Osteoarthritis and Cartilage Open 5 (2023) 100388

Contents lists available at ScienceDirect

Osteoarthritis and Cartilage Open

journal homepage: www.elsevier.com/journals/osteoarthritis-and-cartilage-open/2665-9131

Review

A systematic review demonstrating correlation of MRI compositional parameters with clinical outcomes following articular cartilage repair interventions in the knee☆

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ARTICLE INFO

Handling Editor: Professor H Madry

Keywords:
Compositional MRI
Quantitative MRI
T2 mapping
Cartilage repair
Knee cartilage
Clinical outcomes
MR relaxometry
Outcome scores
Osteoarthritis

ABSTRACT

Objective: Compositional-MRI parameters enable the assessment of cartilage ultrastructure. Correlation of these parameters with clinical outcomes is unclear. This systematic review investigated the correlation of various compositional- MRI parameters with clinical outcome measures following cartilage repair or regeneration interventions in the knee.

Design: This study was registered with PROSPERO and reported in accordance with PRISMA. PubMed, Institute of Science Index, Scopus, Cochrane Central Register of Controlled Trials, and Embase databases were searched. All studies, regardless of type, that presented correlation of compositional- MRI parameters with clinical outcome measures were included. Two researchers independently performed data extraction and QUADAS-2 analysis. Compositional-MRI parameter change following intervention and correlation with clinical outcome measures were evaluated.

Results: 19 studies were included. Risk of bias was generally low. 5 different compositional parameters were observed from the included studies. However, due to the significant variability in the reporting of compositional-MRI parameters across studies, meta-analyses were possible only for T2 values and T2 index values (T2 value of repair cartilage relative to normal cartilage). Correlation of T2 values of repair cartilage with clinical outcome score was r = 0.33 [0.15, 0.52]. Correlation of T2 index with clinical outcome score was r = 0.52 [0.32, 0.77].

Conclusions: Correlation between T2 values and clinical outcome scores following knee cartilage repair were found. The heterogeneity of the correlations extracted from the included studies limited the scope for the meta-analysis. Thus, standardised, high-quality studies are required for better assessment of correlation between compositional MRI parameters and clinical outcome measures after cartilage repair.

Registration number: PROSPERO CRD42021287364.
Study protocol available on PROSPERO website.

1. Background

Articular cartilage defects in the knee are a common and significant problem across all age groups, causing pain, deterioration in function and reduced quality of life [1–4]. Cartilage defects can be caused by acute trauma or chronic repetitive overload [5]. A focal cartilage defect can cause pain in and of itself [1,6] and over time the defect may progress with increasing loss of cartilage [7–9]. Hence, cartilage repair and regeneration has attracted considerable attention and effort from a wide range of stakeholders.

Since cartilage tissue has a limited intrinsic healing potential with no endogenous repair mechanism [10], numerous techniques to repair or

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https://doi.org/10.1016/j.ocarto.2023.100388
Received 2 February 2023; Accepted 21 July 2023

regenerate cartilage have been researched and practised. These aim to improve clinical outcomes for patients and slow or halt progression of cartilage degeneration. The effectiveness of these procedures are typically assessed using clinical, imaging, and biomarker outcomes. As described by the National Center for Advancing Translational Sciences (NCATS) Toolkit for Patient-Focused Therapy Development, a clinical outcome is a measurable change in symptoms, overall health, ability to function, quality of life, or survival outcomes that result from giving care to patients [11]. A range of clinical outcome measures [12] are seen in literature related to cartilage repair or restoration. Among them, the International Knee Documentation Committee score (IKDC) [13], the Knee Injury and Osteoarthritis Outcome Score (KOOS) [14], the Western Ontario and McMaster Universities Arthritis Index (WOMAC) [15], the Lysholm score [16], and visual analogue scales (VAS) for pain and function, appear frequently.

Arthroscopy gives direct visual assessment of the cartilage, however does have limitations in terms of outcomes. It's correlation with histopathological assessment has demonstrated tendency to overestimate lesion grading, particularly in larger lesions [17,18]. As an invasive procedure arthroscopy infers risks to patients including intra-articular infection, and venous thromboembolism [19].

Multiple imaging modalities are employed to assess articular cartilage in the knee. Radiographic imaging is typically first line imaging for OA due to its wider availability and cost-effectiveness [20,21]. However, plain-radiography is unable to delineate early cartilage thinning [22], gives no indication of cartilage quality, and the correlation between plain-radiographic appearance and clinical scores in knee OA is reported to be low [23]. For Computed tomography (CT) arthrogram, correlation with clinical outcomes [24,25] is yet to be established [26] Magnetic Resonance Imaging (MRI) has the greatest sensitivity in evaluating cartilage thinning and early osteophytes and is therefore more useful than Plain-radiographs and CT in early pre-radiographic osteoarthritis [27]. A wide range of qualitative and quantitative MRI methods have been used to assess articular cartilage. Several MRI-based scoring schemes have been developed to facilitate a standardised, reproducible, semi-quantitative approach for the morphological assessment of cartilage repair. In this respect, the Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) score [28,29] and the Henderson classification [30] are widely used for the morphological assessment of cartilage repair. These semi-quantitative scores have demonstrated limited correlations with clinical outcomes following cartilage repair, dependent on type of repair surgery [31,32].

In cartilage, glycosaminoglycan (GAG) chains generate osmotic swelling pressure within the collagen network to maintain the low friction and load bearing characteristics of the tissue [33]. As such, the organisation and content of these molecules have a direct influence on the biomechanical quality of the cartilage. Quantitative MR (qMR) imaging techniques, also referred to as compositional-MRI techniques or parameters, have the key advantage of being sensitive to these biochemical and microstructural changes in the cartilage extracellular matrix (ECM), hence the potential to inform about the biomechanical quality of cartilage tissue even prior to manifestation of morphological changes [34,35]. Among qMR techniques, the measurement of T2 [36–38], T2* [39,40], and T1rho relaxation time-constants (relaxometry) of MR-tissue-contrast mechanisms are the most widely used. These measurements reflect the ECM quality, particularly the collagen content, collagen fibre orientation, and water content [34], and have been shown to correlate with clinical symptoms [41] related to cartilage defects and OA of the knee.

Other qMR techniques have been employed for quantitative evaluation of cartilage. Degradation of cartilage ECM leads to greater diffusion of water within the matrix. Consequently, measuring the Apparent Diffusion Coefficient (ADC) using Diffusion-weighted-imaging (DWI), can infer the status of the cartilage ECM, with increased diffusivity linked to structural degradation of the ECM [42]. Sodium imaging, (MRI using 23Na nuclei instead of conventional hydrogen-1H nuclei) reflects GAG content in cartilage. Decreased sodium values are seen in early OA [43]. Glycosaminoglycan Chemical Exchange Saturation Transfer imaging (gagCEST) is sensitive to the cartilage GAG content, and decreased gagCEST values are seen in damaged cartilage [44]. Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) maps cartilage GAGs [45]. Unlike the other compositional-MRI techniques dGEMRIC requires a contrast injection. In OA, the level of GAGs in cartilage decreases and consequently dGEMRIC parameter (T1-quantification) decrease in increasing cartilage damage, which has been shown to correlate with radiographic appearance [46]. Both Sodium and gagCEST MRI of cartilage are not yet in routine clinical application as they are primarily validated at 7 T field strength, but the increasing number of publications arising from research studies trialling these techniques for in-vivo cartilage imaging at 3 T field strength [44,47–50] have created both the interest and the momentum in applying these techniques for cartilage assessment.

Two previous systematic reviews [31,32] primarily focusing on the correlation between morphological MRI scores and clinical outcomes, reported weak to moderate correlation between T2 relaxation and selected clinical outcomes, as few of the included studies had also considered T2 values or T2 index (repair tissue T2 values divided by native cartilage T2 values) in addition to morphological MRI scores, following OATS or ACI procedures. However, the two reviews didn't find common ground for correlation between T2 relaxation and clinical outcomes for respective repair procedures, and the clinical relevance of compositional-MRI parameters that reflect cartilage quality remains uncertain. Due to the potential capability of non-invasive (or minimally invasive in the case of dGEMRIC) assessment of cartilage biochemical or structural composition that influence cartilage quality, it is important to evaluate and understand the association between compositional-MR parameters and clinical outcomes, as such an understanding would facilitate compositional-MR parameters to be used as reliable non-subjective quantitative measures, not only for assessing the clinical state after cartilage repair interventions, but also for better assessment of the chances for progression or remission of the clinical condition. Therefore, this systematic review primarily aimed to assess the correlation between compositional-MR parameters and clinical outcomes following cartilage repair of the knee.

2. Methods

We undertook systematic review of all electronically available literature from studies that included both compositional-MR techniques and clinical outcome tools following cartilage repair or regeneration, and performed a meta-analysis based on those studies that evaluated correlation coefficients between compositional-MR parameters and clinical outcome measures.

2.1. Search terms and search strategy

This review was performed and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [51]. The protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO).

Electronic searches were performed in the citation databases PubMed, Institute of Science Index, Scopus, Cochrane Central Register of Controlled Trials, and Embase, using keywords including “knee”, “cartilage”, “regeneration”, “restoration”, “repair”, “Magnetic Resonance” and “MRI”. The Boolean string for the PubMed search was: *(((knee) AND (cartilage)) AND ((regenerat*) OR (restor*) OR (repair))) AND ((magnetic resonance) OR (MRI)) Filters: Humans, English*. The full search strategy for the PubMed search including the Medical Subject Headings (MeSH) terms is provided in the Supplemental material. Filters were applied to select studies published only in English language and on human subjects. The bibliographies of related systematic reviews were then manually evaluated for articles that will be relevant to this review.

Two researchers independently performed searches and screened studies according to the inclusion and exclusion criteria with a third researcher resolving any disparities.

2.2. Inclusion and exclusion criteria

Inclusion criteria was all studies, including randomised controlled trials, cohort and retrospective studies, which incorporated cartilage regeneration, restoration, or repair interventions for cartilage defects of the knee, and assessed correlation between clinical outcomes and compositional-MRI parameters as an outcome measure. All studies on cartilage repair or regeneration interventions were reviewed including surgical and non-surgical, and chondral or osteochondral techniques. Studies which attempted and reported correlation between compositional-MRI parameters and clinical outcome scores but did not present values for correlation coefficients were also included. No restrictions were imposed on age, year, sex, race, or country where the study was carried out/reported from. Studies that did not report in English language were not included. Animal studies were excluded.

2.3. Data extraction

Two researchers independently extracted data from all included publications, with a third researcher resolving any disparities. To prevent overlapping of publications, potentially duplicated data from the same research group were verified using year and place of recruitment. In the case of duplicated data, only the largest data set was chosen. Data extracted included age, sex, length of follow up, duration of symptoms, articular cartilage defect characteristics, intervention technique, lesion size, frequency of postoperative complications, all reported pre- and post-operative MRI outcome measures, and all reported pre- and post-operative clinical outcome scores (e.g. Lysholm score, visual analogue scale-pain, Western Ontario and McMaster Universities Osteoarthritis Index, Knee Injury and Osteoarthritis Outcome Score). All described correlations, including correlation coefficients, were extracted.

2.4. Appraisal of bias

The quality of studies was evaluated in accordance with the QUADAS-2 tool, utilising the clinical outcome score as a reference standard and compositional-MRI parameters as an index test. A review of the evidence in accordance with each item in the tool as well as the level of evidence based on the criteria established by the Oxford Center for Evidence-Based Medicine was determined by two researchers with a discussion of specific issues and uncertainties, with any disparities resolved by a third researcher.

2.5. Statistical analysis

Correlations between compositional-MRI outcomes and clinical outcomes were extracted from the studies. The Meta-analysis was performed using the 'meta package' (v4.17–0; Balduzzi et al., 2019) within the R

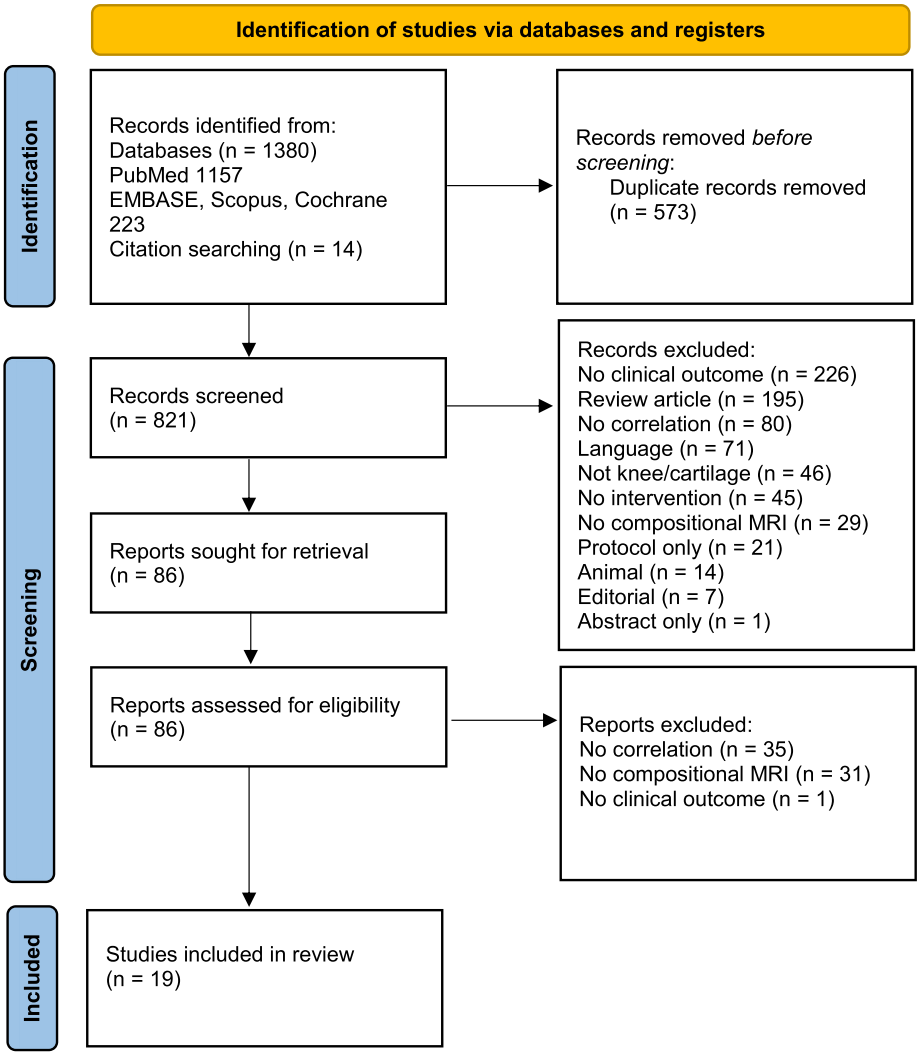

Fig. 1. PRISMA flowchart.

software (R Foundation for Statistical Computing, Vienna, Austria) integrated with the RStudio environment (Boston, USA). Multi-level meta-analysis was used when multiple effect sizes (multiple correlation coefficients in this case) were reported per study [52]. Spearman's and Pearson's correlation coefficients were included in the analysis. These correlation coefficients (r values) were converted using Fisher z transformations to stabilise the variance, 95% confidence interval and p-value were calculated using a random effects model. The derived correlations were reverted back to r values for reporting. The heterogeneity of the studies which reported correlation coefficients (r values) was evaluated using a Chi-squared test. Q and I^2 statistics were calculated to assess the level of heterogeneity.

3. Results

Following searches of databases, registers and manual citation searching, 1410 studies were identified. From these, 589 duplicates were removed. Fig. 1 illustrates the PRISMA flowchart of the process. A total of 19 publications were included in this review.

Figs. 2 and 3 demonstrate results of study quality evaluation based on Quality Assessment of Diagnostic Accuracy Score 2 (QUADAS-2) questions. Quality of studies was generally high with low risk of bias regarding applicability of the patient population, index test (MRI parameter) and reference standard test (clinical outcomes). Blinding of assessors to the MRI and clinical outcomes was not always documented leading to some unclear risk of bias regarding index test and reference standard. However all MRI scans and clinical outcome scores were taken at similar time points.

19 studies met the inclusion criteria and are outlined in Table 1.

Various interventions had been used in different studies, including Autologous Chondrocyte Implantation (ACI) (4) [53–56], Microfracture (5) [55,57–61], Matrix-induced Autologous Chondrocyte Implantation (MACI/MACT) (7) [58,61–66], Knee Joint Distraction (KJD) (1) [67], High Tibial Osteotomy (HTO) (1) [67], Osteochondral Autologous Transfer Surgery (OATS) (4) [66,68–70], injection of Mesenchymal Stem Cells (MSCs) (1) [71]. Considering all the studies selected for this review; Mean ages of the subjects ranged from 29.4 years to 54.14 years with the study on KJD including the eldest participants. Cumulatively, there were more male participants than female participants (314 male, 202 female). The nature of cartilage damage ranged from focal defects to generalised osteoarthritis. Various compositional- MRI parameters have been used including T2-mapping, DWI, dGEMRIC, T1rho, Sodium-23 and CEST. Multiple clinical outcome scores were used including IKDC [13], KOOS [14], WOMAC [15], the Lysholm score [16], and visual analogue scales for pain and function.

MRI-parameter changes following intervention and reported correlations with clinical outcomes are outlined in Table 2. All studies which reported a correlation are included in Table 2. However some of these studies did not present correlation coefficients values in the respective published article. The reasons for not including a specific study in the meta-analysis are also outlined in Table 2.

12 studies reported coefficients for correlation between compositional-MRI parameters and clinical outcome scores [53,55–57,60,61,63,66,68–71]. Out of these, statistically significant correlation coefficients related to T1rho [71], CEST [69], and DWI [60] were reported only once. For Sodium and dGEMRIC imaging, either there were no significant correlations [54,61,67,69] or the study-based definition of the parameter [56,70] limited the comparison with other studies. Hence meta-analysis was not possible for these parameters. The remaining studies reported T2 value correlations with clinical outcomes and were therefore included in meta-analysis. However, as T2 levels were reported using varying methods and differing clinical outcome scores were utilised, these were not pooled together for meta-analysis due to heterogeneity concerns. As such, we undertook two separate meta-analyses.

T2 relaxation time of the repair cartilage correlation with clinical outcomes is outlined in Fig. 4. Correlation was $r = 0.33$ which was highly

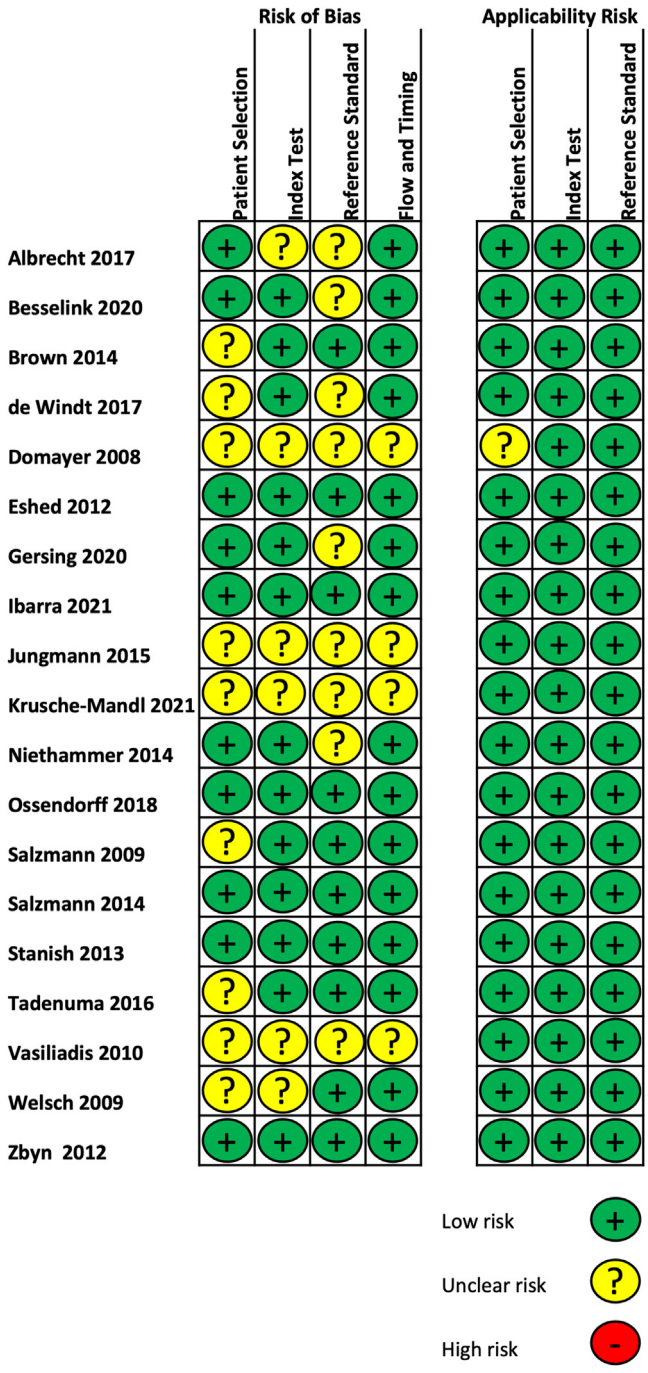

Fig. 2. QUDAS-2 traffic light summary.

significant (Z = 0.3.57, p-value = 0.001). Heterogeneity was low: (Q = 3.95 p-value = 0.41, *tau* [2] = 0.00, I^2 = 0.00%, H^2 = 1.00).

T2 index (repair tissue T2 values divided by native cartilage T2 values) correlation with clinical outcomes is outlined in Fig. 5. Correlation was $r = 0.52$ [0.32, 0.77]. Heterogeneity was low: ($Q = 1.90$ p-value = 0.39, *tau* [2] = 0.00, I^2 = 0.00%, H^2 = 1.00).

As outlined in Table 2, six studies reported reduction in T2 values [53,57,58,62,64,65], and one study reported an increase in T2 value [68], along longitudinal follow-up time points. However, there was not enough data available to evaluate correlation between T2 values and the clinical outcome scores, longitudinally along follow-up time points.

As detailed in Table 1, from the 6 studies selected for meta-analyses, 4 studies had used 3 T field-strength scanners [56,57,60,68], and 2 studies had used 1.5 T field-strength scanners [55,66]. In addition, all 6 seven

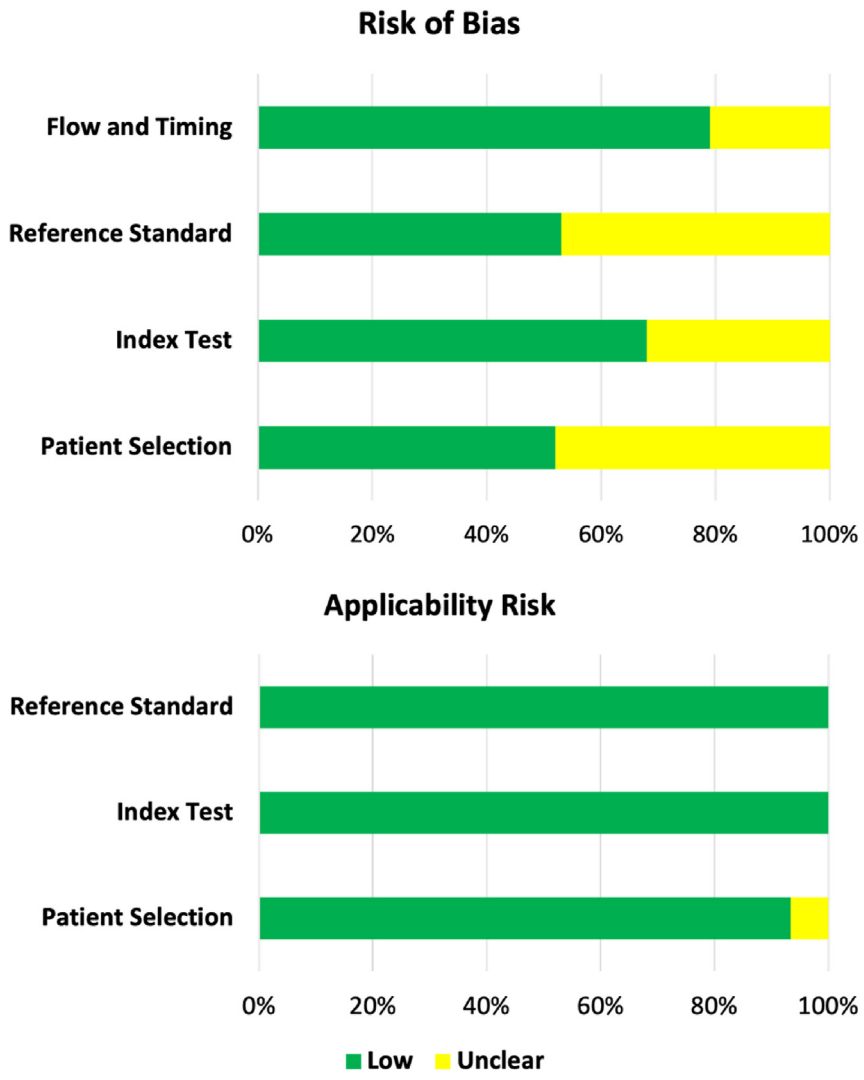

Fig. 3. QUDAS-2 cumulative summary.

studies had used 'Multi-Echo Spin Echo' sequence for scanning, with an 8-channel knee coil for transmission & receiving (although the knee coil utilised was not documented for one study).

4. Discussion

Clinical scores such as the Lysholm Knee Score, IKDC score, or KOOS score, reflect the individual disease burden and overall joint health following knee cartilage repair interventions. Although integral to the assessment of patient experience these scores lack specificity regarding quality and state of the repair tissue itself [72]. In this regard qMRI can offer an evidence based non-subjective quantitative measure of cartilage ECM status and quality, to support clinical decisions. Their promise lies in the potential to detect biochemical and microstructural changes in cartilage ECM at a much earlier stage, before structural cartilage damage is apparent even with high spatial-resolution imaging offered by modern high-field (3 T) MRI systems [44]. The continuous development of MR hardware and software, and the growing body of knowledge on application of qMRI for tissue characterisation, have steadily expanded the efforts to use qMRI for quantification of cartilage quality and bring it towards successful clinical application. Therefore the motivation for this review was to, based on up-to-date evidence, understand how well qMRI outcomes correlate to clinical outcomes following knee cartilage repair interventions.

The rapid development of cartilage qMRI techniques will influence the derived values of the compositional-MRI parameters. This may indirectly affect the outcomes of correlation and meta-analyses when earlier studies are considered together with more recent studies.

Quality of studies was generally moderate, with low risk of bias regarding applicability of patients, index test (compositional-MRI parameter) and reference standard (clinical outcome score). Although most studies employed prospective consecutive sampling, there was a lack of high-level randomised controlled trials. However, this should not have a significant negative impact on results, as the focus of this review is on assessment of compositional-MRI parameters rather than intervention outcome. Blinding of assessments is more relevant and this had been typically undertaken and well documented in the studies selected for this review. Reporting method of compositional-MRI parameters was variable across studies. When numeric levels were reported, studies variously reported global levels, compartmental levels, levels of repair cartilage or ratios of repair cartilage to native cartilage. When presenting index-levels for compositional-MRI parameters, these indices were not always well described making comparison with other index-levels not possible. This made pooling of the studies difficult due to heterogeneity reasons, and limited further meta-analysis. The use of differing clinical outcome scores across the studies also limited our analysis. When selecting appropriate studies for meta-analysis we ensured clinical outcome scores considered were consistent across studies, in type (e.g. Lysholm score) or in pattern

Table 1
Study characteristics. ND* = not documented.

	Sample size	Age (years)	Sex	Intervention	Follow up time	MRI compositional parameter (qMRI sequence)	Field Strength (T)	Scanner Make, Surface Coil	Follow up points MRI	Clinical outcome used	Follow up points clinical
Albrecht 2017 [63]	25	31.8 ± 8.9	18 M 6 W	MACT	24 months	T2 (Sagittal MESE)	3	Siemens Magnetom Trio 8-channel knee coil	3, 6, 12, 24 months	IKDC	Preop,3,6,12,24months
Besselink 2020 [58]	32	KJD 54.14 HTO 48.94	9 M 13 W	KJD vs HTO	2 years	dGEMRIC (3D sagittal inversion recovery FSPGR)	3	Philips Achieva 16-channel knee coil	Preoperative, 1, 2 years KJD, 2 year HTO following plate removal	WOMAC KOOS VAS	Baseline 1 year 2 year
Brown 2014 [71]	9	43.22 ± 16.54	6 M 3 W	OCT	2 years	dGEMRIC T2 (Sagittal 3D FSE)	3	Philips Achieva 8-channel knee coil	Preoperative, 1, 2 years	IKDC, KOOS	Preoperative, 1, 2 years
de Windt 2017 [72]	35	30 ± 8	24 M 11 W	MSCs	18 months	T1rho (Sagittal MAPSS)	3	Philips Achieva 12-channel knee coil	Preoperative, 1 year	KOOS, VAS pain and function, EQ5D	Baseline,3,6,12,18 months
Domayer 2008 [58]	24	41 mean SD 14	17 M 7 W	Microfracture	Mean 29 months SD 14 months	T2 (Sagittal MESE)	3	Siemens Magnetom Trio 8-channel knee coil	One MRI at one follow up with a minimum follow up period of 12 months	Lysholm IKDC	One clinical follow up with a minimum follow up period of 12 months
Eshed 2012 [64]	31	33.6 ± 11.6 range 18–55	7 M 24 W	MACI	17.3 ± 11.2 months (6–49 months)	T2 (Sagittal MESE)	3	GE Signa HDxt 8-channel knee coil	One MRI at one follow up 6–49 months post surgery	IKDC	One clinical follow up 6–49 months post surgery
Gersing 2019 [65]	18	28.7 ± 8.4	13 M 5 W	MACI	2 years	T2 (Sagittal MESE)	3	Philips Ingenia 16-channel knee coil	Preoperative, 3, 6, 12, 24 months	Tegner activity, Lysholm	Preop, 3,6,12,24 months
Ibarra 2021 [59]	35	MACT 33.7 ± 9.4 MFx 35.8 ± 9.1	MACT 17 M 7 W MFx 14 M 10 W	MACI vs microfracture	6 years (4–9)	T2 (Sagittal MESE)	1.5	GE Signa HDxT 8-channel knee coil	Preoperative, 1, 2, 4, 6 years	Lysholm, Tegner score, subjective IKDC, KOOS	Preop 1,2,4,6 years
Jungmann 2015 [69]	20	29.7 ± 12.3	17 M 3 W	Mega-OATS	9 years ±1.9 years	T2 (Sagittal MESE)	3	Siemens Verio 8-channel knee coil	9 years	Lysholm	9 years
Krusche-Mandl 2012 [70]	9	49 (44–55)	7 M 2 W	AOT	7.9 years (7.7–8.2)	T2 Sodium-23 CEST	3	Siemens Magnetom Trio 8-channel knee coil	8 years	IKDC, modified Lysholm, VAS	8 years
Niethammer 20,146 [6]	13	32.9 ± 9.4	ND	MACI	36 months	T2 (Sagittal MESE)	1.5	Siemens Avanto, (coil details ND*)	6,12, 24, 36 m	IKDC	6,12,24,36 m
Ossendorff 2018 [56]	44	38.9 ± 12.1	20 M 24 W	Microfracture vs ACI	10 years	T2 (Sagittal MESE)	1.5	Siemens Avanto, 8-channel knee coil	10 years ±1.4 years	Lysholm, NAS	10 years ± 1.4 years
Salzmann 2009 [67]	18	MACT 32.7 ± 7.2, OCT 33.9 ± 7.5	16 M 2 W	MACT vs OCT	MACT 42.0 ± 17.4 months, OCT 41.3 ± 16.5 months	T2 (Sagittal MESE)	1.5	Siemens Avanto, 8-channel knee coil	MACT 42.0 ± 17.4 months, OCT 41.3 ± 16.5 months	Modified Lysholm, modified Cincinnati, VAS for pain, Tegner	MACT 42.0 ± 17.4 months, OCT 41.3 ± 16.5 months

(*continued on next page*)

Table 1 (*continued*)

	Sample size	Age (years)	Sex	Intervention	Follow up time	MRI compositional parameter (qMRI sequence)	Field Strength (T)	Scanner Make, Surface Coil	Follow up points MRI	Clinical outcome used	Follow up points clinical
										activity scale, Short Form −36	
Salzmann 2014 [54]	59	33.3 ± 10.2	45 M 25 W	ACI	10.9 years ±1.1	T2 (Sagittal MESE)	1.5	Siemens Avanto, 8-channel knee coil	10 years	Lysholm	Preop, post op at same time MRI one time
Stanish 2013 [60]	80	BST and mfx 35.1 ± 9.6 mfx 37.2 ± 10.6	BST 23 M 18 W mfx 25 M 14 W	Microfracture	12 months	T2 (dual-echo FSE)	1.5	ND*	Preoperatively, 1, 12 months	WOMAC, SF-36	Preoperatively, 1, 3, 6 and 12 months
Tadenuma 2016 [57]	8	37.2 ± 12.5	3 M 5 W	ACI	5.9 years (3–10 years)	T1 dGEMRIC T2	3	GE Signa HDxT (coil details ND*)	5.9 years (3–10 years)	Lysholm	5.9 years (3–10 years)
Vasiliadis 2010 [55]	36	29.4 (17.5–50.5)	15 M 16 W	ACI	12.9 (9–18 years)	T1 dGEMRIC	1.5	Philips Intera Flex M Body Coil	12.9 years (range, 9–18 years)	KOOS	12.9 years (range, 9–18 years)
Welsch 2009 [61]	20	36.0 ± 10.4	ND	Microfracture vs MACT	Mfx 32.6 ± 16.7 months MACT 31.7 ± 18.3 months	T2 (Sagittal MESE) DWI (3D DW-PSIF)	3	Siemens Magnetom Trio 8-channel knee coil	MFX: 32.6 ± 16.7 months; MACT: 31.7 ± 18.3 months	Lysholm	MFX: 32.6 ± 16.7 months; MACT: 31.7 ± 18.3 months
Zbyn 2012 [62]	18	36.7 ± 10.7	11 M 7 W	Bone marrow stimulation vs MACT	Bone marrow stimulation 33.5 ± 25.3 months, MACT 33.2 ± 25.7 months	T2 (2D-TSE) Sodium-23 (3D-GRE)	7	Siemens Magnetom 28-channel knee coil	Bone marrow stimulation 33.5 ± 25.3 months, MACT 33.2 ± 25.7 months	IKDC, Modified Cincinnati Knee Rating	Bone marrow stimulation 33.5 ± 25.3 months, MACT 33.2 ± 25.7 months

Table 2
MRI parameter changes and correlation with clinical outcomes.

	MRI parameter change following intervention	MRI correlation with clinical outcome	Correlation Coefficient[a] and statistical measures	Included in a Meta analysis Or Reason for not inclusion
Albrecht 2017 [63]	T2 relaxation time of regenerate tissue improved from 3 m to 24 m ($p < 0.003$) Statistically significant decrease in T2 index from 3 to 24 months ($P < 0.011$)	No correlation seen between T2 index and IKDC score	–	No correlation coefficient available
Besselink 2020 [68]	Overall average dGEMRIC change over 2 years non-significant. HTO statistically significant reduction in medial dGEMRIC indices and increase (improvement) lateral side. For KJD changes non-significant	One unit increase in WOMAC associated with an increase in dGEMRIC indices of about 1.6 ms ($p < 0.0001$)	–	No correlation coefficient available
Brown 2014 [71]	No significant difference between mean T2 values in deep zone allograft and control cartilage at 1 or 2 years. T2 values significantly higher in superficial zone of allograft compared with controls at 1 and 2 years	Moderate to strong correlations between relative relaxation rate and IKDC and KOOS	IKDC score ($r = -0.75$, $P = 0.019$) KOOS Pain ($r = -0.86$, $P = 0.003$), KOOS Symptoms ($r = -0.66$, $P = 0.052$), KOOS ADL ($r = -0.89$, $P = 0.001$), KOOS Sports ($r = -0.72$, $P = 0.03$), KOOS QoL ($r = -0.73$, $P = 0.026$)	Relative relaxation rate not comparable to other correlations
de Windt 2017 [72]	No significant difference between T1rho values of the repair cartilage (RC) and healthy cartilage (HC) at 12 months $p > 0.05$	Moderate correlation between T1rho of repair cartilage to healthy cartilage ratio (RC/HC) and VAS pain 12 months, no correlation with KOOS	T1rho and VAS ($r = -0.46$; $p < 0.05$)	No other T1rho studies with correlation coefficients
Domayer 2008 [58]	^{Global} T2 value of repair tissue differed significantly $p < 0.001$ from global T2 values of normal hyaline cartilage	T2 index (T2 value of repair tissue relative to normal cartilage) correlated with outcome of Lysholm score and IKDC subjective knee evaluation form but no correlation with IKDC knee examination form	T2 and Lysholm ($r = 0.64$ $P < 0.001$)	Included in T2 index meta-analysis
			T2 and IKDC ($r = 0.549$ $P = 0.005$)	Included in T2 index meta-analysis
Eshed 2012 [64]	No preoperative MRI	No statistically significant correlation between IKDC and zonal T2 values	T2 and IKDC ($r = -0.31$ $p = 0.109$)	Condylar T2 value correlation not comparable to other correlations
Gersing 2019 [65]	Significant decrease in T2 value between 12 and 24 months, $P = 0.009$	No correlation of T2 value and Tegner activity score $p > 0.05$	–	No correlation coefficient available
Ibarra 2021 [59]	T2 values repaired tissues MACT showed statistically significant decrease $P = 0.001$, MFx not significant change $p = 0.211$.	No correlation seen	–	No correlation coefficient available
Jungmann 2015 [69]	increase in T2 values compared to control contralateral knees	No statistically significant correlation seen for Global T2 values and Lysholm score, and Global T2 side-to-side differences with Lysholm score. Repair tissue T2 values with Lysholm score	Global T2 and Lysholm −0.04	Global T2 values not comparable to other correlations
			Global T2 side-to-side differences with Lysholm −0.35	Global T2 side-to-side differences not comparable to other correlations
			Repair tissue T2 values with Lysholm ($r = 0.36$ $P > 0.05$)	Included in T2 values meta- analysis
Krusche-Mandl 2012 [70]	Statistically significant difference T2 for native and repair cartilage $p = 0.0057$ and for CEST $p = 0.0012$, and for sodium SNR $p = 0.0005$	Statistically significant correlation between T2-mapping and modified Lysholm score	T2 and IKDC -0.233	Native compared to repair not comparable to other correlations
			T2 and Lysholm ($r = -0.667$ 95[a] CI (-0.922; -0.005))	Native compared to repair not comparable to other correlations
			T2 and VAS 0.226	Native compared to repair not comparable to other correlations
			CEST and IKDC 0.050	Not included as no other CEST studies with correlation coefficients
			CEST and Lysholm 0.467	Not included as no other CEST studies with correlation coefficients
			CEST and VAS -0.279	Not included as no other CEST studies with correlation coefficients
			Na SNR and IKDC 0.238	Not included as no other Na SNR studies with correlation coefficients
			Na SNR and Lysholm −0.214	Not included as no other Na SNR studies with correlation coefficients

(*continued on next page*)

Table 2 (*continued*)

	MRI parameter change following intervention	MRI correlation with clinical outcome	Correlation Coefficient[a] and statistical measures	Included in a Meta analysis Or Reason for not inclusion
			Na SNR and VAS -0.152	Not included as no other Na SNR studies with correlation coefficients
Niethammer 2014 [66]	Significant decrease in T2 relaxation from 6 m to 24 and 26 m.	No statistically significant correlation between T2 relaxation time and IKDC scores at 6 month (P = 0.7), 12 month (P = 0.54), 24 month (P = 0.66), or 36 month (P = 0.8). No correlations between T2 and VAS scores	–	No correlation coefficient available
Ossendorff 2018 [56]	No statistically significant difference between groups	Statistically significant correlation between T2 relaxation time and NAS for function and Lysholm score	T2 with NAS (r = 0.319 P = 0.035)	Included in T2 values meta- analysis
			T2 with Lysholm (r = 0.316 P = 0.037)	Included in T2 values meta- analysis
Salzmann 2009 [67]	No preoperative MRI	Among MACT patients Lsyholm score correlated with the RT (repair tissue) T2 value	T2 and Lysholm (r = 0.734 P = 0.038)	Included in T2 values meta- analysis
Salzmann 2014 [54]	Statistically significant lower T2 values compared to contralateral knee	RT (repair tissue) T2 value correlated with postoperative NAS pain score	T2 and NAS (r = −0.28 P = 0.4)	NAS score not comparable to other PROM scores
		No significant relationship between T2 relaxation times and Lysholm score	–	No correlation coefficient available
Stanish 2013 [60]	Compared between treatments not to preop	No correlation between T2 relaxation values with WOMAC score at 12 month follow-up	–	No correlation coefficient available
Tadenuma 2016 [57]	No preoperative MRI	Statistically significant correlation between T1 and clinical outcome	T1 and Lysholm (r = 0.823 P = 0.002)	Included in T2 values meta- analysis
		No correlation between T2 and clinical outcome	T2 and Lysholm (r = −0.128 P = 0.707)	
Vasiliadis 2010 [55]	No preoperative MRI	No correlation seen between dGEMRIC mean T1 values and KOOS scores	–	No correlation coefficient available
Welsch 2009 [61]	No preoperative MRI	Statistically significant correlation between diffusion weighted imaging index and Lysholm score.	DWI index and Lysholm (r = −0.557 P = 0.011)	Not included as no other DWI studies with correlation coefficients
		Weak, non-significant correlation between T2 index and Lysholm score	T2 and Lysholm (r = 0.304 P = 0.193)	Included in T2 index meta- analysis
Zbyn 2012 [62]	No preoperative MRI	No correlation between sodium NMSI in repair tissue and clinical outcome. Medium association between clinical outcome and sodium repair-to-reference signal intensity ratio.	Na NMSI repair tissue and IKDC (r = −0.382 P = 0.276) Na NMSI repair tissue and Cincinnati (r = −0.521 P = 0.123) Na repair-to-reference and IKDC r = −0.502 P = 0.139	Not included as no other Na NMSI studies with correlation coefficients

NMSI- Normalised Mean Signal Intensity, SNR – Signal to Noise Ratio.
'Side-to-Side' = Left knee vs Right knee.
[a] Correlation coefficient presented where available.

(e.g. a decrease in number for a worsening score). Reporting of correlations between clinical outcome scores and compositional-MRI parameters was also inconsistent among the studies. Often these correlations were not the focus of the respective study and therefore it is likely that, for efficiency concerns, some correlation coefficients were not reported, particularly for statistically non-significant correlations. All studies measured clinical and MRI outcomes at similar time points within each study, therefore allowing direct correlation between MRI and clinical outcomes for each respective study. However, between studies, there was variance in which time points were used. This introduces further heterogeneity. Fisher's-Z transformation converts the skewed distribution of the sample correlation (r) into a normal distribution allowing further statistical processes. In Figs. 4 and 5, the transformed Fisher's-Z value for different studies will primarily depend on respective r-value, albeit influenced by the sample size, measurement error, type of correlation, and chance.

In this review, although correlation coefficients from two studies [57, 60] (with two correlations used from one study [57]) could only be included in the T2-index meta-analysis, it demonstrated a moderate correlation between the T2 index and clinical outcome scores, with low heterogeneity between studies. This outcome may lend support for the use of T2 index as a method for quantitative-MRI assessment of cartilage quality. However, the weak correlation found between T2 absolute values and the clinical outcome scores, may indicate the need to improve the evidence-base for it to be used for qMRI assessment of cartilage in relation to clinical outcomes.

Semi-quantitative MRI scoring methods are widely used to assess morphological MRI data in relation to clinical outcomes following interventions. Some of these studies have included compositional-MRI parameter evaluation within the methodology of the study. As examples, a study on hydrogel-based cartilage repair technique [73] reported statistically significant change in MOCART score, a weak correlation between MOCART score and clinical outcome measures, and a negative correlation of MOCART score with T2 values (r = -0.62, P = 0.01), at 24-months. However, at 12-months there was no significant change in MOCART score but the standard deviation of the T2 measurements changed significantly, with the T2 values over time gradually getting closer to those of normal hyaline cartilage. The study states that T2 relaxation time measurements may indicate the maturation of the of repair tissue. A study on Matrix-Associated Autologous Chondrocyte Transplantation (MACT) [74], reported that, between the baseline and the 1-year follow-up, T2-mapping showed a significant zonal

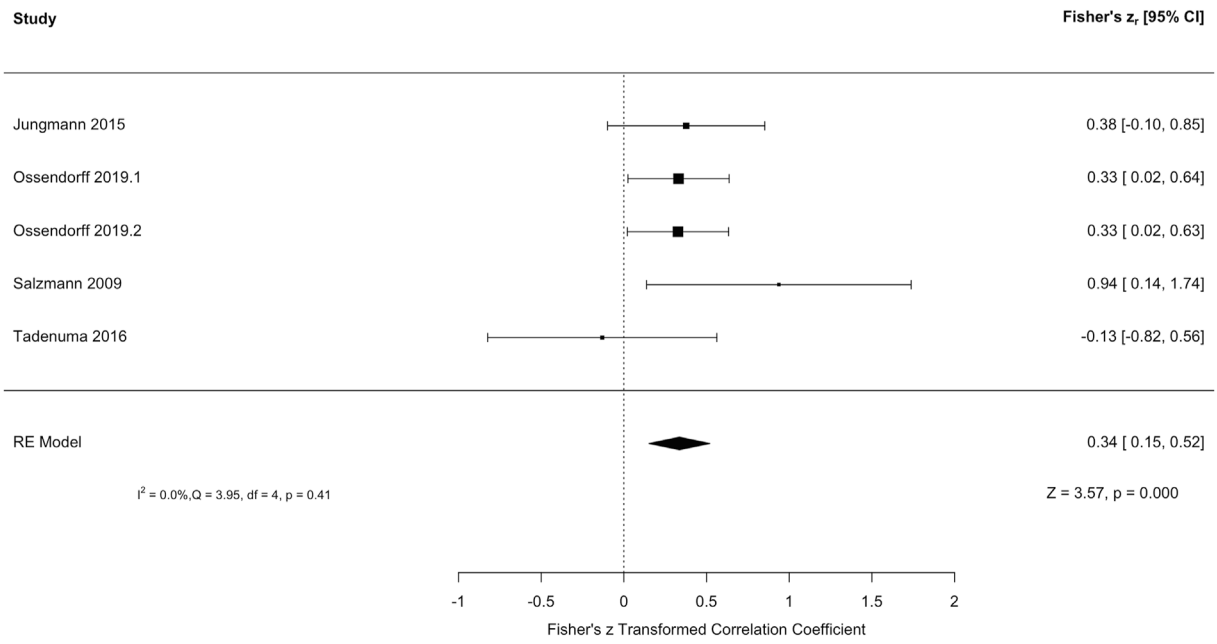

Fig. 4. Forest plot of meta-analysis of T2 values of repair tissue correlation with clinical outcomes.

stratification ($p < 0.05$), but no significant differences were observed on MOCART score. It stated in-vivo zonal T2 assessment may be sensitive enough to characterise the maturation of cartilage repair tissue.

These finding are in-line with the idea that the compositional-MRI parameters are sensitive to changes in cartilage quality even before the manifestation of morphological changes.

The correlations between compositional-MRI parameters and clinical outcome scores also become useful when comparing different treatment options or techniques for cartilage repair. For example, in a study comparing microfracture therapy (MFX) and matrix-associated autologous chondrocyte transplantation (MACT) [60], no differences in Lysholm ($P = 0.420$) or MOCART ($P = 0.209$) score were observed between MFX and MACT. However, T2-mapping showed lower T2 values after MFX compared to MACT ($P = 0.039$), DWI distinguished between healthy cartilage and cartilage repair tissue in both procedures (MFX: $P = 0.001$; MACT: $P = 0.007$), correlations found between the Lysholm score and DWI (Pearson: 0.557; $P = 0.011$), and a trend between the Lysholm score and T2 (Person: 0.304; $P = 0.193$). As such, the additional information from the compositional-MRI related to the cartilage ultrastructure is helpful in evaluating the two treatment procedures.

Ideally, further sub-group analysis would have been undertaken in this review evaluating differing interventions and clinical outcome scores. However, despite multiple other studies utilising T2 mapping, lack of consistency between studies in data analysis as well as in reporting method, made further analysis impossible. Differences in MR parameters are likely between intervention groups, particularly between osteochondral grafting

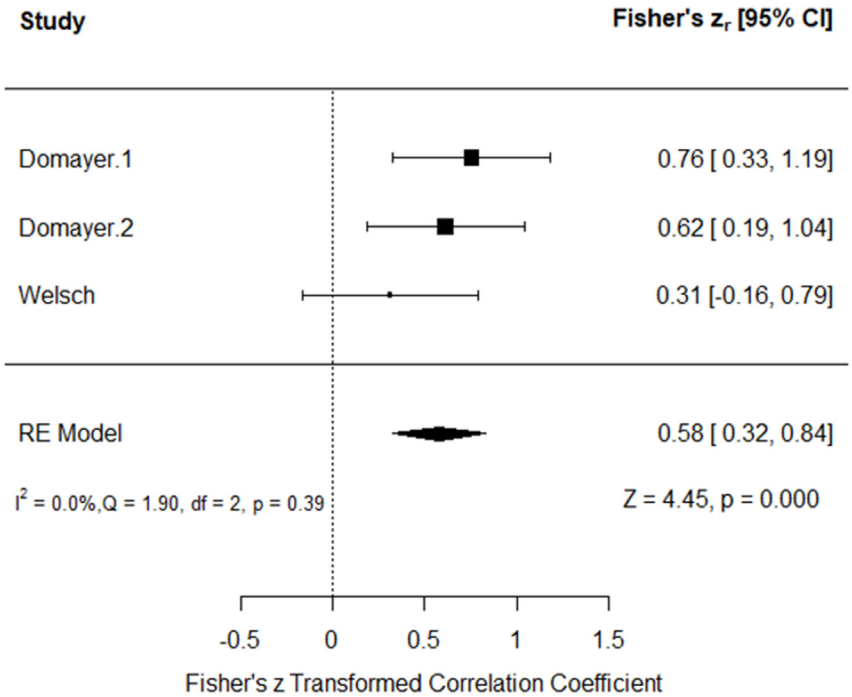

Fig. 5. Forest plot of meta-analysis of T2 index correlation with clinical outcomes.

and repair groups. Due to lack of available data our meta-analysis did not include any data from osteochondral grafting interventions.

Although we anticipated to evaluate the correlation between compositional-MRI parameters and the clinical outcome scores, longitudinally along follow-up time points to understand the predictive potential of the compositional-MRI parameters in relation to the clinical condition, there was not enough data available to perform such an analysis. However, six studies reported reduction in T2 values [53,57,58,62,64,65], along the longitudinal follow-up time points, which may be an indication of improvement in the cartilage ECM.

The hardware and the methods used for the acquisition of MR data, in addition to techniques adopted for processing and analysis of image data, will influence derived qMRI parameter values. Among the research community it is recognised that lack of standardisation of many factors related to the qMRI process leads to variability in measurements across different sites, scanners, and patients. As such, the Quantitative Imaging Biomarkers Alliance (QIBA) has published a profile [75] outlining recommendations for MRI-based Compositional Imaging of Knee Cartilage, with the aim to "improve the value and practicality of quantitative imaging biomarkers by reducing variability across devices, sites, patients, and time". The QIBA profile recommends both T2 and T1rho measurements using a single sequence (MAPSS = magnetization-prepared angle-modulated partitioned k-space spoiled gradient-echo snapshots), and indicates the sequence parameters as well. Among the reasons for QIBA recommendation of the MAPSS protocol are; the statistically significant differences in T2 measures from Multi-slice Multi-echo techniques reported between vendors (10%–25%) [76], and the MSME protocol's proneness to variations introduced by stimulated echoes and magnetization transfer effects [77]. In this context, it is noted from Table 1 that the 'Multi-Echo Spin Echo' sequence was the main choice for the acquisition of T2-maps among the studies included in this review.

QIBA profile for knee cartilage qMRI also provides guidance on image data analysis and reporting. Lack of consistency among studies in reporting the qMRI outcomes was certainly an issue we encountered in performing this review. Therefore we think that the image analysis and reporting based on the knee compartments (Fig. 6), similar to the scheme that QIBA profile outlines, would facilitate better comparison between studies. Further, we also recommend that studies should report both absolute values as well as index values of the qMRI measurements, as biochemical analysis of whole cartilage compartment may not be representative of a single cartilage defect. On the other hand, changes in tri-compartmental osteoarthritis may be better demonstrated by global values. If an index is calculated the calculation should be reported to allow clarity on the value obtained (Fig. 6). In general, availability of full data sets would be helpful in-terms of further analysis of correlation of compositional-MRI parameters with clinical outcomes.

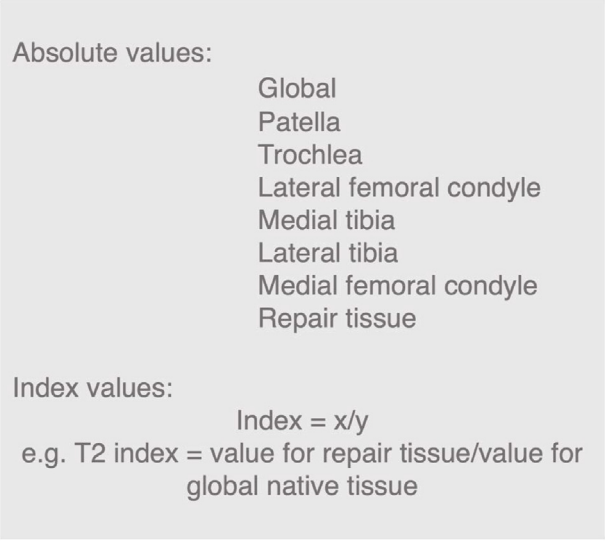

Fig. 6. Recommended presentation of MRI composition parameters.

T2 mapping is the most widespread knee cartilage compositional-MRI technique evident in this review, supporting the recognition it has already received from the QIBA. Although meta-analysis on other parameters was precluded in this review due to lack of available data, the benefits of those techniques may be established by further research.

5. Conclusion

This systematic review highlighted correlation between T2 values and clinical outcome scores following knee cartilage repair. However, significant heterogeneity of the correlations was observed, attributed to variations in compositional-MRI parameters and clinical outcome scores, interventions used, and analytical methods applied. Thus, standardised, high-quality studies following the QIBA guidelines are required for more consistent results to ensure better comparability of data, leading to more comprehensive insights into the role of compositional-MRI in assessing cartilage repair outcomes.

Contributions

All authors have made substantial contributions to.

1. The conception and design of the study, or acquisition of data, or analysis and interpretation of data.

2. Drafting the article or revising it critically for important intellectual content.

3. Final approval of the version to be submitted.

Beth Lineham: Contributed substantially to the conception and design of the study, the acquisition of data, the analysis and interpretation of data, drafting of the article and final approval of the submitted version. This author is the corresponding author and takes responsibility for the integrity of the work as a whole.

Harin Wijayathunga: Contributed substantially to the design of the study, acquisition of data, analysis and interpretation of data, drafting of the article and final approval of the submitted version.

Emma Moran: Contributed substantially to the acquisition of data, analysis and interpretation of data, drafting of the article and final approval of the submitted version.

Farag Shuweihdi: Contributed substantially to the analysis and interpretation of data, statistical expertise, drafting of the article and final approval of the submitted version.

Harun Gupta: Contributed substantially to the analysis and interpretation of data, drafting of the article and final approval of the submitted version. This author is the corresponding author and takes responsibility for the integrity of the work as a whole.

Hemant Pandit: Contributed substantially to the conception and design of the study, the analysis and interpretation of data, drafting of the article and final approval of the submitted version.

Nagitha Wijayathunga: Contributed substantially to the conception and design of the study, the analysis and interpretation of data, drafting of the article and final approval of the submitted version.

Funding source

This paper report presents independent research funded and supported by the National Institute for Health and Care Research (NIHR) Leeds Biomedical Research Centre (BRC). Professor Pandit is a National Institute for Health Research (NIHR) Senior Investigator. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Declaration of competing interest

Beth Lineham: There are no financial or personal interests that could have potentially and inappropriately influenced the integrity of the work in this manuscript to disclose by the author.

Harin Wijayathunga: There are no financial or personal interests that could have potentially and inappropriately influenced the integrity of the work in this manuscript to disclose by the author.

Emma Moran: There are no financial or personal interests that could have potentially and inappropriately influenced the integrity of the work in this manuscript to disclose by the author.

Farag Shuweihdi: There are no financial or personal interests that could have potentially and inappropriately influenced the integrity of the work in this manuscript to disclose by the author.

Harun Gupta: There are no financial or personal interests that could have potentially and inappropriately influenced the integrity of the work in this manuscript to disclose by the author.

Hemant Pandit: There are no financial or personal interests that could have potentially and inappropriately influenced the integrity of the work in this manuscript to disclose by the author.

Nagitha Wijayathunga: There are no financial or personal interests that could have potentially and inappropriately influenced the integrity of the work in this manuscript to disclose by the author.

Acknowledgements

Nil.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ocarto.2023.100388.

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