Utility of Magnetic Resonance Imaging in Diagnosis and Monitoring Enthesitis in Patients with Spondyloarthritis: An OMERACT Systematic Literature Review

Ashish J. Mathew, Simon Krabbe, Richard Kirubakaran, Andrew J. Barr, Philip G. Conaghan, Paul Bird, and Mikkel Østergaard

ABSTRACT. ***Objective.*** A systematic literature review was performed to document published magnetic resonance imaging (MRI) lesion definitions and scoring systems for enthesitis in spondyloarthritis (SpA).

Methods. PubMed, Embase, and Cochrane Library databases were searched for original publications involving adult patients with SpA undergoing MRI of axial/peripheral joints. Selected articles were assessed for quality using a standardized assessment tool and metric indices.

Results. Considering the heterogeneous design, quality, and outcome measures of studies, statistical data pooling was considered inappropriate. A qualitative narrative of results was undertaken based on study designs.

Conclusion. Lack of a comprehensive, validated score warrants additional research to develop an MRI enthesitis scoring system. PROSPERO registration number: CRD42018090537. (First Release March 1 2019; J Rheumatol 2019;46:1207–14; doi:10.3899/jrheum.181083)

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From the Department of Clinical Immunology and Rheumatology, Christian Medical College; Cochrane South Asia, Christian Medical College, Vellore, India; Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen; Copenhagen Center for Arthritis Research (COPECARE), Copenhagen; Center for Rheumatology and Spine Diseases, Rigshospitalet Glostrup, Glostrup, Denmark; UK National Institute for Health Research (NIHR) Leeds Biomedical Research Centre (BRC), Leeds Teaching Hospitals National Health Service (NHS) Trust; Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK; Division of Medicine, University of New South Wales, Sydney, Australia.

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A.J. Mathew, MBBS, DNB, DM, Associate Professor, Department of Clinical Immunology and Rheumatology, Christian Medical College, and PhD Fellow, Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, and COPECARE, Center for Rheumatology and Spine Diseases, Rigshospitalet Glostrup; S. Krabbe, MD, Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, and COPECARE, Center for Rheumatology and Spine Diseases, Rigshospitalet Glostrup; R. Kirubakaran, BSc, MSc, Biostatistician, Cochrane South Asia, Christian Medical College; A.J. Barr, MRCP, PhD, Consultant Rheumatologist and Honorary Senior Lecturer, NIHR Leeds BRC, Leeds Teaching Hospitals NHS Trust; P.G. Conaghan, MBBS, PhD, FRACP, FRCP, Professor of Musculoskeletal Medicine, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, and NIHR Leeds BRC; P. Bird, B Med (Hons), FRACP, PhD, Grad Dip MRI, Associate Professor, Division of Medicine, University of New South Wales; M. Østergaard, MD, PhD, DMSc, Professor, Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, and COPECARE, Center for Rheumatology and Spine Diseases, Rigshospitalet Glostrup.

Address correspondence to A.J. Mathew, Department of Clinical Immunology and Rheumatology, Christian Medical College, Vellore, India, 632004. E-mail: ashishjacobmathew@gmail.com

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Enthesitis, inflammation at the insertion site of tendon, ligament, or joint capsule into bone, is considered a key pathological feature in spondyloarthritis (SpA) and psoriatic arthritis (PsA)[1]. Compared to conventional assessment of enthesitis using clinical scores, magnetic resonance imaging (MRI) detects both soft tissue and intraosseous abnormalities in active enthesitis, potentially aiding early diagnosis and outcome measurement in SpA and PsA[2]. With the advent of the treat-to-target concept and novel therapies, objective and sensitive monitoring of response of enthesitis to therapy is desirable, and a validated MRI scoring system would be a useful adjunct to clinical practice as well as providing additional information as an outcome measure in clinical trials.

The Outcome Measures in Rheumatology (OMERACT) MRI in Inflammatory Arthritis Working Group undertook a systematic literature review to describe the MRI variables, definitions, and scoring systems used to diagnose and monitor enthesitis in SpA. We assessed the quality and reported psychometric qualities, including validity, reliability, and responsiveness of original publications, to understand whether there was a need for a novel MRI scoring system for enthesitis in SpA[3,4].

MATERIALS AND METHODS

Selection criteria and search strategies. We searched Medline, Embase, and Cochrane Library databases from their inception until February 2018 for original publications involving adult patients (> 18 yrs) with SpA in whom

MRI of axial or peripheral joints had been performed using a high-field magnet (≥ 1.5T) to assess enthesitis. Exclusion criteria included studies on enthesitis related to other conditions, such as degenerative, trauma-related, and inflammatory diseases other than SpA. The search strategy was designed to select cross-sectional, case control, randomized controlled, and nonrandomized studies in the English language containing at least 1 term from each of the following search blocks: (1) spondyloarthritis, spondylarthritis, psoriatic arthritis, or ankylosing spondylitis; (2) enthesopathy, enthesitis or enthesis; and (3) magnetic resonance imaging or MRI. The selected studies were evaluated for definitions of MRI enthesitis lesions, quality of studies using a standardized assessment tool, and for their metric qualities.

Selection of studies and data extraction. Two reviewers (AJM and SK) independently selected the studies and systematically screened the titles and abstracts, applying inclusion and exclusion criteria. Selected articles were retrieved in full, and the same reviewers assessed each article for its eligibility. Disagreements between the reviewers on article selection were resolved by discussion. Data were extracted to a standardized form. Any discordance in opinion was resolved by consensus and involvement of a third reviewer (MØ). The data extraction sheet contained the following information: author, year of publication, study design, study population, number of participants, intervention, comparator, MRI field strength, sequences used, MRI sites used for evaluating enthesitis, definitions of MRI inflammatory and structural enthesitis, and scoring system used (Table 1).

Quality assessment of selected studies. A standardized tool (Supplementary Table 1, available with the online version of this article) for quality assessment of the analyzed studies based on a set of 12 predefined criteria addressing the following components was developed and assessed in a binary mode (yes/no): study population, enthesitis imaging feature, outcome of interest, study design and analysis, and data presentation. Concepts from review of quality assessment tools in systematic reviews of observational studies were adapted for developing these criteria[5]. Quality was reported on a scale of 0–12, with higher scores indicating better quality. Included studies that scored < 3 on the scale were excluded from the final analysis.

Psychometric properties of included studies. Each selected article was analyzed and assessed to determine whether it satisfied certain aspects of validity. The following metric qualities were evaluated: face and content validity, construct validity, criterion validity, and discriminant validity (reliability and responsiveness; Table 2).

Statistical analysis. Details of the studies were reported with descriptive statistics such as frequencies and percentages for categorical data and mean and SD for continuous data. Because of variability in studies, metaanalysis could not be performed. PROSPERO registration number: CRD42018090537.

RESULTS

Literature search. The study selection process is depicted in a PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow diagram (Figure 1).

Study characteristics. Attributes of the included studies are summarized in Table 1[2,6–43]. The majority of included studies were of cross-sectional design (20; 51%)[2,6–17,19–24,28]. Eight case-control[18,25–27,29–32], 6 cohort[33,34,35,36,37,38], 3 randomized controlled trials[39,40,41], and 2 other longitudinal studies[42,43] were included. Study populations involved SpA in 22, ankylosing spondylitis in 7, and PsA in 9 studies, and chronic low back pain in 1 study. In total, 1534 individuals (range 8–127) in different groups were evaluated for MRI enthesitis in all the studies together. Peripheral enthesitis were evaluated in 24 (62%) studies[7,10,11,15–29,31,32,34,36,38,39], axial enthesitis in 8 studies[6,8,12,15,14,36,42,43], and enthesitis at both sites using whole-body MRI in 7 studies[2,9,30,33,37,40,41]. Both T1-weighted (T1w) and T2w fat-suppressed or its comparable sequences were included in all the studies. Comparison with other methods of evaluating enthesitis [ultrasonography (US) and clinical assessment] was described in 10 studies[7,9,10,11,18,30,31,32,35,36], while 5 studies compared different MRI sequences to assess enthesitis[6,13,14,25,42]. Only 4 studies compared efficacy of MRI against a gold standard[11,13,35,42].

Qualitative assessment of enthesitis at different regions was used in 82% of studies. Only 8 studies mentioned a semiquantitative or quantitative MRI scoring system[2,14,16,17,19,25,39,40]. No studies described a validated, comprehensive MRI scoring system measuring all the aspects of enthesitis in any region. The majority of studies defined inflammatory enthesitis as enhancement of ligaments, increased signal intensity, perientheseal increased signal intensity, adjacent bone marrow edema (BME), soft tissue signal around ligaments or tendons, thickening of ligaments, capsulitis in sacroiliac joints, extracapsular soft tissue enhancement, Achilles tendon diameter of BME, perientheseal fluid and/or tendinitis in T1w post-gadolinium, or short-tau inversion recovery sequences. Entheseal structural damage defined by few studies includes bone erosions, enthesophytes, focal signal intensity changes, and calcaneal spur in T1w sequences[2,7,16,25,27,28,29,32].

Quality assessment of included studies. Quality scores assessed using a standardized tool are provided in Table 2. With 1 exception, all 38 studies met the minimal quality requirement score of 4. High quality scores (10–12) were present in only 2 studies[2,40], while the remaining 36 studies had moderate quality scores (5–9).

Assessment of psychometric properties. Table 2 describes psychometric properties of the selected studies. Face validity was assessed in 33 (87%) studies, content validity in 19 (50%) studies, and construct validity of MRI as related to ultrasound (US) and clinical examination in 5 (13%) and 6 (16%) studies, respectively. Five studies reported construct validity of different MRI sequences in relation to each other[6,13,14,25,42]. Criterion validity of MRI in relation to histology was described only by Tan, *et al*[22]. Reliability of MRI in detecting enthesitis using various scoring methods was reported by 26 (68%) studies in which images were evaluated by 2 independent readers who were blinded to clinical outcomes. Responsiveness of various MRI enthesitis scores was reported in 6 (18%) studies, of which 3 showed statistically significant changes ($p < 0.05$)[37,40,41].

DISCUSSION

Axial and peripheral enthesitis constitutes a core feature of SpA and PsA. The OMERACT PsA core domain set includes enthesitis, which makes it mandatory to be assessed in all clinical trials and observational studies[44]. MRI allows sensitive assessment of enthesitis in clinical trials. We have critically evaluated the published literature for available

Table 1. Characteristics of included studies.

Study	Study Population	No. Participants	Intervention	Comparator	MRI Field Strength	Sequences	MRI Sites	Scoring Systems
Cross-sectional studies								
Fournié, *et al*[12]	AS fulfilling Amor criteria and PsA based on seronegative joint disease with psoriasis	8 (5; 3)	MRI	NA	NA	T1W Gd	Anterior chest wall	Qualitative
McGonagle, *et al*[16]	SpA with plantar fasciitis; mechanically induced plantar fasciitis	28 (17; 11)	MRI	NA	0.5; 1.5	T1W; SPIR	Plantar fascia	Semiquantitative
Olivieri, *et al*[19]	SpA with dactylitis	6	MRI	NA	1.5	T1W; T2W FS; GRE-T2W	Finger tendon insertions	Semiquantitative
Tan, *et al*[24]	DIP joint PsA; DIP joint OA; healthy subjects	30 (10; 10; 10)	MRI	NA	1.5	T1W; T2W FS; PD; 3DGE; T1W FS Gd	DIP joints	Qualitative
McQueen, *et al*[17]	PsA	10	MRI	NA	0.6	T1W; T1W Gd; STIR	2nd–5th finger	Semiquantitative
Tan, *et al*[22]	DIP joint PsA; DIP joint OA; healthy subjects	30 (10; 10; 10)	MRI	NA	1.5	T1W; T2W FS; PD; 3DGE; T1W FS Gd	DIP joints	Qualitative
Marzo-Ortega, *et al*[15]	SpA; RA	20 (10; 10)	MRI	NA	1.5	T1W; DCE-MRI; SPIR FS Gd	MCP joints	Qualitative
Maksymowicz, *et al*[14]	SpA or suspected SpA	35	MRI T1W FS Gd	MRI T2W FS	1.5	T1W; T1W FS; T2W FS; T1W FS Gd	Enthesitis of SIJ ligaments	Semiquantitative
Feydy, *et al*[28]	SpA; controls hospitalized low-back pain	75 (51; 24)	MRI	NA	1.5	T1W; STIR	Heel enthesitis	Qualitative
Althoff, *et al*[9]	SpA	75	MRI	NA	1.5	T1W; STIR	Whole-body	Qualitative
Aydin, *et al*[10]	SpA with swollen knee	21	MRI	US	1.5	T1W; T2 SPIR; TI SPIR; TI SPIR Gd	Knee entheses	Qualitative
Braum, *et al*[11]	Suspected inflammatory joint disease	69	MRI	Clinical	1.5	T1W; T1W FS Gd; STIR	Collateral ligaments of finger joints	Qualitative
Paramarta, *et al*[20]	Knee or ankle arthritis: SpA; RA; crystal arthritis	41 (13; 20; 8)	MRI	NA	1.5	T1W; T2W FS; STIR; T1W FS Gd	Knee and ankle entheses	Qualitative
Ramírez, *et al*[21]	Greater trochanter pain: SpA/RA/no inflammatory disease	40	MRI	NA	1.5	T1W; T2W FS	Greater femoral trochanter	Qualitative
Poggenborg, *et al*[2]	PsA; SpA; healthy subjects	48 (18; 18; 12)	MRI	NA	3	T1W; STIR	Whole-body	Semiquantitative
Tan, *et al*[23]	PsA with dactylitis; healthy subjects	22 (12; 10)	MRI	NA	1.5	T2W FS; T1W; TSE; T1W FS Gd	Fingers/toes	Qualitative
Agten, *et al*[6]	Suspected SpA	68	MRI T1W Gd	MRI STIR	1.5; 3.0	T1W FS Gd; STIR	T12-S1 interspinous and supraspinous ligaments	Qualitative
Giraudo, *et al*[13]	Suspected SpA	106	MRI T2W; MRI PD	T1W Gd	3	T2W; PD; T1W; T1W FS Gd	SIJ anterior and posterior ligaments	Qualitative
Aivazoglou, *et al*[8]	SpA	16	MRI	NA	1.5	T1W FS; T1W FS Gd; STIR	Enthesitis of SIJ ligaments	Qualitative
Maldonado, *et al*[7]	SpA	40	MRI	US; CR	1.5	T1W; T1W FS Gd; T2W FS or STIR	Achilles tendon insertion; plantar fascia	Qualitative
Case control studies								
Olivieri, *et al*[18]	SpA fulfilling Amor's criteria and showing severe Achilles enthesitis	19 pathologic 9 normal tendons	MRI	US	0.5	T1W, PD, T2W	Ankle	Qualitative
Lambert, *et al*[29]	AS; healthy subjects	111 (17; 94)	MRI	NA	1.5	T1W; T2W; PD; T2W FS or STIR	Shoulder	Qualitative
Erdem, *et al*[27]	AS; healthy subjects	33 (23; 10)	MRI	NA	1.5	T1W; T2W; STIR	Heel enthesitis	Qualitative
Wiell, *et al*[32]	PsA; RA; healthy subjects	25 (15; 5; 5)	MRI	US	0.6	T1W; STIR; T1W Gd	Fingers/toes	Qualitative
Emad, *et al*[26]	PsA/AS/ReA/IBD/Skin psoriasis; healthy subjects	76 (56; 20)	MRI	NA	1.5	T1W; T1W Gd	Knee entheses	Qualitative

Table 1. Continued.

Study	Study Population	No. Participants	Intervention	Comparator	MRI Field Strength	Sequences	MRI Sites	Scoring Systems
Weckbach, *et al*[30]	PsA	30	MRI	Clinical	1.5	STIR, VIBE; VIBE Gd	Whole-body	Qualitative
Wiell, *et al*[31]	SpA; non-SpA; healthy subjects	37 (12; 15; 10)	MRI	US	0.6	T1W; STIR; T1W Gd	Achilles tendon and enthesis	Qualitative
Chen, *et al*[25]	PsA; healthy subjects	16 (9; 7)	MRI 3D UTE Cones	MRI T1W	3	3D UTE Cones; T1W	Achilles tendon	Qualitative
Cohort studies								
Godfrin, *et al*[35]	Entheseal pain at multiple sites	33	MRI	Clinical	1.5	T1W; T2W; T1W FS Gd and/or STIR	Not described	Qualitative
Eshed, *et al*[34]	SpA with hindfoot pain	27	MRI	NA	0.2; 1.5	T1W; STIR; T1W FS Gd; T1W GRE FS	Heel enthesitis	Qualitative
Karpitschka, *et al*[37]	AS	10	MRI	NA	1.5	T1W; STIR	Whole-body	Qualitative
Huang, *et al*[36]	AS	58	MRI	CR; Clinical	1.5	T2W; T1W; STIR; T1W FS Gd	Hip	Qualitative
Althoff, *et al*[33]	SpA	41	MRI	Clinical	1.5	T1W; STIR	Whole-body	Qualitative
Marzo-Ortega, *et al*[38]	SpA	10	MRI	NA	1.5	T1W; T2W FS; T1W FS Gd	Depending on symptoms	Qualitative
Tan, *et al*[43]	AS fulfilling modified New York criteria	9	MRI	NA	1.5	T1, TSE, STIR	SIJ and spine of each patient	Semiquantitative
de Hooge, *et al*[42]	Chronic back pain	127	MRI T1W FS Gd	MRI STIR	1.5	T1W; T1W FS Gd; STIR	SIJ enthesitis/capsulitis	Qualitative
Randomized controlled trials								
Dougados, *et al*[39]	SpA with heel enthesitis	24	MRI	NA	Not reported	T1W; STIR	Heel enthesitis	Qualitative
Song, *et al*[41]	SpA	76	MRI	NA	1.5	T1W; STIR	Whole-body	Qualitative
Krabbe, *et al*[40]	SpA	49	MRI	NA	3	T1W; STIR	Whole-body	Semiquantitative

Numbers in parentheses denote no. participants in each group of study population. AS: ankylosing spondylitis; SpA: spondyloarthritis; PsA: psoriatic arthritis; RA: rheumatoid arthritis; OA: osteoarthritis; MCP: metacarpophalangeal joint; DIP: distal interphalangeal joint; SIJ: sacroiliac joints; T1W: T1-weighted; T2W: T2-weighted; Gd: gadolinium; FS: fat suppressed; SPIR: spectral pre-saturation with inversion recovery; GRE: gradient recalled echo; PD: proton density; 3D-GE: 3D gradient echo; STIR: short-tau inversion recovery; DCE: dynamic contrast enhanced; TSE: turbo spin echo; VIBE: volumetric interpolated breath-hold sequence; UTE: quantitative ultrashort echo time; US: ultrasound; CR: conventional radiograph; ReA: reactive arthritis; IBD: inflammatory bowel disease; MRI: magnetic resonance imaging; NA: not applicable.

Table 2. Psychometric properties and quality scores of selected studies (n = 38).

Study	Face Validity*	Content Validity*	Construct Validity*	Criterion Validity*	Reliability*	Responsiveness*	Quality Scoring
Cross-sectional studies							
McGonagle, *et al*[16]	YES	YES	NO	NO	YES	NO	9
Olivieri, *et al*[19]	YES	NO	NO	NO	NO	NO	7
Tan, *et al*[24]	YES	NO	NO	NO	YES	NO	7
McQueen, *et al*[17]	YES	YES	NO	NO	YES	NO	8
Tan, *et al*[22]	NO	NO	NO	YES	NO	NO	5
Marzo-Ortega, *et al*[15]	NO	NO	NO	NO	YES	NO	7
Maksymowicz, *et al*[14]	NO	NO	NO	NO	NO	NO	6
Althoff, *et al*[9]	YES	YES	NO	NO	YES	NO	7
Aydin, *et al*[10]	YES	YES	YES	NO	YES	NO	8
Braum, *et al*[11]	YES	YES	YES	NO	NO	NO	7
Ramírez, *et al*[21]	YES	NO	NO	NO	NO	NO	8
Paramarta, *et al*[20]	YES	YES	NO	NO	YES	NO	7
Poggenborg, *et al*[2]	YES	YES	YES	NO	YES	NO	10
Tan, *et al*[23]	YES	YES	NO	NO	YES	NO	7
Giraudo, *et al*[13]	YES	NO	NO	NO	YES	NO	7
Agten, *et al*[6]	NO	NO	YES	NO	YES	NO	8
Maldonado, *et al*[7]	YES	YES	YES	NO	YES	NO	7
Aivazoglou, *et al*[8]	YES	NO	YES	NO	NO	NO	7
Case control studies							
Olivieri, *et al*[18]	YES	YES	YES	NO	NO	NO	6
Lambert, *et al*[29]	YES	YES	NO	NO	YES	NO	6
Erdem, *et al*[27]	YES	YES	NO	NO	YES	NO	5
Wiell, *et al*[32]	YES	NO	NO	NO	NO	NO	8
Emad, *et al*[26]	YES	NO	NO	NO	YES	NO	6
Weckbach, *et al*[30]	YES	NO	YES	NO	YES	NO	7
Feydy, *et al*[28]	YES	NO	NO	NO	YES	NO	8
Wiell, *et al*[31]	YES	YES	YES	NO	YES	NO	9
Chen, *et al*[25]	YES	YES	YES	NO	NO	NO	6
Cohort studies							
Godfrin, *et al*[35]	YES	NO	YES	NO	YES	NO	6
Eshed, *et al*[34]	YES	YES	NO	NO	YES	NO	6
Huang, *et al*[36]	YES	NO	YES	NO	YES	NO	9
Karpitschka, *et al*[37]	YES	YES	YES	NO	YES	YES	9
Althoff, *et al*[33]	YES	YES	NO	NO	YES	NO	8
Marzo-Ortega, *et al*[38]	YES	YES	YES	NO	YES	YES	8
Tan, *et al*[43]	YES	NO	NO	NO	NO	YES	8
de Hooge, *et al*[42]	YES	NO	YES	NO	NO	YES	9
Randomized controlled trials							
Dougados, *et al*[39]	NO	NO	NO	NO	NO	NO	7
Song, *et al*[41]	YES	NO	NO	NO	YES	YES	9
Krabbe, *et al*[40]	YES	YES	NO	NO	YES	YES	11

* Face validity was defined as expert opinion on the credibility of scoring system used in each article to measure enthesitis. Content validity estimated the reliability of the scoring system used in each study to measure the full spectrum of outcome – inflammatory and structural changes. Construct validity was achieved when MRI evaluation of enthesitis correlated with the following concepts of enthesitis: (1) clinical assessment of enthesitis using a validated enthesitis score (e.g., MASES), (2) ultrasound or radiographic assessment of enthesitis sites, and/or (3) comparison of different sequences of MRI in assessing enthesitis. Criterion validity was achieved when MRI evaluation of enthesitis correlated with a gold standard (e.g., histology). Reliability was defined in studies mentioning inter-rater reliability measures of scoring consistency between and within MRI readers, e.g., inter/intraclass correlation coefficients or $\varkappa$ statistics. Responsiveness was achieved in studies documenting statistically significant changes in relation to treatment introduction or change. MRI: magnetic resonance imaging; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score.

methods of evaluating enthesitis using MRI in patients with SpA and PsA, and identified notable limitations regarding standardization of MRI enthesitis definitions across studies and validity of available semiquantitative scores as outcome measures. The findings suggest there is no currently available reliable and validated MRI scoring system for enthesitis. Many studies have included different definitions of MRI lesions suggestive of enthesitis, hindering direct comparison of the available methods. A fifth of the selected studies described a semiquantitative scoring system, albeit without standardization and internal validity, because all were developed based on expert opinion.

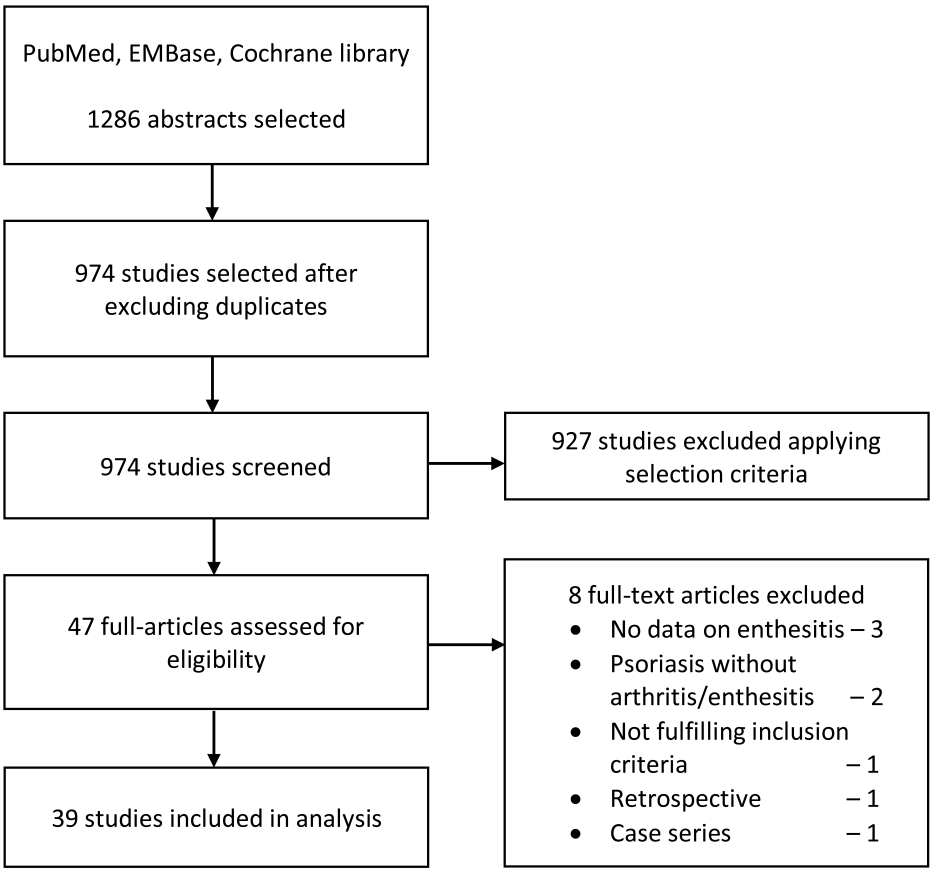

Figure 1. Flow diagram of article selection (PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses).

Poor content validity of reported scoring methods was another limitation of the literature. Most studies have focused on assessing inflammatory aspects of enthesitis and not the structural variables, which denote chronic, irreversible changes. MRI inflammatory lesions are amenable to change and responsive to therapy. Wide variation in the entheseal sites to be assessed adds to the challenge in standardization. Lack of a standardized definition to define the borders of enthesitis makes it difficult to differentiate it from other inflammatory variables, such as synovitis and tenosynovitis, thus increasing the variability of scores in each study.

Construct validity was evaluated in relation to US and clinical examination. Most of the studies showed poor correlation between MRI and US. This again emphasizes the lack of standardized definitions of MRI enthesitis lesions. Limited information exists regarding criterion validity because only 1 study compared MRI with histology. Lack of significant responsiveness of available qualitative and semiquantitative MRI enthesitis scores suggests limited utility as outcome measures in clinical trials.

The above-mentioned limitations and the lack of validated, generally accepted MRI enthesitis assessment systems warrant the development of a reliable and feasible MRI enthesitis scoring system to increase the utility of MRI as an outcome measure in SpA and PsA clinical trials.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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