trend in favor of scaffold procedures (Figure 5).

Table 3
Included studies and details: author, year published, study type, country, source of funding, scaffold type and mean follow up (months). Abbreviations: RCT (randomized control study), PCT (prospective cohort study), RCS (retrospective cohort study), MACT (matrix-associated autologous chondrocyte transplantation), MACI (matrix-associated chondrocyte implantation), AMECI (arthroscopic matrix-encapsulated autologous chondrocyte implantation).

Ref	Author & Year	Study Type	Country	Funding	Scaffold (SC)	Mean follow up (months)
[50]	Welsh 2008	PCS	Austria	Austrian Science Fund	MACT: Hyalograft C	24
[47]	Trattnig 2008	PCS	Europe	Austrian Science Fund	MACT: Hyalograft C	32
[27]	Kon 2009	PCS	Italy	Nil	MACT: Hyalograft C	60
[51]	Welsch 2009	PCS	Austria	Austrian Science Fund	Hyalograft C	32
[7]	Basad 2010	RCT	Germany	Nil	MACI: Collagen fiber bilayer	24
[25]	Kon 2011	PCS	Italy	Nil	Hyalograft C	90
[11]	Crawford 2012	RCT	US	Histogenics Corporation	NeoCart	26
[38]	Petri 2013	RCS	Germany	Nil	CaReS MACT	36
[3]	Anders 2013	RCT	Germany	Nil	Chondrogide AMIC	48
[40]	Saris 2014	RCT	Europe	Sanofi	MACI (ACI-MAIX)	24
[48]	Volz 2017	RCT	Germany	Geistlich Pharma AG	Chondrogide AMIC	60
[42]	Sofu 2017	RCS	Turkey	Nil	Hyalofast	24
[8]	Brittberg 2018	RCT	Europe	Sanofi	MACI: collagen fiber bilayer	60
[26]	Kon [RCT] 2018	RCT	Europe	Fin-Ceramica	MaioRegen	48
[30]	Meza 2019	PCS	Mexico	Nil	MACI: collagen fiber bilayer	48
[35]	Niemeyer [Reop] 2019	RCS	Germany	CO.DON AG	MACI: collagen fiber bilayer	24
[34]	Niemeyer [RCT] 2019	RCT	Germany	CO.DON AG	Spherox	24
[36]	Niemeyer [Treat] 2019	RCS	Germany	CO.DON AG	MACI: collagen fiber bilayer	60
[20]	Hoburg 2019	RCT	Germany	CO.DON AG	Spherox	36
[49]	Wang 2020	RCS	US	Nil	TruFit	42
[22]	Ibarra 2021	RCT	Mexico	Nil	MACT: AMECI	72

Table 4
Study participant details including number, demographics, participation allocation to microfracture (MF) or scaffold (SC), concomitant surgery at time of intervention (%nm=% not mentioned). Data not reported (-).

Ref	Study	Participants (n)	Mean Age (yrs)	Age range (yrs)	Gender M:F	BMI	Intervention allocation (n)		Concomitant surgery (%)
							MF	**SC**	
[11]	Crawford 2012	30	40.4+/-9	-	25:5	28+/-4	9	21	No
[48]	Volz 2017	47	34+/-11	27–47	37:10	26.8+/-3.9	13	34	No
[50]	Welsh 2008	20	40.5+/-12.3	20–64	15:5	-	10	10	No
[30]	Meza 2019	17	ns	18–55	9:8	26.12	7	10	70.59
[40]	Saris 2014	144	33.85	21–53	93:51	26.4+/-4	72	72	Yes (%nm)
[34]	Niemeyer [RCT] 2019	102	37+/-9	-	61:41	25.7+/-3.1	50	52	No
[8]	Brittberg 2018	128	MF 34 SC 38	18–54	82:46	-	65	63	Yes (%nm)
[26]	Kon [RCT] 2018	118	MF 35.2+/-10.2 SC34+/-10.9	-	67:33	MF 25.6 SC 25.2	49	51	No
[36]	Niemeyer [treat] 2019	254	MF 37 SC 36	-	150:104	-	127	127	No
[27]	Kon 2009	80	29.8	-	60:20	-	40	40	40.8
[42]	Sofu 2017	43	41.67	-	16:27	23	19	24	No
[3]	Anders 2013	38	37.3	21–50	31:7	26.7	10	28	No
[7]	Basad 2010	60	34.2	-	42:17	26.3	20	40	10
[20]	Hoburg 2019	102	37+/-9	-	61:41	25.8+/-3.1	50	52	No
[38]	Petri 2013	20	MF 41.7+/-13.2 SC 35.8+/-11.4	-	10:10	26.3+/-4.1	10	10	No
[51]	Welsch 2009	20	35.6+/-8.9	20–52	12:8	MF 23.3 SC 24.5	10	10	No
[47]	Trattnig 2008	20	MF 27.1+/-16.3	19–66	18:2	-	10	10	No
[25]	Kon 2011	41	SC 37.4+/-8.2	-	41:0	-	20	21	53.7
[35]	Niemeyer [Reop] 2019	254	MF 36.94+/-10.86 SC 36.84+/-10.91	-	150:104	-	127	127	No
[49]	Wang 2020	132	MF 40.7+/-11.5 SC 42.9+/- 12.8	-	91:41	MF 27.5+/-3.9 SC 26.7+/-7.7	66	66	No
[22]	Ibarra 2021	48	MF 35.8+/-9.1 SC 33.7+/-9.4	18–50	31:17	MF 26.6+/-3.1 SC 25.5+/-3.1	24	24	50
	Total	1718			1102:597	13/20 studies	718	802	6/20 studies

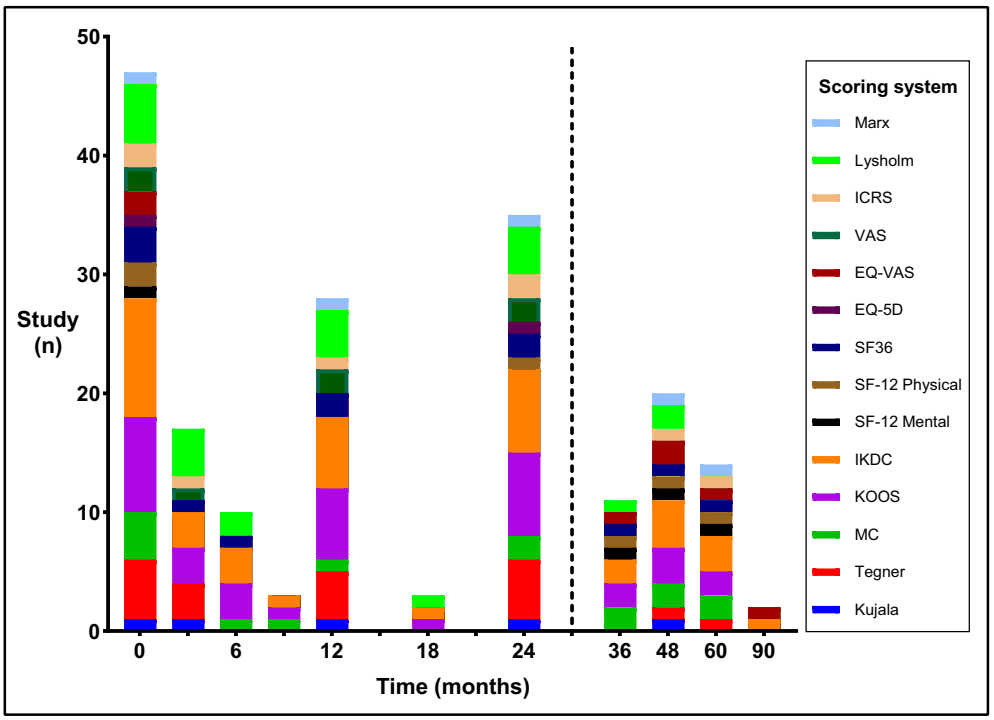

Figure 3. Patient-reported scoring systems used from baseline (0 months) to 90 months. Studies may have used multiple scoring systems. Abbreviations: International Cartilage Repair Society (ICRS), Visual Analog Scale (VAS), EuroQol Visual Analog Scale (EQ-VAS), Short Form (SF), International Knee Documentation Committee (IKDC), Knee Injury and Osteoarthritis Outcome Score (KOOS), Modified Cincinnati (MC).

4.4. Failure and adverse events

The definition of "failure" and documentation of adverse events (AE, thirteen studies; Table 5) was variable and inconsistent across studies. Failure definition ranged from need for re-operation to worse clinical outcome than baseline. AE documentation ranged from arthralgia, septic arthritis, muscle atrophy to joint crepitation. Seven studies defined 'failure' and ten studies reported failure rates. Ten studies reported AEs. Crawford 2012 and Ibarra 2021 subdivided AEs into minor and major events [11,22].

4.5. Histology outcomes

Histological outcomes varied from presence of fibrocartilagenous matrix in both groups (Volz [48], Table 6) to a higher level of normal or nearly normal cartilage in the scaffold group. Six studies conducted a histological analysis: three after twelve months and three after twenty-four months (Table 6). Four used the International Cartilage Repair Society (ICRS) score and two used the Bern score. The ICRS score is based on three domains (integration to border zone, macroscopic appearance, degree of defect repair) with an overall score from 0 –12 (score 8–11 classed as grade II indicating a 'nearly normal' cartilage assessment). The Bern score assesses cartilage repair across three domains (intensity and uniformity, distance between cells and extra-cellular matrix produced, cell morphology) with an overall score ranging from 0-9.

Two studies assessed the ICRS score using video imaging during second look arthroscopy [22,34]. Ibarra et al. stated that the correlation co-efficient between the two surgeons carrying out the second look arthroscopy was 0.7 [22]. Four studies assessed a tissue biopsy though the size and location was not described [48,40,22,7]. Depth of the lesion was described as 'osteochondral' by Volz et al. [48] and as 'cylindrical full thickness' by Basad et al [7]. Only Volz et al. specified the staining markers used i.e. Safranin-O, collagen type I and type II [48].

5. Discussion

Our systematic review and meta-analysis found that scaffold-associated procedures are superior to MF two years post-procedure, with final outcome scores demonstrating a trend in favor of scaffold procedures in terms of patient-reported outcomes (IKDC) at up to five years post-procedure. Superiority of patient-reported outcomes, failure and adverse events, and histological outcomes were evaluated.

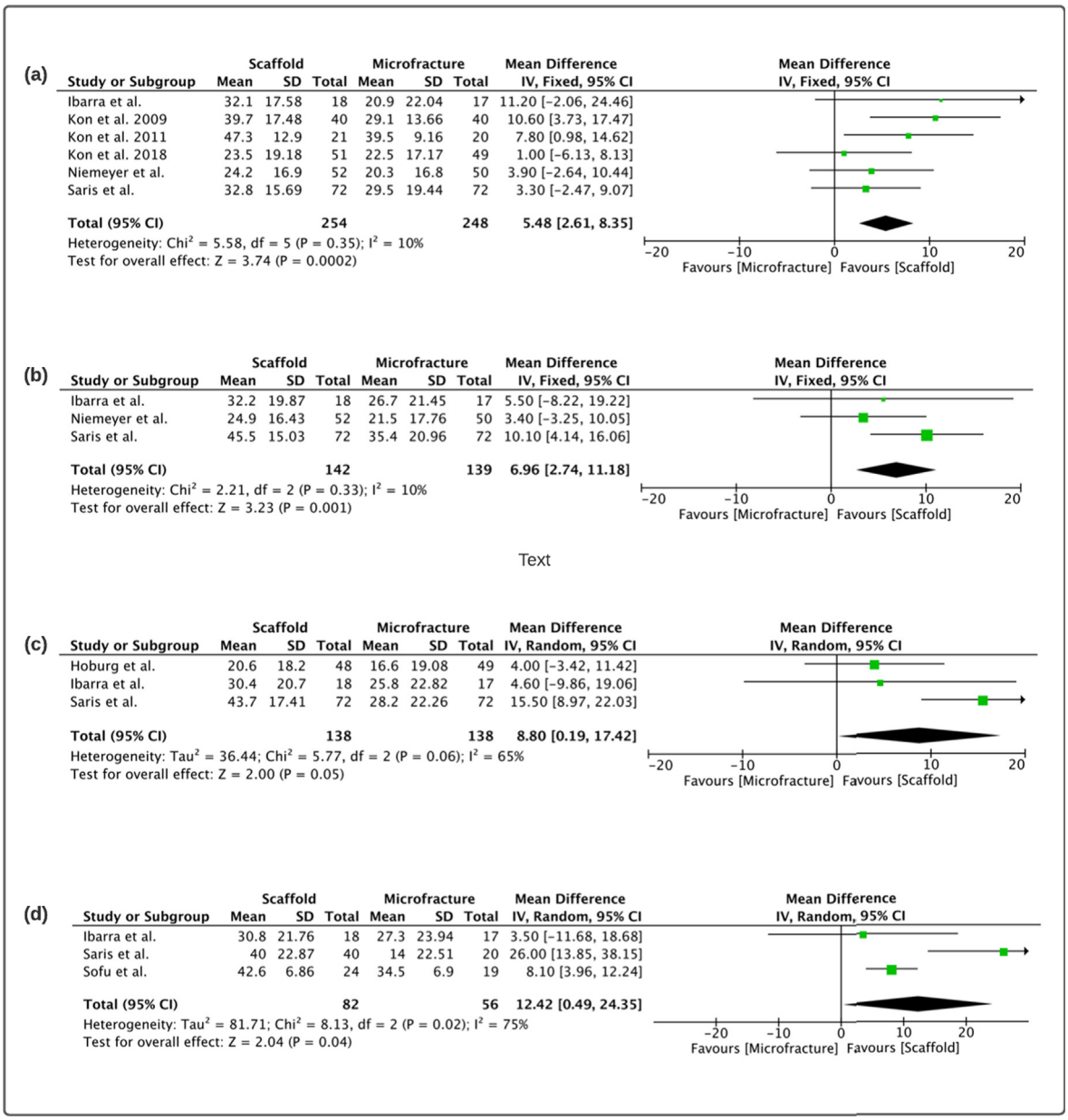

Figure 4. Meta-analyses of patient reported outcomes. a. IKDC b. KOOS pain c. KOOS ADL d. Lysholm. Abbreviations: IKDC (International Knee Documentation Committee), KOOS (Knee Injury and Osteoarthritis Score), ADL (Activities of Daily Living).

Previous SRs that only included RCTs of surgical knee cartilage repair techniques (SKCRT) were affected by study heterogeneity; one SR was unable to undertake a meta-analysis due to varying methodology [28]; another was unable to recommend any overall treatment due to the small study numbers with low risk of bias [12]; a third SR, by Zamborsky et al., concluded that MF had higher failure rates using Level 1 evidence [54]. However, their SR did not take into account non-randomized control trials or grey literature as a representation of clinical practice. Our SR included RCTs (n = 10) and NRSIs (n = 11) with the expectation that a broader range of data would be generated for analysis. The heterogeneity permitted limited quantitative analysis and qualitative analysis was also performed. The three main outcomes that were evaluated were clinical outcomes, failure and adverse events, and histology.

5.1. Clinical outcomes

Patient-reported outcomes were used to evaluate the response to treatment. In this SR, fourteen different scoring systems were used. Meta-analysis of the most prevalent scoring system showed that a higher improvement in patient reported out-

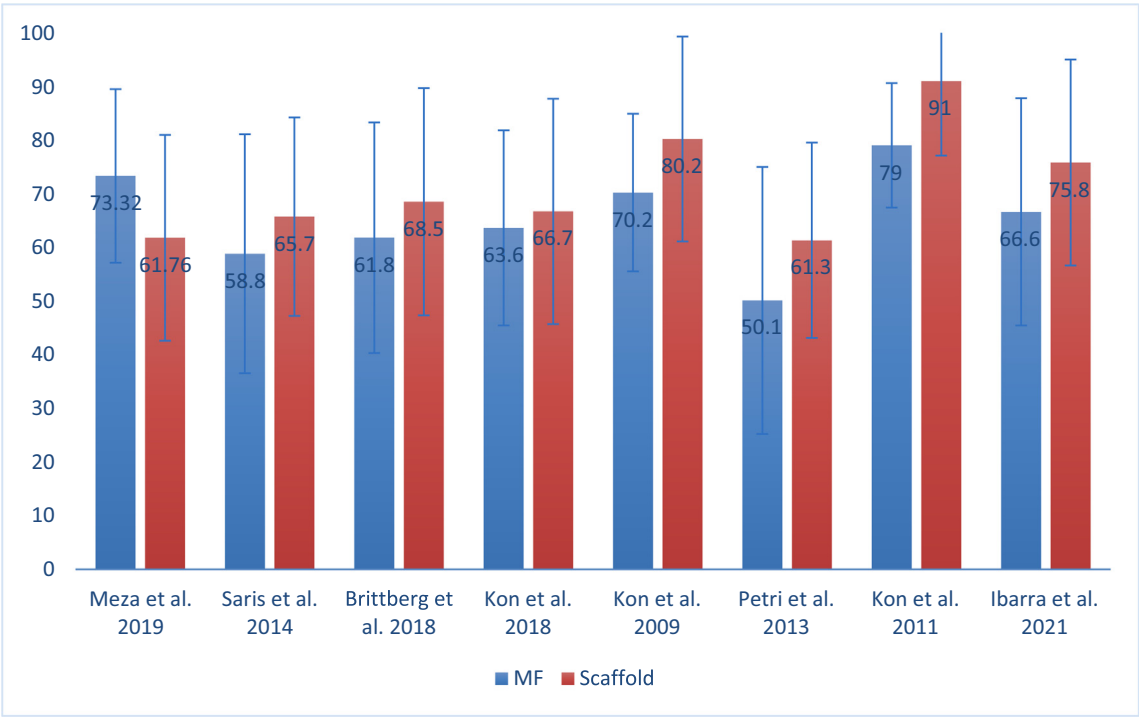

Figure 5. Final score of MF vs scaffold using the IKDC score and not included in the meta-analysis. 87.5% studies demonstrated that scaffold-associated procedures resulted in a higher overall mean score.

Table 5
Studies that reported the definition of failure, failure rates (%) and adverse outcomes (n). Data not reported (-).

Ref	Study	Definition of failure	Failure Rate (%)		Adverse events (n)	
			MF	**SC**	**MF**	**SC**
[11]	Crawford 2012	-	-		1 major 24 minor	1 major 62 minor
[48]	Volz 2017	-	-		1	1
[40]	Saris 2014	Anytime after week 24, both the physician and patient global assessment result was the same or worse than the baseline	2.8	0	60	55
[34]	Niemeyer [RCT] 2019	-	-		4	1
[8]	Brittberg 2018	Anytime after week 24, both the physician and patient global assessment result was the same or worse than the baseline	0.028		3	1
[26]	Kon [RCT] 2018	Need for re-intervention on the same defect based on the persistence or recurrence of symptoms	0.032	-	5	16
[27]	Kon 2009	Patient requiring re-operation because of symptoms due to the primary defect	2.5	0	1	0
[42]	Sofu 2017	-	0.052	0	0	1
[7]	Basad 2010	-	6.67		-	
[20]	Hoburg 2019	Patient required 2nd surgery	20	0	73	67
[25]	Kon 2011	Patient requiring re-operation because of symptoms due to the primary defect	5	0	-	
[49]	Wang 2020	-	-	1.5	-	4
[22]	Ibarra 2021	Revision surgery due to symptoms of > 50% detachment	8.3	0	1 major 33 minor	1 major 33 minor

comes was reported in the scaffold group. However, this analysis was only permitted to be carried out at two years post-procedure and limited by study heterogeneity. KOOS ADL score was further limited by a p-value of 0.05 (Figure 4).

A total of eight studies reported final outcome scores for IKDC, which was the most prevalent scoring system. However, due to insufficient reporting of data, it was only possible to perform meta-analysis of six studies, limiting outcome data to two years post-procedure to minimize heterogeneity. Nevertheless, analysis of all eight studies that reported final outcome scores extending up to 90 months post-intervention, revealed that all but one study demonstrated an improvement in IKDC

Table 6
Studies that analyzed histology specimens post operatively. Missing data or values not stated (-).

Study	Patients (n)	Time (months)	Histology Score				Study Comments
			ICRS	**ICRS Score**	**Bern**	**Bern Score**	
Volz 2017	2	24	Yes	-	No	-	Both groups: presence of fibrocartilaginous matrix without evidence of residual material
Meza 2019	17	12	Yes	MF 8.57+/-2.07 SC 10.86+/-0.38	No	-	SC group significantly better than MF (p = 0.01)
Saris 2014	116	24	Yes	-	No	-	No significant difference found
Niemeyer [RCT] 2019	16	24	Yes	-	Yes	-	No significant difference found
Basad 2010	2	12	No	-	No	-	Discontinued after 2 patients
Ibarra 2021	35	12	Yes	MF 9+/-1.8 SC 10.7+/-1.3	No	-	Higher level of normal or nearly normal cartilage in SC group

scores with scaffold procedures that persisted at 90 months. Any potential analysis of outcomes scores was limited by the diversity of scores, missing raw data and low patient numbers. Validated scoring systems for chondral pathology recommended by the ICRS include both the IKDC and KOOS.

As cartilage repair surgery techniques are relatively new, there is a paucity of reported long-term outcomes in the literature. In this SR five studies reported five-year outcomes and there are trials in progress (Table 2). Long-term data reporting results of surgical intervention may be aided by the development of a database to register and follow-up patients undergoing cartilage surgery. Niemeyer [Reop] et al. used the German health register to compare the reoperation rate within 2 years between groups [35]. They concluded that MF was associated with a higher rate (p = 0.498): however meniscal surgery as well as arthroplasty was included in the definition of re-operation, thus making it difficult to evaluate whether either technique prevents the progression of OA.

5.2. Failure rate and adverse events (AEs)

In this SR, seven studies defined 'treatment failure' and the definition differed as either the requirement for re-operation or a worsening clinical assessment (Table 5). Both MF and scaffold-associated procedures are surgically invasive techniques. Though at first glance, failure rates appear to be higher in the MF group, there is a disparity in the definition of treatment failure to objectively evaluate safety and survival analysis. The lack of clarity and transparency in 'defining, evaluating and reporting' outcomes is unfortunately applicable to orthopedic RCTs in general with only 7% defining 'failure' in a previous analysis [16].

Generally, the definition of AEs by International Organisation for Standardisation (ISO) is the accepted standard [23]. Under ISO guidelines, all AEs require reporting even if they appear unrelated to the intervention. It remains unclear which outcomes were considered an AE in studies that did not cite their AE classification system. This uncertainty is further compounded by the drop-out rate across studies (mean 9.67%) citing 'patient choice' and 'unknown reason' under-representing any potential concerns about either intervention.

5.3. Patient demographics and lesion characteristics

This SR revealed a gender disparity of female participants (35.14%) compared to male participants (64.86%). Yet no studies investigated sex-dependent differences to treatment considering that previous studies have shown sex-dependent differences include hyaline cartilage morphology, and rate of chondrogenesis [9,24,37]. Sex-dependent differences are important as women have a higher overall incidence of knee OA [46]. Interestingly, the Niemeyer research group investigated sex-dependent differences in a separate cohort study treated with autologous chondrocyte implantation (ACI) and found that female patients with patella OCDs had a worse prognosis than their male counterparts [29].

In this SR, the collective age range was 18–66 years as reported by 42.86% studies though patients aged above fifty were only included in two studies from 2008 [38,49]. Whole joint deterioration may occur with age in addition to the limited regenerative capacity of articular cartilage. Historically, this led to the suggestion of an upper age limit for bone marrow stimulation procedures. Two questionnaire studies of arthroscopy surgeons reported that 32.2% (n = 302) and 50% (n = 147) respectively would only offer cartilage repair surgery to patients aged below fifty years [14,39].

The combination of patient demographics and lesion characteristics continues to provide debate as to the optimal treatment and highlights the inconsistency in available evidence. To date, there are no definitive guidelines or globally accepted algorithm in choosing the most appropriate surgical management. Furthermore clinical practice is often determined by surgeon experience, choice, cost effectiveness, and access to techniques [14,39]. Despite ongoing clinical trials (Table 2), it appears that a consensus will be difficult to reach, especially considering the variable quality of studies (Figure 2).

5.4. Histological analysis

Histological outcomes were affected by a disparity in assessment (Table 6). Despite study designs including a histological analysis, only Meza et al and Ibarra et al analyzed all study participants (n = 52) and reported ICRS values [30,22]. In contrast, Niemeyer et al. used the Bern histological score [34]. No studies specified the size and location of the biopsy and furthermore two studies carried out an analysis only using a video based analysis during the second look arthroscopy. Basad 2010 acknowledged the difficulty in persuading an asymptomatic patient to undergo an invasive procedure to obtain a biopsy and discontinued this subsection of study protocol after performing biopsies on two patients [7]. Histological analysis remains contentious as the limiting factor of MF is the formation of fibrocartilage rather than native hyaline cartilage. The International Cartilage Repair Society (ICRS) advocates a histological assessment of cartilage repair procedures but noted its limitations including the range of histological scores, lack of validation in human models, requirement for a 2 mm size osteochondral (including the subchondral bone) tissue sample, sample fragmentation due to poor chemical fixation techniques e.g. aldehyde [31]. The ICRS recommended adding Safranin-O to the fixation formula and staining with haematoxylin and eosin. Only Volz et al. described the staining method which included safranin-O and markers for type I and II collagen [48].

One meta-analysis of all SKCRTs had two significant conclusions: firstly that MF had had poorer histological outcomes compared to cartilage regeneration techniques. Secondly, for cartilage regeneration techniques, cartilage histology scores improve, or mature, with increasing time since surgery to demonstrate more hyaline-like cartilage [13]. However no significant difference was found amongst the different generations of scaffolds when correlated to clinical outcomes in keeping with our findings that scaffold procedures were clinically superior to MF. Histological analysis will always be limited by the number of patients willing to undergo a second procedure and the lack of a standardized technique.

5.5. Critical bias

Two Cochrane critical bias tools were applied: RoB 2 (RCTs) and ROBINS-I (NRSIs) [44,45]. Both appraise risk factors other than study design using a series of signaling questions. The tools are not stringent flowcharts and afford a degree of leeway. An example is that one recent SR of SKCRTs used the RoB 2 tool and judged most studies as 'high' risk of bias in one domain based on the inability to blind the operating surgeon [53]. Yet closer examination of the Cochrane signaling questions accepts that blinding is not feasible in surgical trials and instead asks the appraiser to question the internal validity of the study i.e. whether there was imbalance between treatment groups, deviation from usual practice or analysis in the wrong intervention group. Thus no studies in this SR were deemed 'at risk' based on the inability to blind the operating surgeon alone.

Two studies were deemed 'high' or 'serious' risk (appendix A). One reason was due to confounding of patients with concomitant surgery. Five studies enrolled patients undergoing concomitant surgery, either ligament reconstruction or meniscal repair or resection (range 10–70.59%)(Table 4). The bias of concurrent surgery is recognized by the International Cartilage Repair Society (ICRS) [18]. Meniscal pathology increases the incidence of FCDs and subjecting patients to multiple invasive procedures is unethical. Therefore the ICRS recommends that a concomitant meniscal resection, if less than 50%, is acceptable if used as a separate study arm. Conversely, ligamentous injuries suggest a traumatic etiology to chondral pathology causing instability. Therefore the ICRS recommends that patients with concurrent ligament surgery should be excluded unless all participants undergo concomitant ligament reconstruction [18].

Though not part of the critical appraisal tool per se, an inherent bias was noted due to a minority reporting trial outcomes despite the increasing use of scaffold-associated procedures globally. Several studies were published by the same author or research group (e.g. Welsch 2008, Welsch 2009 and Trattnig) [50,51,47]. An additional risk of bias occurred in enrolling the same patient population e.g. Niemeyer [Reop] 2019 and Niemeyer [Treat] 2019, though studies measured different outcomes [35,36]. Taking into account the variable methodological quality, these factors only serve to further undermine their findings and preclude the use of meaningful quantitative analysis.

5.6. Systematic review limitations

This SR analyses the outcomes of two interventions, namely MF and scaffold-associated procedures. MF itself can be augmented with a wide range of injectable supplements, such as mesenchymal stem cells (MSCs), platelet rich plasma (PRP), hyaluronic acid (HA) and injectable implants that solidify in situ trapping MSCs e.g. BST-CarGel [4,6,41]. Augmented MF techniques are termed 'enhanced MF' or 'MF plus.' Such interventions were excluded to reduce heterogeneity in the MF control group.

Finally, scaffold-associated procedures also encompass a wide array of scaffold device design (Appendix C). One example included in this SR was spherox: made by cells grown in culture to form a matrix and compacted into spheroid 'scaffolds' thus differing in design to other forms of scaffolds. Historically, and in this SR, all scaffold-associated procedures were analyzed as the same group. However, there are a low number of studies directly comparing scaffold types or evaluating multiple SKCRTs further convoluting the superiority of one scaffold design over another. As scaffold use increases, a rise in clinical trials would also be expected and ensuing elucidation over optimal scaffold design. In order to optimize new scaffold

designs that are considered for human trials, a proposal would be to select those that show greater efficacy in animal trials and this could be further streamlined based on a gold standard animal model.

Despite the noted improvement in the general standard of SKCRT studies (RCTs and NRSIs) since 2004, a quality appraisal of meta-analytical SKRCT studies concluded that the quality of SRs remains variable with 40.1% studies judged low and 38.6% deemed very low using the Cochrane SR Grades of Recommendation, Assessment, Development and Evaluation (GRADE) [18,19,21]. Thus care must be taken when using the SR meta-analyses to inform clinical guidelines.

5.7. Future studies

The use of scaffold technology is ever increasing as researchers and engineers continuously experiment with scaffold design. In the United Kingdom the National Institute of Health and Care Excellence (NICE) will review its own guidelines following the completion of several RCTs including the UK based SISMIC study (Scaffold Insertion and MF compared to MF alone for osteochondral defects in the knee) projected to end in 2024. In the absence of a national register it is vital to follow-up patients undergoing cartilage repair surgery. The International Cartilage Regeneration & Joint Preservation Society, originally the ICRS 1997, published its first annual report in 2019 creating the first global clinical database [10].

6. Conclusion

This SR found that scaffold-associated procedure outcomes are superior to in terms of patient-reported outcomes (IKDC) to manage knee FCDs at two years post-procedure. No significant difference was noted post two years, although there was a trend favoring scaffolds.

Although failure, adverse events (AEs) and histological analysis were limited by study heterogeneity and missing data outcomes, our study does suggest that guidelines may need to be reviewed when considering scaffold versus MF in the management of FCD, taking into account clinical efficacy, cost, availability and surgeon skill level.

Further studies should standardize clinical scoring systems, explicitly define failure, and perform follow up histological analysis ethically.

Long-term, education and support should be made available for researchers and surgeons undertaking surgical trials, NRSIs or RCTs, to improve the internal validity and outcome reporting of studies. This approach will generate robust data, reduce publication bias and provide direction in the development of cartilage repair interventions. Furthermore, larger existing institutes should be encouraged to undertake long-term clinical studies to better determine technique safety and superiority.

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 1. Database search strategy performed for Medline, Embase, CINAHL and Scopus

Medline	Embase
1. exp Knee/or exp Knee Joint/ or knee.mp.	1. knee.mp. or exp knee/
2. exp Patella/or patella mp.	2. patella.mp. or exp patella/
3. exp Patellofemoral Joint/ or patellofemoral.mp.	3. exp patellofemoral joint/ or patellofemoral.mp.
4. femoropatellar.mp.	4. femoropatella.mp.
5. trochlea*.mp.	5. trochlea*.mp.
6. femoral condyle.mp.	6. exp femoral condyle/ or condyle*.mp.
7. 1 or 2 or 3 or 4 or 5 or 6	7. 1 or 2 or 3 or 4 or 5 or 6
8. MACI.mp.	8. MACI.mp.
9. AMIC.mp.	9. AMIC.mp.
10. MACT.mp.	10. MACT.mp.
11. scaffold.mp. or exp Tissue Scaffolds/	11. scaffold.mp. or exp tissue scaffold/
12. chondr* transplant*.mp.	12. chondr* transplant*.mp.
13. chondr*implant.mp.	13. exp chondrocyte implantation/ or chondr* implant*.mp.
14. osteochondr* regeneration.mp.	14. osteochondr* regeneration.mp.

Appendix 1 (*continued*)

Medline	Embase
15. chondr* replacement.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating, sub-heading word, key heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 16. (marix adj2 chondr*).mp.[mp = title, abstract, original title, name of substance word, subject heading word, floating, sub-heading word, key heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 17. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 18. microfracture*.mp. 19. 7 and 17 and 18	15. chondr* replacement.mp. [mp = title, abstract, heading word, drug trade name, original title, device, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 16. (matrix adj2 chondr*).mp.[mp = title, abstract, heading word, drug trade name, original title, device, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] 17. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 18. exp microfracture/ or microfracture*.mp. 19. 7 and 17 and 18
CINAHL	Scopus
Knee OR patella OR patellofemoral OR femoropatellar OR trochlea AND "chondr* implant*" OR "chondr* transplant*" OR "scaffold" OR "osteochondr* regeneration" OR matrix N1 chondr*AND microfracture*	(microfracture*) AND (knee OR patella OR patellofemoral OR femoropatellar OR trochlea* OR condyle*) AND (maci OR amic OR mact OR "scaffold" OR "chondr* implant*" OR "chondr* tranplant*" OR "osteochondr* regeneration" OR "chondr* replacement" OR (matrix AND w1 AND chondr*))

Appendix 2. Critical appraisal bias and reasoning for studies deemed high or serious risk

RoB 2 for Randomised Control Trials (RCTS)

	Domain	**Judgement**	**Reason**
Volz 2017	Randomisation process	High	Baseline differences: five out of seven centres closed for low recruitment number (n < 6) after two years collection of follow-up Study underpowered Deviations likely to have affected outcomes
Ibarra 2021	Confounding	High	Concomitant surgery

ROBINS-I for Non Randomised Study Interventions (NRSIs)

	Domain	**Judgement**	**Reason**
Meza 2019	Confounding	Serious	Concomitant surgery and non identical time points for different outcomes

Appendix C. Included study details including full title, scaffold, company and scaffold design

Study	Title	Scaffold	Company	Design
Crawford 2012	NeoCart, an autologous cartilage tissue implant, compared with microfracture for treatment of distal femoral cartilage lesions: An FDA phase-II prospective, randomized	NeoCart	Histogenics	Type I collagen fiber and 6 week cell culture

(*continued on next page*)

Appendix C (*continued*)

Study	Title	Scaffold	Company	Design
	clinical trial after two years.			
Volz 2017	A randomized controlled trial demonstrating sustained benefit of Autologous Matrix-Induced Chondrogenesis over microfracture at five years.	ChondroGide	Geistlich	Bilayer type I/III collagen fiber membrane
Welsh 2008	Cartilage T2 assessment at 3-T MR imaging: In vivo differentiation of normal hyaline cartilage from reparative tissue after two cartilage repair procedures - Initial experience.	Hyalograft C	Anika Therapeutics	Esterified hyaluronate fibers with cell culture
Meza 2019	Arthroscopic Treatment of Patellar and Trochlear Cartilage Lesions with Matrix Encapsulated Chondrocyte Implantation versus Microfracture: Quantitative Assessment with MRI T2-Mapping and MOCART at 4-Year Follow-up. Cartilage.	MACI	Vericel	Type I/III porcine collagen bilayer with cell culture
Saris 2014	Matrix-Applied Characterized Autologous Cultured Chondrocytes Versus Microfracture: Two-Year Follow-up of a Prospective Randomized Trial.	MACI (ACI-MAIX)	Vericel	Type I/III porcine collagen bilayer
Niemeyer [RCT] 2019	A Prospective, Randomized, Open-Label, Multicenter, Phase III Noninferiority Trial to Compare the Clinical Efficacy of Matrix-Associated Autologous Chondrocyte Implantation With Spheroid Technology Versus Arthroscopic Microfracture for Cartilage Defects	Spherox	Co.DON	Cultured spherical aggregates of chondrocytes and extracellular matrix
Brittberg 2018	Matrix-Applied Characterized Autologous Cultured Chondrocytes Versus Microfracture: Five-Year Follow-up of a Prospective Randomized Trial.	MACI	Vericel	Type I/III porcine collagen bilayer with cell culture
Kon [RCT] 2018	A multilayer biomaterial for osteochondral regeneration shows superiority vs microfractures for the treatment of osteochondral lesions in a multicentre randomized trial at 2 years.	MaioRegen	Fin-Ceramica	Collagen fibers on porous hydroxyapatite
Niemeyer [treat] 2019	Treatment Costs of Matrix-Associated Autologous Chondrocyte Implantation Compared With Microfracture: Results of a Matched-Pair Claims Data Analysis on the Treatment of Cartilage Knee Defects in Germany.	MACI	Vericel	Type I/III porcine collagen bilayer with cell culture
Kon 2009	Arthroscopic second-generation autologous chondrocyte implantation compared with microfracture for chondral lesions of the knee: Prospective nonrandomized study at 5 years.	Hyalograft C	Anika Therapeutics	Esterified hyaluronate fibers with cell culture
Sofu 2017	Results of Hyaluronic Acid-Based Cell-Free Scaffold Application in Combination With Microfracture for the Treatment of Osteochondral Lesions of the Knee: 2-Year Comparative Study.	Hyalofast	Anika Therapeutics	Esterified hyaluronate fibers
Anders 2013	A Randomized, Controlled Trial Comparing Autologous Matrix-Induced Chondrogenesis (AMIC®) to Microfracture: Analysis of 1- and 2-Year Follow-Up Data of 2 Centers.	Chondrogide	Geistlich	Bilayer type I/III collagen membrane

Appendix C (*continued*)

Study	Title	Scaffold	Company	Design
Basad 2010	Matrix-induced autologous chondrocyte implantation versus microfracture in the treatment of cartilage defects of the knee: a 2-year randomised study. Knee Surgery,	MACI	Vericel	Type I/III porcine collagen bilayer with cell culture
Hoburg 2019	Matrix-Associated Autologous Chondrocyte Implantation with Spheroid Technology Is Superior to Arthroscopic Microfracture at 36 Months Regarding Activities of Daily Living and Sporting Activities after Treatment.	Spherox	Co.DON	Spherical aggregates of chondrocytes and extracellular matrix
Petri 2013	CaReS® (MACT) versus microfracture in treating symptomatic patellofemoral cartilage defects: A retrospective matched-pair analysis.	CaReS MACT	Ars Arthro (Kinetics)	Fibrous collagen Type I (rat tail) with cell culture
Welsch 2009	Multimodal approach in the use of clinical scoring, morphological MRI and biochemical T2-mapping and diffusion-weighted imaging in their ability to assess differences between cartilage repair tissue after microfracture therapy and matrix-associated autologous chondrocyte transplantation	Hyalograft C	Anika Therapeutics	Esterified hyaluronate gel with cell culture
Trattnig 2008	Differentiating normal hyaline cartilage from post-surgical repair tissue using fast gradient echo imaging in delayed gadolinium-enhanced MRI (dGEMRIC) at 3 Tesla.	Hyalograft C	Anika Therapeutics	Esterified hyaluronate fibers with cell culture
Kon 2011	Articular Cartilage Treatment in High-Level Male Soccer Players: A Prospective Comparative Study of Arthroscopic Second-Generation Autologous Chondrocyte Implantation Versus Microfracture.	Hyalograft C	Anika Therapeutics	Esterified hyaluronate fibers with cell culture
Niemeyer [Reop] 2019	Matrix-Associated Chondrocyte Implantation Is Associated With Fewer Reoperations Than Microfracture: Results of a Population-Representative, Matched-Pair Claims Data Analysis for Cartilage Defects of the Knee.	MACI	Vericel	Type I/III porcine collagen bilayer with cell culture
Wang 2020	Synthetic Biphasic Scaffolds versus Microfracture for Articular Cartilage Defects of the Knee: A Retrospective Comparative Study	TruFit	Smith & Nephew	Poly-L-lactide fibers on porous calcium sulphate
Ibarra 2021	Arthroscopic Matrix-Assisted Autologous Chondrocyte Transplantation Versus Microfracture	Neoveil	Gunze	Polyglycolic scaffold

Appendix D. Included study cartilage lesion demographics including size (cm^2), location (MFC medial femoral condyle; LFC lateral femoral condyle) and lesion grade using the International cartilage repair Society (ICRS). Data not reported (-)

Study	Lesion size (cm^2)		Lesion location (n)		Lesion Grade ICRS (patient n)
	MF	**SC**	**MF**	**SC**	
Crawford 2012	2.69	ns	-		3
Volz 2017	2.9	3.6	"mostly femoral condyle"		3, 4
Welsh 2008	2.55	5.34	MFC 8; LFC 2		"full thickness"
Meza 2019	1.21+/-0.27	1.18+/-0.25	Trochlea 8; MP 1; LP 1		-
Saris 2014			MFC 53	MFC 54	3 (36)4
			LFC 15	LFC 13	(104)
	4.7+/-1.8	4.9+/-2.8	Trochlea 4	Trochlea 5	

(*continued on next page*)

Appendix D (*continued*)

Study	Lesion size (cm^2)		Lesion location (n)		Lesion Grade ICRS (patient n)
	MF	**SC**	**MF**	**SC**	
Niemeyer [RCT] 2019	2+/-0.8	2.2+/-0.7	Femur 101; Femur and patella 1		<3 (36); ≥3 (77)
Brittberg 2018	4.9	5.1	MFC 44 LFC 15 Trochlea 4	MFC 48 LFC 13 Trochlea 4	3 (31)4 (97)
Kon [RCT] 2018	3.5+/-1.6	3.4+/-1.5	Condyle 23 Trochlea 6 Patella 20	Condyle 37 Trochlea 2 Patella 12	-
Kon 2009	2.5	2.2	MFC 54; LFC 22; Trochlea 4		3, 4
Sofu 2017	3.6+/-1.3		MFC 32; LFC 11		3, 4
Anders 2013	2.9	3.6	-		3 (17); 4 (21)
Basad 2010	4–10		Condyle 45; Patella or trochlea 15		3, 4
Hoburg 2019	2+/-0.8	2.2+/-0.7	Femur 100; Femur and patella 1		<3 (26); ≥3 (77)
Petri 2013	3+/-1.2	3.4+/-2	-		3, 4
Welsch 2009	3.37+/-1.61	4.99+/-2.0	Femoral condyle		-
Trattnig 2008	2.82	5.12	MFC 16; LFC 2		-
Kon 2011	1.9+/-0.6	2.1+/-0.5	MFC 12 LFC 4 Trochlea 3 Both condyles 1	MFC 13 LFC 4 Trochlea 2	3, 4
Wang 2020	2.2+/-1.8	3+/-1.7	MFC 33 LFC 16 Trochlea 17	MFC36 LFC 15 Trochlea 15	-
Ibarra 2021	1.7+/-0.7	1.0+/-0.9	MFC 17; LFC 15; trochlea 7; patella 10		4

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