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REVIEW

Comparison of Clinical Manifestations in Rheumatoid Arthritis vs. Spondyloarthritis: A Systematic Literature Review

Philip J. Mease · Mohit Kumar Bhutani · Steven Hass · Esther Yi · Peter Hur · Nina Kim

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ABSTRACT

Introduction: Misclassification of spondyloarthritis (SpA) as rheumatoid arthritis (RA) may lead to delayed SpA diagnosis and suboptimal therapeutic outcomes. Here, we evaluate the literature on clinical manifestations in patients with SpA and RA, particularly seronegative RA, to understand the potential overlap, distinctions, and most reliable approaches to accurate diagnosis.

Methods: In this systematic literature review, conducted according to PRISMA guidelines, we searched key biomedical databases for English-language publications of original research articles (up to July 23, 2020) and rheumatology conference abstracts (January 1, 2018–July 31, 2020) reporting key SpA clinical presentations in patients with SpA or RA. Publications were assessed for eligibility by two independent reviewers; discrepancies were resolved by a third. Studies were evaluated for publication quality using the Downs and Black checklist.

Results: Of 4712 records retrieved, 79 met the inclusion criteria and were included in the analysis. Of these, 54 included study populations with SpA and RA, and 25 with seropositive and/or seronegative RA. Entheseal abnormalities were more frequently reported among patients with SpA than RA and with seronegative vs. seropositive RA. Psoriasis, nail psoriasis, and dactylitis were exclusively seen in SpA vs. RA. In most publications (70 of 79), advanced imaging techniques allowed for more accurate distinction between SpA and RA. Overlapping clinical characteristics occur in SpA and RA, including inflammation and destruction of joints, pain, diminished functional ability, and increased risk for comorbidities. However, of 54 studies comparing SpA and RA populations, only seven concluded that no distinction can be

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P. J. Mease
Swedish Medical Center/Providence St. Joseph Health and University of Washington, Seattle, WA, USA

M. K. Bhutani
Novartis Healthcare Pvt Ltd, Hyderabad, India

S. Hass
H.E. Outcomes, LLC, Los Angeles, CA, USA

E. Yi · P. Hur
Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA

N. Kim
Baylor Scott & White Health, Temple, TX, USA

N. Kim
University of Texas at Austin, Austin, TX, USA

P. J. Mease (✉)
Seattle Rheumatology Associates, 601 Broadway, Suite 600, Seattle, WA 98122, USA
e-mail: pmease@philipmease.com

made based on the SpA manifestations and outcomes examined.
Conclusions: Typical SpA-related clinical symptoms and signs were observed in patients with RA, suggesting that misclassification could occur. Availability of advanced imaging modalities may allow for more prompt and comprehensive evaluation of peripheral manifestations in SpA and RA, reducing misclassification and delayed diagnosis.

PLAIN LANGUAGE SUMMARY

Spondyloarthritis (SpA) is a group of chronic, inflammatory diseases that includes axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA), in addition to other peripheral forms of SpA. AxSpA primarily affects the spine and can cause chronic back pain. PsA occurs in patients with the skin condition psoriasis and patients often experience symptoms including joint pain, stiffness, and swelling. Quick and accurate diagnosis of SpA is necessary to prevent joint damage and physical limitations. Rheumatoid arthritis (RA) is characterized by pain, swelling, and stiffness in multiple joints, and delayed diagnosis and treatment can have lasting effects. However, many patients with SpA and RA who initially seek medical care often experience delayed diagnoses. This study evaluated the literature on symptoms in patients with SpA and RA, particularly patients with RA without antibodies typically associated with the disease, to understand the potential overlap, differences, and most reliable ways to accurately diagnose patients. Data from 79 records were included in the analysis, 54 of which included study populations with SpA and RA. Skin and nail psoriasis, as well as swelling of the fingers and toes, was only seen in patients with SpA. Most studies showed that enhanced imaging allowed for distinguishing between SpA and RA. This study showed that typical signs and symptoms of SpA, including inflammation and joint pain, could also be seen in patients with RA, which suggests that challenges exist for accurately identifying SpA. This highlights the importance of advanced imaging to diagnose and treat patients with SpA in a timely manner.

Keywords: Axial spondyloarthritis; Psoriatic arthritis; Rheumatoid arthritis; Rheumatic diseases; Spondyloarthropathies

Key Summary Points
Misclassification of spondyloarthritis (SpA) as rheumatoid arthritis (RA) can lead to delayed diagnosis and treatment and poor outcomes for patients with SpA.
This study evaluated the literature for clinical manifestations of SpA and RA to understand the potential overlap, distinction, and most reliable approaches for accurate diagnosis.
Clinical manifestations observed exclusively in SpA included psoriasis, nail psoriasis, and dactylitis.
Advanced imaging techniques, such as ultrasonography and magnetic resonance imaging, provided a more accurate distinction between SpA and RA.
While SpA manifestations were observed among patients with RA, improvement and standardization of imaging protocols can positively impact clinical outcomes and quality of life.

INTRODUCTION

Spondyloarthritis (SpA) refers to a group of chronic, inflammatory diseases that includes axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA), as well as other peripheral types of SpA including enteropathic arthritis, reactive arthritis, and undifferentiated SpA [1, 2]. AxSpA predominantly involves inflammation of the sacroiliac joints and spine; inflammation of the spinal vertebrae, connective tissue, and joints

causes chronic back pain and may eventually lead to the fusion of vertebral units [1]. AxSpA with radiographic sacroiliitis is termed radiographic axSpA, also known as ankylosing spondylitis (AS), and fulfills the definition of AS based on the 1984 modified New York criteria and the 2009 Assessment of SpondyloArthritis international Society criteria for radiographic axSpA [3]. Conversely, axSpA without radiographic sacroiliitis, which does not meet the modified New York criteria for AS, can be subclassified as nonradiographic axSpA [3]. The prevalence of axSpA ranges from 0.9 to 1.4% in the US adult population [4]. However, the true disease prevalence is not known, partly due to the significant delays in diagnosis and recognition; recent reports indicate a mean diagnostic delay of 6.7 years [5]. Challenges in distinguishing inflammatory back pain (IBP), a key symptom of axSpA that affects the spine and sacroiliac joints, from other forms of low back pain in the general population are a primary contributor to delay or lack of diagnosis, especially among patients without definitive radiographic sacroiliitis [4]. AxSpA is associated with substantial physical, economic, and emotional liabilities [4].

PsA has a prevalence of approximately 100–200 per 100,000 in the general adult population and an incidence rate of 3.6–7.2 per 100,000 patient-years [6]. PsA manifests with axial disease, peripheral joint inflammation, enthesitis, dactylitis, and skin and nail psoriasis, either alone or in combination [7]. A PsA diagnosis delayed by as few as 6 months may be associated with worse peripheral joint erosions, progressive joint damage, and substantial physical limitations [7].

Rheumatoid arthritis (RA), with an estimated global age-standardized point prevalence and annual incidence rate of 246.6 and 14.9 per 100,000 population, respectively, is characterized by pain, swelling, and stiffness in multiple joints [8]. Disability is common and substantial; in a large US study, 35% of patients with RA had employment-related disability after 10 years [9]. Prompt diagnosis and treatment are associated with improved clinical and radiographic outcomes, as well as the probability of remission; diagnosis delays beyond 3 months may be detrimental [10].

Infiltration of the joint synovia with inflammatory cells and cellular mediators (cytokines) is the hallmark of arthritis in both RA and SpA [11]. Resultant lytic destruction of bone and cartilage follows in both RA and SpA; in SpA, there are also areas of bony proliferation and ankylosis [12]. Inflammation of ligament and tendon insertions into bone (enthesitis) and bone itself (osteitis) are also characteristic pathologies of SpA [1, 2]. However, several key factors distinguish SpA from other types of arthritis, including the distribution and type of musculoskeletal manifestations and particular extra-articular features, as well as genetic associations and structural outcome [12]. Joint damage in RA comprises widespread destruction with minimal or no indications of repair; in AS, damage to the spine or joint is usually accompanied by remodeling [12]. The pathophysiology of chronic inflammatory diseases is rooted in the interaction network of proinflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-1, IL-6, IL-17, and IL-23 [13]. For many patients with inflammatory conditions such as RA and SpA, their response to inhibitors of these inflammatory cytokines may differ, suggesting a disease-dependent, hierarchical cytokine effect [13]. Ongoing studies implicate TNF-α, IL-1, and IL-6 in RA pathology and TNF-α, IL-17, and IL-23 in SpA [13]. Thus, correct diagnosis is important when steering the patient toward appropriate therapies.

As many patients with axSpA, PsA, and RA initially seek medical care from primary care physicians or other nonrheumatology healthcare providers, correct and prompt diagnosis is variable and often delayed. Numerous recommendations and guidelines exist to promote early rheumatology referrals [14–16]. Early diagnosis and treatment before irreversible changes occur are crucial for optimal disease management and improved patient quality of life. Diagnostic algorithms for axSpA [1], PsA [17], and RA [18] are available as a guide for rheumatologists in their clinical assessments. Overall, diagnosis relies on clinical judgement of features that are characteristic of each disease

spectrum, including the patient's history of symptoms and manifestations, physical findings, laboratory workup, and imaging information. However, overlap in clinical manifestations of inflammatory rheumatic diseases, particularly early in the disease course, may lead to misdiagnosis. Thorough evaluation of disease presentations is crucial to guide decisions pertaining to treatment and patient care. This systematic review assesses the available evidence on overlapping clinical manifestations associated with axSpA, PsA, and RA to better understand whether disease misclassification, and therefore delayed diagnosis, may occur.

METHODS

Data Sources

This systematic literature review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [19]. We searched the MEDLINE Literature Analysis and Retrieval System Online (including MEDLINE In-Process), *Excerpta Medica* (Embase), BIOSIS Previews, and Evidence-Based Medicine Reviews databases for original research articles (up to July 23, 2020) reporting studies on clinical manifestations of SpA and RA. The list of search terms is provided in Table S1. Additionally, abstract archives of the American College of Rheumatology/Association of Rheumatology Health Professionals Annual Meeting and the European League Against Rheumatism Annual European Congress of Rheumatology were searched (January 1, 2018–July 31, 2020) to identify abstracts not yet indexed in the aforementioned biomedical databases at the time of the search. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Eligibility Criteria and Article Selection

Eligible records for inclusion were English-language, noninterventional, original research studies of adult patients that either included both RA and SpA or seropositive and/or seronegative RA as major populations and that also reported SpA-related clinical manifestations. The key inclusion and exclusion criteria are described in Table 1. Abstracts of all records retrieved from the literature search were screened for eligibility by two independent reviewers; discrepancies were reconciled by a third.

Data Extraction and Quality Assessment

Data from the final list of included publications were extracted by one reviewer and validated by a second independent reviewer; any discrepancies were resolved by a third reviewer. For each record, the study title, year of publication, study design, total study population, objective, inclusion/exclusion criteria, baseline patient data, outcomes assessed, and authors' conclusions were extracted. Baseline patient data collected included age, sex, geographic region, race/ethnicity, proportion of patients with rheumatoid factor (RF) and anticyclic citrullinated peptide (anti-CCP) expression, and disease and symptom duration. Outcomes extracted comprised current and historical SpA-related clinical manifestations, imaging, laboratory tests, and disease activity measures. Clinical manifestation outcomes included oligoarthritis, polyarthritis, IBP, peripheral arthritis, enthesitis, uveitis, dactylitis, psoriasis, nail disease (psoriatic nail psoriasis or nail psoriasis), inflammatory bowel disease (specifically Crohn's disease and ulcerative colitis), and good response to nonsteroidal anti-inflammatory drugs. Imaging outcomes consisted of sacroiliitis on imaging, active (acute) inflammation on magnetic resonance imaging (MRI) suggestive of sacroiliitis, definitive radiographic sacroiliitis, structural damage, hip involvement, and spinal deformities. Laboratory tests comprised HLA-B27 expression and elevated C-reactive protein (CRP) levels. Subjective measures of disease activity included physician global assessment (PGA); patient-reported outcome (PRO) measures were pain and fatigue on a visual analog

Table 1 Details of systematic literature review methodology

Databases	*Electronic databases*: MEDLINE, MEDLINE In-Process, Embase, BIOSIS Previews, and Evidence-Based Medicine Reviews
	Conference databases: ACR/ARHP Annual Meeting and EULAR Annual European Congress of Rheumatology archives
Time frame	*Full text articles*: up to July 23, 2020
	Conference abstracts: January 1, 2018–July 31, 2020
Inclusion criteria	*Population*: studies including adult patients with either both RA and SpA or seropositive and/or seronegative RA
	Outcomes:
	SpA-related clinical manifestations (documented history and current manifestations):
	– Sacroiliitis on imaging
	– Active (acute) inflammation on MRI suggestive of sacroiliitis
	– Oligoarthritis
	– Polyarthritis
	– Definitive radiographic sacroiliitis
	– IBP
	– Peripheral arthritis
	– Enthesitis
	– Uveitis
	– Dactylitis
	– Psoriasis
	– Nail disease (psoriatic nail disease or nail psoriasis)
	– IBD, specifically Crohn's disease and ulcerative colitis
	– Good response to NSAIDs
	– HLA-B27
	– Elevated CRP
	– Structural damage, hip involvement, spinal deformities
	Study design: nonrandomized controlled trials, including prospective and retrospective observational, case control, prospective and retrospective longitudinal, and cross-sectional studies
Exclusion criteria	Non-English-language articles
	Interventional studies focusing on the evaluation of clinical efficacy and/or safety, including RCTs, nRCTs, or single-arm trials
	Reviews, editorials, case reports, case series, commentaries, animal and in vitro studies, and studies focusing on clinical efficacy and safety of an intervention
	Publications not relevant to the study objective

Table 1 continued

Critical appraisal tools	Downs and Black Quality Index for assessing risk of bias [20]
Data extraction	Total number of patients analyzed, number of patients with outcome, mean, SD, SE, median, range, 95% CI, and *P* values, as applicable

ACR American College of Rheumatology, *ARHP* Association of Rheumatology Health Professionals, *CRP* C-reactive protein, *EULAR* European League Against Rheumatism, *IBD* inflammatory bowel disease, *IBP* inflammatory back pain, *MRI* magnetic resonance imaging, *nRCT* nonrandomized controlled trial, *NSAID* nonsteroidal anti-inflammatory drug, *RA* rheumatoid arthritis, *RCT* randomized controlled trial, *SpA* spondyloarthritis

scale such as patient global assessment (PtGA) of disease activity.

The procedural quality of each publication was evaluated using the Downs and Black Quality Index for evaluating risk of bias [20]. Briefly, study methodology was assessed using 26 questions examining the characteristics of study reporting, external validity, and internal validity (bias and confounding) (Table S2). The total possible score on the Downs and Black scale was 27, with higher numbers indicating higher methodological quality or lower risk of bias.

RESULTS

Study Selection, Characteristics, and Quality Assessment

The initial search yielded 4712 records, from which 79 unique studies were identified for inclusion after screening (Fig. 1) [21–99]. Of these, 54 included study populations with RA and SpA [21–74], and 25 included study populations with seropositive and/or seronegative RA [75–99]. SpA-related outcomes or manifestations reported in included studies assessed by clinical examination and/or imaging comprised peripheral arthritis [21–28, 30–36, 38–42, 45–52, 57–63, 66, 68, 71, 72, 74–99], polyarthritis [22, 33, 36, 78, 79], and oligoarthritis [22, 33], enthesitis or enthesopathy [22–29, 31–33, 36, 44, 45, 47–49, 54–56, 60, 63, 66, 67, 69, 71, 72, 75, 84], psoriasis [21–23, 25, 26, 30, 59, 70, 74], dactylitis [21, 27, 33, 36, 46, 55, 71–73], nail psoriasis [21, 23, 28, 54, 59, 72], axial disease (IBP [25, 26, 32, 33, 38, 48, 55, 61–63, 69], spinal deformities [33, 37, 38, 43, 51, 64, 90], hip involvement or damage [35, 47, 64, 90], and sacroiliitis [43, 55, 90]), extra-articular manifestations (uveitis [53, 55, 70] and inflammatory bowel disease [70, 74]), and laboratory measures (HLA-B27 positivity [24–26, 53, 55, 65, 69, 78] and elevated CRP levels [21, 34, 46, 47, 49, 65, 76, 89, 99]). Other data reported included PROs (pain [30, 34, 38, 40, 46, 57, 61, 76, 98], fatigue [30, 38, 98], and PtGA of disease activity [30, 34, 38, 61, 62, 77, 81, 98]), and PGA of disease [30, 38, 62, 77, 81]. Imaging methods used across included studies comprise ultrasonography [21–23, 25, 26, 28, 29, 31, 32, 34, 39, 44, 47, 48, 50, 54–56, 59, 66, 67, 69, 71, 72, 74, 75, 82, 84, 85], classic radiography (i.e., X-ray) [29, 33, 36, 40, 45, 46, 51, 56, 68, 75–80, 83, 86, 89, 93, 95, 99], computed tomography [43], and MRI [24, 27, 37, 41, 47, 49, 57, 60].

Study characteristics are described in Table 2. The 79 included analyses, published between 1997 and 2020, were conducted in Europe (n = 47), North America (n = 11), Asia (n = 8), Africa (n = 4), South America (n = 1), and combined populations across multiple geographical regions, including Europe, Asia, North America, North Africa, and Oceania (n = 8). Of those studies reporting information on study design and setting, most were prospective cohort (n = 41) or cross-sectional (n = 21) studies in single (n = 31) or multicenter (n = 19) settings, comprising a study population of 35–117,794 patients with SpA and RA. Across all studies, the

proportion of men with SpA and RA (both seropositive and seronegative) ranged from 17.4 to 87.5% and from 6.7 to 68.2%, respectively. Included patients with SpA and RA (both seropositive and seronegative) had a mean age of 30.9–54.5 years and 41.6–67.3 years, respectively, and a mean disease duration of 8.0–1083.6 months and 2.5–192.0 months, respectively.

The methodological quality of each study included in the analysis is described in Table S3; the overall scores on the quality index ranged from 9 to 15 (index range 0–27). For questions assessing study reporting, scores ranged from 5 to 8 (index range 0–11), with most studies ($n = 59$) having a score ≥ 7. For questions assessing external validity, scores ranged from 0 to 2 (index range 0–3); most records had a score of 0. For questions assessing internal validity (bias), scores ranged from 2 to 5 (index range 0–7), with 53 studies having a score of 4. Lastly, for questions assessing internal validity (confounding–selection bias), scores ranged from 1 to 3 (index range 0–6), with most studies ($n = 73$) having a score of 1. For questions relating to internal and external validity, "unable to determine" and "no" responses were both scored as 0, which lowered the overall validity scores of included studies. Notably, some of the questions in the Downs and Black checklist are relevant only to interventional studies, which were excluded from this review; therefore, this may have contributed to lower

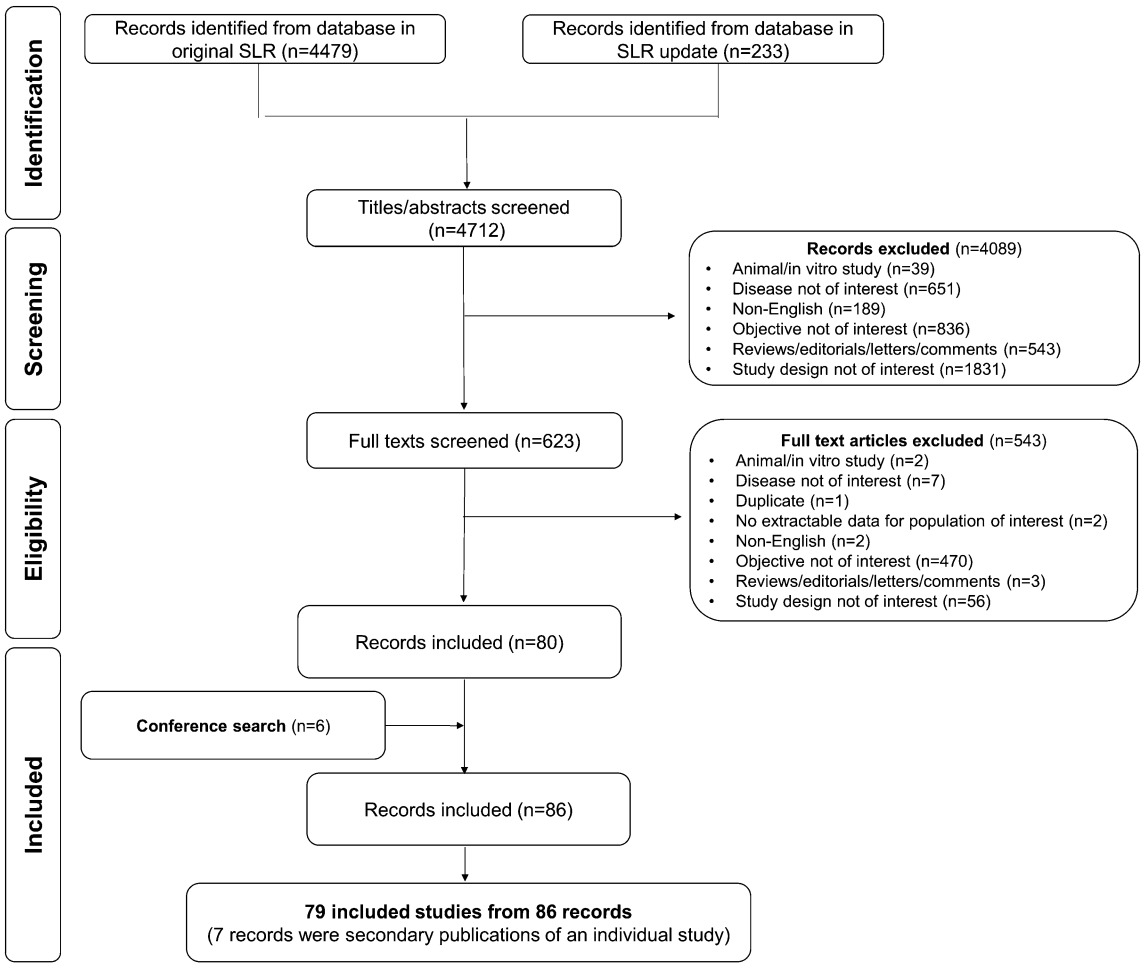

Fig. 1 PRISMA diagram for article selection. *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses, *SLR* systematic literature review

Table 2 Characteristics of articles reporting SpA manifestations among patients with SpA and RA

Study	Study design	Country	Study population, *N*	Male, %	Primary SpA manifestation(s)	Examination site(s)	Primary examination method(s)
Tinazzi et al. [21]	Prospective cohort	Italy	96	RA, 26 PsA, 59	Enthesitis, dactylitis	Hand	Ultrasonography
Zabotti et al. [22]	Prospective cohort	Italy	60	RA, 21 PsA, 42	Peripheral arthritis, enthesitis	Hand	Ultrasonography
Zabotti et al. [23]	Cross-sectional	Italy	73	S^+ RA, 48 S^- RA, 13 PsA, 56	Enthesitis, psoriasis/nail psoriasis	Hand	Ultrasonography, integrated rheumatology/dermatology evaluation
Narváez et al. [24]	Prospective cohort	Spain	37	RA, 20 PsA, 35	Enthesitis	Wrist, hand	MRI
Ottaviani et al. [25]	Case control	France	114	RA, 26 PsA, 22	Peripheral arthritis	Shoulder	Ultrasonography
Ebstein et al. [26]	Cross-sectional	France	97	RA, 17 SpA, 68	Enthesitis	Foot, elbow, knee	Ultrasonography
Mathew et al. [27]	Prospective cohort	India	36	RA, 22 PsA, 44	Peripheral arthritis, enthesitis	Hand	MRI
Fournié et al. [28]	Prospective cohort	France	41	RA, 24 PsA, 55	Peripheral arthritis, enthesitis	Finger	Ultrasonography
Falsetti et al. [29]	Prospective cohort	Italy	598	RA, 30 PsA, 48	Enthesitis	Heel	Ultrasonography

Table 2 continued

Study	Study design	Country	Study population, *N*	Male, %	Primary SpA manifestation(s)	Examination site(s)	Primary examination method(s)
Ogdie et al. [30]	Retrospective cohort	United States	4827	S^+ RA, 24 S^- RA, 23 PsA, 46 AxSpA, 61	Peripheral arthritis, other	NR	NR
Erturk et al. [31]	Cross-sectional	Turkey	93	S^+ RA, 8 S^- RA, 11 AxSpA, 17	Enthesitis	Hand	Ultrasonography
Genc et al. [32]	Prospective cohort	Turkey	62	RA, 8 AxSpA, 78	Enthesitis	Shoulder, knee, heel, foot	Ultrasonography
Helliwell et al. [33]	Prospective cohort	Australia, Belgium, Canada, France, Ireland, Morocco, New Zealand, South Africa, Italy, Spain, Sweden, United Kingdom, United States	1124	RA, 29 PsA, 52	Peripheral arthritis, enthesitis, dactylitis, spinal deformities	Heel, knee, hand, finger	Radiography
Sakellariou et al. [34]	Cross-sectional	Italy	156	RA, 28 PsA, 32	Peripheral arthritis	Wrist, hand, foot	Ultrasonography, radiography

Table 2 continued

Study	Study design	Country	Study population, *N*	Male, %	Primary SpA manifestation(s)	Examination site(s)	Primary examination method(s)
Low et al. [35]	Prospective cohort	Ireland	58	S^+ RA, 44 S^- RA, 30 PsA, 25	Other	Hip, waist	Synovial biopsy by needle arthroscopy
Inanc et al. [36]	Prospective cohort	Turkey	303	RA, 17 PsA, 36	Peripheral arthritis	Hand, foot	Radiography
Baraliakos et al. [37]	Prospective cohort	Germany	40	RA, 12 AxSpA, 50	Spinal deformities	Cervical spine	MRI
Michelsen et al. [38]	Cross-sectional	Norway	1791	RA, 32 PsA, 51 AxSpA, 67	Peripheral arthritis, IBP, spinal deformities, other	NR	NR
Ceccarelli et al. [39]	Cross-sectional	Italy	113	RA, 16 PsA, 47	Peripheral arthritis	Wrist, knee	Ultrasonography
Reddy et al. [40]	Prospective cohort	United States	19,588	RA, 25 PsA, 48	Peripheral arthritis, other	Spine, neck	Radiography
Cimmino et al. [41]	Prospective cohort	Italy	102	RA, 14 PsA, 47	Peripheral arthritis	Wrist, hand	MRI
Liphardt et al. [42]	Prospective cohort	Germany	298	RA, 29 PsA, 41	Peripheral arthritis	Hand	Hand dynamometer

Table 2 continued

Study	Study design	Country	Study population, *N*	Male, %	Primary SpA manifestation(s)	Examination site(s)	Primary examination method(s)
Fauny et al. [43]	Retrospective cohort	France	244	RA, 22 AxSpA, 87	Spinal deformities	Vertebra	Computed tomography
Batticciotto et al. [44]	Retrospective cohort	Italy	35	RA, 15 SpA, 40	Enthesitis	Wrist, hand	Ultrasonography
Ichikawa et al. [45]	Prospective cohort	Japan	220	S^+ RA, 51 S^- RA, 30 PsA, 57	Peripheral arthritis, enthesitis	Hand, foot	Radiography
Lindqvist et al. [46]	Prospective cohort	Sweden	1036	RA, 30 PsA, 42 AxSpA, 71	Peripheral arthritis, other	NR	Radiography
Ramírez et al. [47]	Cross-sectional	Spain	107	NR	Peripheral arthritis, enthesitis, hip damage or involvement	Hip	Ultrasonography, radiography
Harman et al. [48]	Prospective cohort	Turkey	142	RA, 15 AxSpA, 60 pSpA, 62	Peripheral arthritis, enthesitis	Shoulder, elbow, wrist, hand, knee	Ultrasonography

Table 2 continued

Study	Study design	Country	Study population, *N*	Male, %	Primary SpA manifestation(s)	Examination site(s)	Primary examination method(s)
Abrar et al. [49]	Prospective cohort	Germany	53	RA, 55 PsA, 53	Enthesitis	Hand	MRI
Figus et al. [50]	Cross-sectional	Italy, Croatia, Bulgaria	106	NR	Peripheral arthritis	Wrist	Ultrasonography
Murphy et al. [51]	Prospective cohort	Ireland	38	RA, 40 SpA 61	Peripheral arthritis	Hand, foot	Radiography
Kruithof et al. [52]	Prospective cohort	Belgium	142	RA, 48 PsA, 64 SpA, 79	Peripheral arthritis	Knee	Synovial biopsy by needle arthroscopy
Noche et al. [53]	Cross-sectional	Cameroon	24	RA, 19 AxSpA, 88	Ophthalmic manifestations	Eye	Routine ophthalmic examination
Idolazzi et al. [54]	Cross-sectional	Italy	88	RA, 27 PsA, 51	Enthesitis, psoriasis/nail psoriasis	Nails	Ultrasonography
D'Agostino et al. [55]	Cross-sectional	France	194	NR	Enthesitis	Pelvis, knee, foot	Ultrasonography
Falsetti et al. [56]	Retrospective cohort	Italy	200	NR	Enthesitis	Shoulder	Ultrasonography, radiography
Cimmino et al. [57]	Prospective cohort	Italy	17	RA, 20 PsA, 29	Peripheral arthritis	Wrist, hand	MRI

Table 2 continued

Study	Study design	Country	Study population, *N*	Male, %	Primary SpA manifestation(s)	Examination site(s)	Primary examination method(s)
Roman-Ivorra et al. [58]	Cross-sectional	Spain	197	RA, 18 PsA, 18	Peripheral arthritis, other	Hand	Hand dynamometer
Sandobal et al. [59]	Prospective cohort	Argentina	62	NR	Peripheral arthritis, psoriasis/nail psoriasis	Nails	Ultrasonography
Schoellnast et al. [60]	Retrospective cohort	Austria	39	RA, 19 PsA, 33	Peripheral arthritis, enthesitis	Wrist, hand	MRI
Bailly et al. [61]	Prospective cohort	France	165	RA, 19 AxSpA, 56	Other	NR	NR
Cemeroğlu et al. [62]	Retrospective cohort	Turkey	90	RA, 22 AxSpA, 69	Other	NR	NR
Leeb et al. [63]	Cross-sectional	Austria	255	RA, 68 PsA, 68	Peripheral arthritis, other	NR	NR
Harter et al. [64]	Retrospective cohort	United Kingdom	49,094	NR	Hip damage or involvement	Fractures of the hip and vertebra	NR
Illeez et al. [65]	Retrospective cohort	Turkey	321	RA, 18 AS, 69	–	Blood	Immunoassays

Table 2 continued

Study	Study design	Country	Study population, *N*	Male, %	Primary SpA manifestation(s)	Examination site(s)	Primary examination method(s)
Ahmed et al. [66]	Prospective cohort	Egypt	35	NR	Peripheral arthritis, enthesitis	Wrist, hand	Ultrasonography
Ward et al. [67]	Prospective cohort	United States	41	RA, 24 SpA, 55	Enthesopathy	Ankle	Ultrasonography
Helenius et al. [68]	Case control	Finland	64	RA, 8 AxSpA, 68 SpA, 57	–	Jaw	Stomatognathic examination, radiography
Milutinovic et al. [69]	Prospective cohort	Serbia	102	RA, 23 AxSpA, 77 SpA, 64	Enthesitis	NR	Ultrasonography
Aletaha et al. [70]	Case control	United States	117,794	NR	–	NR	NR
Smerilli et al. [71]	Cross-sectional	Italy	60	RA, 23 PsA, 53	Enthesitis	Hand	Ultrasonography
Tinazzi et al. [72]	Prospective cohort	Italy	82	RA, 29 PsA, 41	Enthesitis	Hand	Ultrasonography
Rothschild et al. [73]	Prospective cohort	United States	246	NR	Dactylitis	NR	NR
Matschke et al. [74]	Cross-sectional	United Kingdom	30	RA, 28 AS, 67	–	Knee	Ultrasonography

Table 2 continued

Study	Study design	Country	Study population, *N*	Male, %	Primary SpA manifestation(s)	Examination site(s)	Primary examination method(s)
Grosse et al. [75]	Prospective cohort	France	108	CCP^+, 72 CCP^-, 28	RA serostatus comparison	Wrist, hand	Ultrasonography, radiography
Mouterde et al. [76]	Prospective cohort	France	748	S^+ RA, 23 S^- RA, 23	RA serostatus comparison	Wrist, hand, foot	Radiography
Slimani et al. [77]	Cross-sectional	Algeria	249	S^+ RA, 14 S^- RA, 16	RA serostatus comparison	Hand, foot	Radiography
Liu et al. [78]	Retrospective cohort	United States	80	S^+ RA, 50 S^- RA, 50	RA serostatus comparison	Hand	Radiography
Oprea et al. [79]	Prospective cohort	Romania	66	S^+ RA, 7 S^- RA, 19	RA serostatus comparison	Hand	Radiography
Barra et al. [80]	Prospective cohort	Canada	841	S^+ RA, 23 S^- RA, 31	RA serostatus comparison	Hand, foot	Radiography

Table 2 continued

Study	Study design	Country	Study population, *N*	Male, %	Primary SpA manifestation(s)	Examination site(s)	Primary examination method(s)
Deveci et al. [81]	Cross-sectional	Turkey	48	S^+ RA, 15 S^- RA, 13	RA serostatus comparison	Blood	Immunoassays
Hamdi et al. [82]	Cross-sectional	Tunisia	118	NR	RA serostatus comparison	Wrist, hand	Ultrasonography
Asikainen et al. [83]	Prospective cohort	Finland, Sweden	312	NR	RA serostatus comparison	Hand, foot	Radiography
Azuaga-Piñango et al. [84]	Retrospective cohort	Spain	145	NR	RA serostatus comparison	Wrist, hand	Ultrasonography
Azuaga-Piñango et al. [85]	Prospective cohort	Spain	205	NR	RA serostatus comparison	Wrist, hand	Synovial biopsies using arthroscopy, ultrasonography
Rauwel et al. [86]	Prospective cohort	France	487	S^+ RA, 20 S^- RA, 26	RA serostatus comparison	Hand, foot	Radiography
Hermosillo [87]	Prospective cohort	Mexico	64	NR	RA serostatus comparison	NR	NR
Morales-Arango et al. [88]	Prospective cohort	Mexico	28	Total, 22	RA serostatus comparison	NR	NR

Table 2 continued

Study	Study design	Country	Study population, *N*	Male, %	Primary SpA manifestation(s)	Examination site(s)	Primary examination method(s)
Shin et al. [89]	Retrospective cohort	South Korea	109	S^+ RA, 19 S^- RA, 13	RA serostatus comparison	Hand, foot	Radiography
Sahatçiu-Meka et al. [90]	Prospective cohort	Kosovo	250	S^+ RA, 26 S^- RA, 26	RA serostatus comparison	Hand, foot, shoulder, knee, elbow, hip, spine	Clinical assessment
Sahatçiu-Meka et al. [91]	Retrospective cohort	Kosovo	250	S^+ RA, 27 S^- RA, 27	RA serostatus comparison	Hand	NR
Rajapaksa et al. [92]	Case control	Sri Lanka	162	S^+ RA, 16 S^- RA, 13	RA serostatus comparison	NR	Immunoassays
Shin et al. [93]	Prospective cohort	South Korea	1198	NR	RA serostatus comparison	Hand, foot	Radiography
Modi et al. [94]	Cross-sectional	United States	884	NR	RA serostatus comparison	NR	NR
Shankar et al. [95]	Cross-sectional	India	211	Total, 12	RA serostatus comparison	Hand	Radiography
Fujinami et al. [96]	Prospective cohort	Japan	30	NR	RA serostatus comparison	Blood	Immunoassays

Table 2 continued

Study	Study design	Country	Study population, *N*	Male, %	Primary SpA manifestation(s)	Examination site(s)	Primary examination method(s)
Othman et al. [97]	Retrospective cohort	Malaysia	80	S^+ RA, 17 S^- RA, 18	RA serostatus comparison	Ankle, elbow, knee, shoulder, hand, wrist	Immunoassays
Cappelli et al. [98]	Cross-sectional	United States	165	Total, 18	RA serostatus comparison	NR	PROs
Choi et al. [99]	Prospective cohort	Belgium	241	S^+ RA, 26 S^- RA, 33	RA serostatus comparison	NR	Radiography

AS ankylosing spondylitis, *axSpA* axial spondyloarthritis, *CCP* cyclic citrullinated peptide, *IBP* inflammatory back pain, *MRI* magnetic resonance imaging, *NR* not reported, *PRO* patient-reported outcome, *PsA* psoriatic arthritis, *pSpA* peripheral spondyloarthritis, *RA* rheumatoid arthritis, S^+ *RA* seropositive RA, S^- *RA* seronegative RA, *SpA* spondyloarthritis

checklist scores for studies included in this review.

Clinical Manifestations and Outcomes in SpA vs. RA

Peripheral Arthritis

Overall, 65 studies reported data on peripheral arthritis (Fig. 2). Key outcomes included findings from both clinical examination (Clinical Disease Activity Index, Disease Activity Score in 28 joints [DAS28], swollen joint count, tender joint count, morning stiffness, grip strength, and synovial biopsy by needle arthroscopy) and imaging (synovitis by imaging, joint effusion, joint space narrowing, periostitis, erosion, periosteal inflammation on MRI, bursitis, joint osteolysis, juxta-articular new bone formation, and bone cyst formation). A total of 26 studies evaluated peripheral arthritis as a primary focus of their study, making comparisons among patients with SpA and RA; of these, only two concluded that there were no differences between SpA and RA based on MRI [41] and ultrasonographic and MRI [47] findings (Table 3). In general, the frequency of presence or absence of peripheral arthritis was relatively equal among patients with SpA and RA. However, several studies noted specific anatomical sites that were more prominently affected by SpA than RA. Ottaviani and colleagues reported ultrasound findings indicating that patients with SpA had a higher frequency of acromioclavicular joint synovitis than those with RA, as well as lower occurrence of subacromial and subdeltoid bursitis, glenohumeral effusion, and humeral bone erosion [25]. Office extremity MRI revealed that periosteal inflammation at the first interphalangeal joint was exclusively present among patients with PsA vs. RA, whereas synovitis in the metacarpophalangeal (MCP) joint was observed more frequently among patients with RA vs. PsA [27]. At

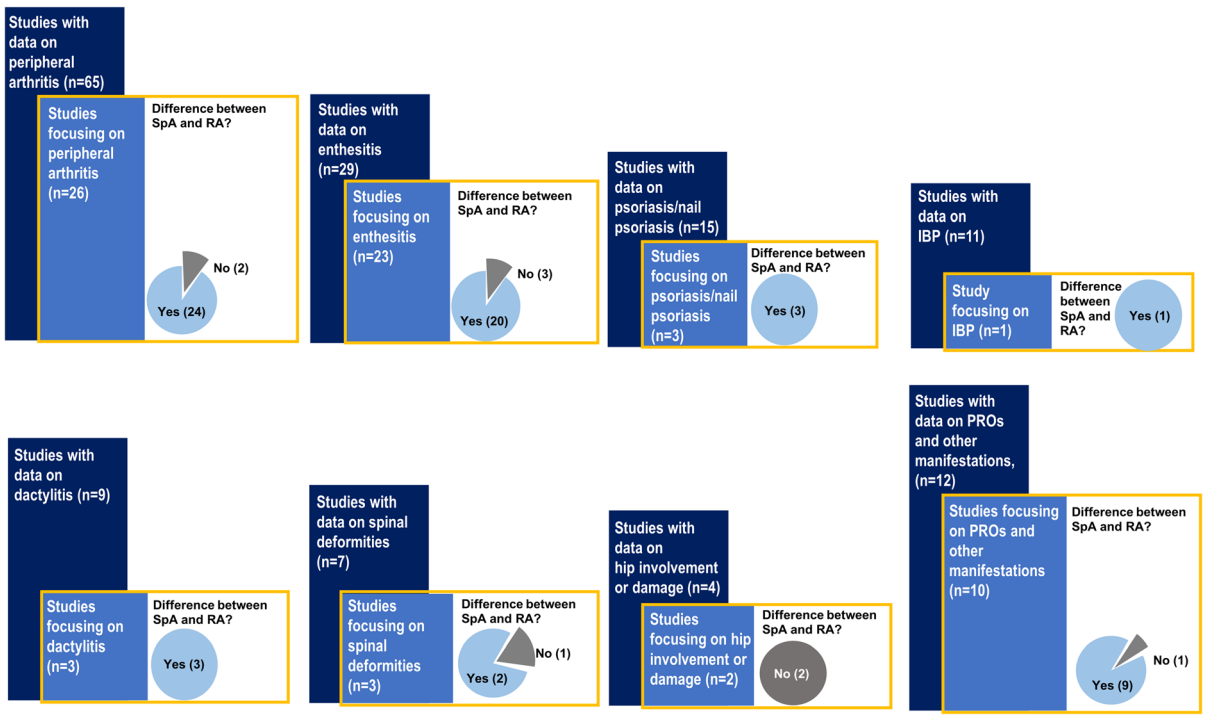

Fig. 2 Summary of the number of studies reporting SpA clinical manifestations and the authors' conclusions regarding the feasibility of distinguishing between SpA and RA populations. *IBP* inflammatory back pain, *PRO* patient-reported outcome, *RA* rheumatoid arthritis, *SpA* spondyloarthritis

baseline, tibiotalar joint synovitis was observed significantly more frequently in patients with SpA and gout by ultrasound vs. those with RA and reactive arthritis; after 1 year, tibiotalar joint synovitis was observed more frequently in the RA group than in the SpA, gout, and reactive arthritis groups [48]. Subtalar and talonavicular joint synovitis were observed more frequently in the early RA group than in the SpA, gout, and reactive arthritis groups [48]. Ultrasound findings of synovitis and erosions at the distal interphalangeal joints were exclusively observed in PsA vs. RA, and joint effusion was frequently seen at radiocarpal and midcarpal joints in RA vs. PsA [66]. Effusion at the third proximal interphalangeal (PIP) joint was detected more significantly in PsA than RA [66]. A registry analysis revealed similarities with regard to swollen joint count and tender joint count among patients with seronegative RA and SpA [30]. Of note, Figus and colleagues highlighted that although clinical examinations showed no differences between RA and PsA, ultrasound studies detected significant score differences in joint effusion, synovial hypertrophy, Doppler signal, II MCF, and wrist between oligoarticular PsA and RA, but no differences were observed between polyarticular PsA and RA [50].

Enthesitis

A total of 29 studies reported data on enthesitis or enthesophytes (Fig. 2). Suboutcomes included tenosynovitis, pulley inflammation, soft tissue or bone marrow edema, entheseal erosion, and inflammation of the tendon or peritendon. Overall, 23 studies focused their evaluation on enthesitis, comparing imaging findings among patients with SpA and RA. Of these, only three concluded that there were no differences in this manifestation among patients with SpA vs. RA based on ultrasonographic [26, 32] and both ultrasonographic and MRI [47] findings (Table 3). In general, enthesitis on imaging was found almost exclusively in patients with SpA (particularly PsA) vs. RA, with few exceptions. Batticciotto and colleagues reported that significantly more patients with early RA had erosions in ≥ 1 MCP joint as visualized by ultrasound than those with early SpA, and significantly more patients with early SpA showed paratenonitis of the extensor tendons in ≥ 1 finger than those with early RA [44]. Tibialis posterior tenosynovitis appeared to be more specific for RA, whereas Achilles' tendonitis was more frequent in axSpA and reactive arthritis [48]. Ahmed and colleagues reported that tenosynovitis was observed more frequently at the extensor tendons among patients with RA than those with PsA and at the flexor tendons in patients with PsA than those with RA [66]. While examining extrasynovial changes indicative of enthesitis by ultrasound, Fournié and colleagues described pseudotenosynovitis, characterized by diffuse inflammation of the digital soft tissue, in the fingers of patients with PsA; they conclude that pseudotenosynovitis may play a role in the development of dactylitis [28]. Of 34 patients with SpA who underwent careful clinical (i.e., physical) examination by an independent examiner, 88 of 612 entheses (14%) were deemed clinically abnormal in 21 patients (62%); however, with ultrasound imaging, 220 entheses (36%) were considered abnormal in 32 patients (94%) [55].

Psoriasis and/or Nail Psoriasis

Overall, 15 studies reported data on psoriasis and/or nail psoriasis (Fig. 2). Three focused their analyses on this clinical manifestation, comparing them among patients with PsA and RA; all three studies concluded that psoriasis and/or nail psoriasis occurred exclusively in patients with PsA vs. RA (Table 3) [23, 54, 59]. Of patients initially diagnosed with early seronegative RA, 25% were reclassified as having early PsA after presenting with cutaneous or nail psoriasis upon further rheumatology–dermatology evaluation [23]. One patient initially presented with seronegative oligoarthritis, and a diagnosis of PsA was suspected because of a family history of psoriasis; this patient was then formally diagnosed with PsA with the subsequent development of skin lesions [24].

IBP

Overall, 11 studies reported data on IBP (Fig. 2). Key outcomes assessed included Bath

Table 3 Summary of SpA manifestations among patients with SpA and RA, and authors' conclusions regarding the feasibility of differentiating the two diseases

Study	Primary manifestation outcome(s)	Sub-outcome(s)	Results	Can SpA and RA be differentiated?
Tinazzi et al. [21]	Enthesitis	Flexor tenosynovitis	Of 1732 measurements performed in 864 pulleys, patients with PsA had significantly thicker pulleys in every digit vs. those with RA	Yes
	Dactylitis	–	Among patients with PsA with or without a history of dactylitis, only the second-digit A1 pulley was thicker in patients with previous dactylitis	
			The mean thickness of PsA pulleys remained significantly higher than those of RA when patients with PsA with previous dactylitis were excluded, except for the A1 pulley of the second finger	
Zabotti et al. [22]	Peripheral arthritis	Synovitis	Joint synovitis was more frequently detected in early RA than early PsA (91.1 vs. 59.6%, respectively; $P = 0.0001$)	Yes
	Enthesitis	Flexor tenosynovitis, soft tissue edema	At the MCP joint, inflammation of the peritendon extensor digitorum tendon was seen in 2.5% of the joints in early RA vs. 54.1% of the joints in early PsA ($P = 0.0001$)	
			At the PIP joint, central slip enthesitis was exclusively observed in early PsA ($P = 0.0045$)	
			Soft tissue edema was detected almost exclusively in fingers of patients with PsA ($P = 0.0002$)	
Zabotti et al. [23]	Enthesitis	Peritendon inflammation	Ultrasound studies revealed peritendon inflammation of the extensor digitorum tendon exclusively among patients with PsA vs. S^- RA ($P = 0.006$)	Yes
	Psoriasis, nail psoriasis	–	Of patients initially diagnosed with early S^- RA, 25% were reclassified as early PsA after presenting with cutaneous or nail psoriasis upon further rheumatology-dermatology evaluation	
			Integrated ultrasonography and dermoscopy improved the recognition of subclinical psoriatic findings; the specificity for PsA diagnosis from 83.3% (dermoscopy alone) and 88.1% (ultrasound alone) to 90.5%	

Table 3 continued

Study	Primary manifestation outcome(s)	Sub-outcome(s)	Results	Can SpA and RA be differentiated?
Narváez et al. [24]	Enthesitis	Bone marrow edema, tenosynovitis	MRI findings of enthesitis and extensive diaphyseal bone marrow edema were seen exclusively in early PsA (12/17 patients; 71%) vs. early RA ($P = 0.0001$)	Yes
			Both diffuse and pronounced soft tissue edema spreading to the subcutis were observed more frequently among patients with early PsA vs. early RA ($P = 0.002$)	
			No significant differences were noted in the frequency of synovitis, bone erosions, subchondral bone edema, or tenosynovitis between the two groups	
			The extensor tendons were more frequently involved in RA, and the flexor tendons were more frequently involved in PsA ($P = 0.014$)	
	Psoriasis	–	1 patient initially presented with S^- oligoarthritis, but a diagnosis of PsA was suspected because of a family history of psoriasis; this patient was then diagnosed with PsA months after the MRI with the presentation of skin lesions	
Ottaviani et al. [25]	Peripheral arthritis	Synovitis, bursitis, joint effusion, bone erosion	In ultrasound studies, patients with SpA had a higher frequency of acromioclavicular joint synovitis vs. those with RA (66 vs. 5%; $P < 0.0001$), and lower occurrence of subacromial and subdeltoid bursitis (39 vs. 67%; $P = 0.015$), glenohumeral effusion (5 vs. 28%; $P = 0.008$), and humeral bone erosion (10 vs. 56%; $P < 0.0001$)	Yes
Ebstein et al. [26]	Enthesitis	Enthesophytes	The mean (SD) MASEI score was 8.5 (7.3) for patients with RA and 7.8 (6.5) for those with SpA	No
			The mean (SD) GUESS score was 5.8 (3.1) for RA and 6.3 (3.9) for SpA	
Mathew et al. [27]	Peripheral arthritis	Periosteal inflammation at MCP and PIP joints, synovitis	Office extremity MRI revealed that periosteal inflammation at the first interphalangeal joint was exclusively present among patients with PsA vs. RA	Yes
			Synovitis in the MCP joint was observed more frequently among patients with RA than those with PsA ($P = 0.008$)	
	Enthesitis	Flexor tenosynovitis, bone marrow edema	Diaphyseal bone marrow edema ($P = 0.004$) and flexor tenosynovitis ($P = 0.008$) were detected more frequently in patients with PsA vs. RA	

Table 3 continued

Study	Primary manifestation outcome(s)	Sub-outcome(s)	Results	Can SpA and RA be differentiated?
Fournié et al. [28]	Peripheral arthritis	Synovitis, joint erosion	Synovitis was observed by ultrasound in all fingers with RA (25/25; 100%) vs. 76% of fingers with PsA (19/25 fingers)	Yes
			Joint erosions were observed in 19 of 25 fingers with RA (76%) by ultrasound vs. 52% of fingers with PsA (13/25 fingers)	
	Enthesitis	Tenosynovitis, enthesophytes	Extrasynovial changes indicative of enthesitis were observed by ultrasound imaging in 84% of fingers with PsA vs. none with RA	
			Pseudotenosynovitis, characterized by diffuse inflammation of digital soft tissues, was also observed in 4 fingers with PsA; this may play a role in the development of dactylitis	
Falsetti et al. [29]	Enthesitis	Enthesophytes	Ultrasonography studies revealed a significantly lower prevalence of posteroinferior calcaneal enthesophytosis in RA vs. PsA ($P < 0.05$)	Yes
Ogdie et al. [30]	Peripheral arthritis	CDAI, SJC, TJC	Patients with SpA (PsA and axSpA) had significantly lower TJC vs. those with RA; patients with SpA and S^- RA had significantly lower SJC vs. those with S^+ RA	Yes
	Other	PGA, PtGA, pain and fatigue VAS	Patients with S^+ RA had a higher mean PGA score vs. those with S^- RA or PsA, but a lower score than those with axSpA	
			Patients with S^+ RA had a mean PtGA score comparable with that of patients with S^- RA but lower than those with PsA or axSpA	
Erturk et al. [31]	Enthesitis	Erosion and calcification at tendons	Hypoechogenicity of quadriceps tendon ($P = 0.037$), bone erosion at the quadriceps tendon attachment ($P = 0.003$), and calcification at the Achilles' tendon ($P = 0.023$) were observed more frequently in patients with S^- than those with S^+ RA	Yes
			More patients with AS had bone erosion at the common extensor tendon ($P < 0.001$), calcification at the Achilles' tendon ($P = 0.024$), and erosion at the triceps tendon ($P = 0.035$) than those with S^- RA	

Table 3 continued

Study	Primary manifestation outcome(s)	Sub-outcome(s)	Results	Can SpA and RA be differentiated?
Genc et al. [32]	Enthesitis	Enthesophytes	Authors did not find any difference in the frequency of tendon involvement and entheseal abnormalities among patients with RA and AS by ultrasound	No
			The most frequently affected entheseal sites in the lower limbs were the suprapatellar, infrapatellar, and Achilles' tendon in both groups	
Helliwell et al. [33]	Peripheral arthritis	Joint osteolysis, juxta-articular new bone formation	Juxta-articular new bone formation and osteolysis were observed more frequently via radiography among patients with SpA (polyarticular and nonpolyarticular PsA) vs. RA	Yes
	Enthesitis	Entheseal erosion	Entheseal erosion and new bone formation were observed more frequently via radiography among patients with polyarticular PsA vs. polyarticular RA	
	Dactylitis	–	Significantly more patients with polyarticular PsA had dactylitis vs. those with RA ($P < 0.001$)	
	Spinal deformities	Spinal pain and stiffness	Spinal pain and stiffness were observed more frequently among patients with polyarticular PsA vs. RA	
Sakellariou et al. [34]	Peripheral arthritis	Synovitis	Serum calprotectin significantly correlated with ultrasonographic synovitis in early onset, untreated PsA vs. RA	Yes
Low et al. [35]	Other	Body composition	Patients with S^- RA had significantly increased BMI ($P = 0.033$) and waist circumference ($P = 0.017$), but not hip circumference ($P = 0.248$) vs. those with S^+ RA	Yes
			Patients with PsA had significantly increased BMI ($P < 0.001$), waist circumference ($P = 0.001$), and hip circumference ($P < 0.001$) vs. those with S^+ RA but not S^- RA	
			There was a significant correlation between waist circumference and both synovitis ($r = 0.31$, $P = 0.018$) and vascularity ($r = 0.34$, $P = 0.010$) at arthroscopy	

Table 3 continued

Study	Primary manifestation outcome(s)	Sub-outcome(s)	Results	Can SpA and RA be differentiated?
Inanc et al. [36]	Peripheral arthritis	Erosive disease	In this study, 16 of 79 RF^- patients with RA (20%), 104 of 129 RF^+ patients with RA (81%), and 7 of 56 patients with PsA (12.5%) had anti-CCP antibodies	Yes
			Patients with RA and anti-CCP antibodies had significantly higher disease activity, greater loss of function, and more frequent erosive disease than those with RA without anti-CCP antibodies	
			In a subgroup analysis, anti-CCP antibodies in RF^- patients with RA were also associated with erosive disease	
			All patients with PsA and anti-CCP antibodies had symmetrical polyarthritis with higher number of swollen joints	
Baraliakos et al. [37]	Spinal deformities	Bone marrow edema	In a small study of patients with RA (n = 34) and AS (n = 6) complaining of neck pain, bone marrow edema was found in 21 patients with RA (62%) and three with AS (50%); however, the occurrence and severity of bone marrow edema did not correlate with neck pain severity	No
Michelsen et al. [38]	Peripheral arthritis	CDAI, DAS28, SJC, TJC, morning stiffness	In this cross-sectional study, DAS28 (P = 0.003) and CDAI (P = 0.028) were significantly higher in PsA vs. RA	Yes
	IBP	BASDAI, BASFI	Patients with axSpA had significantly higher BASDAI (P = 0.009) and BASFI (P = 0.030) vs. those with RA or PsA	
	Spinal deformities	Spinal pain and stiffness	Patients with axSpA reported significantly more spine pain and stiffness at night vs. those with RA ($P < 0.001$) or PsA (P = 0.003)	
	Other	PtGA, pain and fatigue VAS	PGA and patient-reported pain and fatigue were significantly lower in RA ($P < 0.015$) vs. PsA or axSpA	
Ceccarelli et al. [39]	Peripheral arthritis	Synovitis, DAS28	DAS28 values were significantly higher among patients with RA vs. PsA (P = 0.0001)	Yes
			Synovitis was significantly more prevalent and severe in RA vs. PsA (mean [SD] total ultrasound score of 13.1 [9.8] vs. 5.0 [6.5]; P = 0.0001, respectively)	

Table 3 continued

Study	Primary manifestation outcome(s)	Sub-outcome(s)	Results	Can SpA and RA be differentiated?
Reddy et al. [40]	Peripheral arthritis	Erosion, SJC, TJC	SJC ($P < 0.012$) and TJC ($P < 0.001$) were significantly higher among patients with RA vs. PsA	Yes
			Joint erosions ($P = 0.020$) and deformity ($P = 0.021$) were significantly more prevalent in RA vs. PsA	
	Other	mHAQ, pain	mHAQ ($P < 0.001$) and pain ($P = 0.020$) scores were significantly higher in RA vs. PsA	
Cimmino et al. [41]	Peripheral arthritis	Synovitis	When patients with PsA and RA were matched for disease severity, dynamic MRI showed similar patterns of synovitis based on the mean (SD) rate of early enhancement (1.0 [0.6] and 1.3 [0.7], respectively) and relative enhancement (87.1 [39.2] and 107.3 [48.2], respectively)	No
Liphardt et al. [42]	Peripheral arthritis	Grip strength	Patients with RA had significantly lower grip strength vs. those with PsA, psoriasis, and the control group	Yes
		Hand function	With regard to hand grip, those with RA, PsA, and psoriasis performed significantly worse vs. the control group	Yes
Fauny et al. [43]	Spinal deformities	Vertebral fractures	The prevalence of vertebral fractures was similar in patients with RA and AS	No
Batticciotto et al. [44]	Enthesitis	Erosion in MCP joints, paratenonitis	Ultrasound showed that significantly more patients with early RA (5/20; 25%) had erosion in $\geq$ 1 MCP joint vs. those with early SpA (0/15; $P = 0.036$)	Yes
			Ultrasound showed that significantly more patients with early SpA (12/15; 80%) had paratenonitis of the extensor tendons in $\geq$ 1 finger vs. those with early RA (6/20; $P = 0.003$)	
Ichikawa et al. [45]	Peripheral arthritis	Erosion, joint osteolysis, juxta-articular bony proliferation	Radiography of the hands and feet revealed that juxta-articular bony proliferation is the most important factor differentiating PsA from S^+ and S^- RA ($P < 0.001$ for all)	Yes
	Enthesis	Diffuse soft tissue swelling	Diffuse soft tissue swelling of the fingers and feet was significantly higher in patients with PsA vs. those with S^+ RA ($P < 0.001$ for both) and S^- RA ($P = 0.005$ and $P = 0.004$, respectively)	

Table 3 continued

Study	Primary manifestation outcome(s)	Sub-outcome(s)	Results	Can SpA and RA be differentiated?
Lindqvist et al. [46]	Peripheral arthritis	SJC, TJC	Authors compared disease characteristics of patients with PsA at enrollment in the Swedish Early PsA register (SwePsA) and at follow-up after 2 years; disease characteristics were also compared with those from the Swedish Early RA register (Ramona)	Yes
			At enrollment, patients with RA had a larger number of SJC ($P < 0.0001$) and TJC ($P < 0.0001$) compared with patients with PsA; at follow-up, patients with polyarticular PsA had significantly more TJC than those with RA	
	Other	CRP, ESR, pain VAS, PtGA	At enrollment, patients with RA had significantly higher mean ESR ($P < 0.0001$) and CRP ($P < 0.0001$) vs. those with PsA; additionally, those with early RA had a significantly higher mean HAQ score ($P < 0.0001$), pain ($P = 0.0311$), and PtGA ($P < 0.0051$)	
			At the 2-year follow-up, ESR and CRP remained significantly higher in patients with RA ($P < 0.0001$ and $P = 0.0001$, respectively) vs. PsA	
			Patients with RA had significantly higher ESR and CRP both on inclusion ($P = 0.0003$ and $P = 0.0026$, respectively) and 2 years later ($P = 0.0026$ and $P = 0.0001$) vs. those with polyarticular PsA	
			At follow-up, patients with polyarticular PsA had significantly higher PtGA score vs. those with RA	
Ramírez et al. [47]	Peripheral arthritis	Bursitis	No sonographic or MRI features were distinctive of SpA	No
	Enthesitis	Tendinitis, enthesopathy	Neither ultrasound nor MRI was useful in classifying enthesitis in the great trochanter as mechanical or inflammatory	
	Hip damage or involvement	Erosion	A significantly higher proportion of patients with noninflammatory musculoskeletal disease had erosion in the gluteus minimus tendon ($P = 0.038$) as detected by ultrasonography vs. those with SpA	

Table 3 continued

Study	Primary manifestation outcome(s)	Sub-outcome(s)	Results	Can SpA and RA be differentiated?
Harman et al. [48]	Peripheral arthritis	Synovitis	Tibiotalar joint synovitis was observed on ultrasound significantly more frequently in patients with SpA and gout ($P < 0.05$) vs. those with RA and reactive arthritis; after 1 year, tibiotalar joint synovitis was observed more frequently in the RA group vs. SpA, gout, and reactive arthritis ($P < 0.05$)	Yes
			Subtalar and talonavicular joint synovitis were observed more frequently in the early RA group compared with the SpA, gout, and reactive arthritis groups ($P < 0.05$)	
	Enthesitis	Tenosynovitis, tendinitis	Tibialis posterior tenosynovitis was significantly more common in the RA group vs. the SpA, gout, and reactive arthritis groups ($P < 0.001$)	
			Tibialis posterior tenosynovitis appeared to be more specific for RA, whereas Achilles' tendinitis was more frequent in axial SpA and reactive arthritis	
Abrar et al. [49]	Enthesitis	Bone erosion, tenosynovitis	Patients with PsA had thicker flexor tendon pulleys vs. RA (mean difference, 0.16 mm; $P < 0.001$); this was accompanied by a higher degree of associated inflammatory changes (mean difference from RA, 4.7; $P = 0.048$)	Yes
			A strong correlation between accessory pulley inflammation and overall PsA MRI score as well as inflammatory PsA MRI subscores (flexor tenosynovitis, synovitis, and periarticular inflammation) was observed for almost all fingers	
Figus et al. [50]	Peripheral arthritis	Joint effusion, synovitis	Although clinical examinations showed no differences between RA and PsA, ultrasound detected significant differences in the score of joint effusion ($P < 0.021$), synovial hypertrophy ($P < 0.001$), Doppler signal ($P < 0.011$), II MCF ($P < 0.000$), and wrist ($P < 0.032$) between oligoarticular PsA and RA	Yes
			No differences were found between RA and polyarticular PsA	

Table 3 continued

Study	Primary manifestation outcome(s)	Sub-outcome(s)	Results	Can SpA and RA be differentiated?
Murphy et al. [51]	Peripheral arthritis	Erosion, joint space narrowing	At 1 year, the hand periarticular bone mineral density measurements were significantly lower in RA vs. SpA ($P = 0.044$)	Yes
			A decrease in hand periarticular bone mineral density of LSC > 2.04% was observed in 7 of 20 patients with RA (35%) vs. 3 of 18 patients with SpA (17%)	
			A decrease in axial bone mineral density of LSC > 2.8% was observed in three patients with RA (15%) vs. 7 with SpA (39%)	
			Persistent disease activity, measured by Ritchie articular index or CRP, was associated with a greater rate of periarticular bone loss in RA and a greater rate of axial bone loss in SpA	
Kruithof et al. [52]	Peripheral arthritis	Synovial histopathology	Vascularity, and neutrophil and $CD163^+$ macrophage counts were greater in SpA than RA ($P < 0.05$), but synovial lining layer thickness and the number of $CD83^+$ dendritic cells were greater in RA ($P < 0.05$)	Yes
			In RA, 44% of histopathology samples had positive staining for intracellular citrullinated proteins, and 46% of MHC-HC gp39 peptide complexes vs. none of these markers in SpA samples	
			When samples of patients who were treated with DMARDs and/or corticosteroids were excluded, vascularity ($P < 0.001$) and the number of neutrophils ($P = 0.01$) were increased in PsA vs. RA, and staining for intracellular citrullinated proteins and MHC-HC gp39 peptide complexes was present exclusively in RA	
Noche et al. [53]	Ophthalmic manifestations	Uveitis	Among 16 patients with RA and 8 patients with AS, anterior uveitis was observed in 6 of 8 patients with AS, and none with RA	Yes
Idolazzi et al. [54]	Enthesitis	Tenosynovitis, paratenonitis	Power Doppler signal at the nail bed enthesis was exclusively seen in patients with PsA vs. those with psoriasis, RA, and osteoarthritis and healthy controls	Yes
	Psoriasis, nail psoriasis	–	The nail plate was significantly thicker in patients with PsA, psoriasis, and osteoarthritis vs. those with RA	

Table 3 continued

Study	Primary manifestation outcome(s)	Sub-outcome(s)	Results	Can SpA and RA be differentiated?
D'Agostino et al. [55]	Enthesitis	Enthesopathy	Of 164 consecutive patients presenting at a rheumatology clinic with SpA, 161 had $\geq$ 1 abnormal enthesis by ultrasound examination (the three patients without enthesitis had undifferentiated SpA, PsA, and reactive arthritis); 18 of 30 patients with RA (60%) had any abnormal entheses ($P < 0.0001$)	Yes
			Of 34 patients with SpA who underwent clinical examination, 88 of 612 entheses (14%) were deemed clinically abnormal in 21 patients (62%) and 220 of 612 entheses (36%) were considered abnormal by ultrasound in 32 patients (94%; $P < 0.0001$ for both)	
Falsetti et al. [56]	Enthesitis	Enthesopathy	Of 900 shoulders examined among 450 symptomatic consecutive outpatients with SpA, RA, osteoarthritis, and controls, deltoidal proximal insertion enthesitis was detected in 10 shoulders, most frequently in PsA (17%)	Yes
			Ultrasonography revealed thickening and hypoechogenicity of the enthesis	
Cimmino et al. [57]	Peripheral arthritis	Synovitis	MRI studies revealed that the volume of inflammation was significantly higher in RA vs. PsA for two of three extensor compartments and in the joint synovial membrane ($P = 0.002$ and $P < 0.001$, respectively)	Yes
Roman-Ivorra et al. [58]	Peripheral arthritis	Modified Sharp/van der Heijde score	Patients with RA had worse mean modified Sharp/van der Heijde score than those with PsA (45.81 vs. 7.8)	Yes
	Other	Hand and grip strength	Patients with RA presented with worse mean grip strength in both the left (11.02 vs. 20.06) and right (11.22 vs. 20.79) hands vs. those with PsA	
Sandobal et al. [59]	Peripheral arthritis	Synovitis	Patients with PsA (106/350 joints) and psoriasis (8/200 joints) had increased power Doppler signal in the distal interphalangeal joints vs. those with RA (no signal; $P = 0.0001$); authors concluded that this was an indication of subclinical synovitis	Yes
	Psoriasis, nail psoriasis	–	Patients with PsA (82/350 nails) and psoriasis (41/200 nails) had increased power Doppler signal in nail beds vs. those with RA (6/270 nails; $P = 0.0001$)	

Table 3 continued

Study	Primary manifestation outcome(s)	Sub-outcome(s)	Results	Can SpA and RA be differentiated?
Schoellnast et al. [60]	Peripheral arthritis	Periostitis, bone cyst	Periostitis occurred more frequently in patients with PsA vs. RA (78 vs. 0%; $P < 0.05$) in MRI studies	Yes
	Enthesitis	Bone marrow edema and erosion, tenosynovitis	Significantly more patients with RA showed bone erosions vs. those with PsA (86 vs. 17%; $P < 0.05$); however, nonsignificant differences were seen with regard to bone marrow edema, bone cysts, and tenosynovitis between the two groups	
Bailly et al. [61]	Other	Pain, PtGA	Levels of pain and PtGA were numerically higher among patients with axSpA vs. RA	Yes
Cemeroğlu et al. [62]	Other	PGA, PtGA	The mean (SD) PGA scores for patients with RA vs. AS were 4.1 (2.9) and 4.8 (2.8), respectively	No
			The mean (SD) PtGA scores for patients with RA vs. AS were 4.6 (2.4) and 4.9 (3.1), respectively	
Leeb et al. [63]	Peripheral arthritis	SJC, TJC	Mean (SD) SJC for one PsA cohort and two RA cohorts (RA1 and RA2) were 1.6 (2.0), 1.9 (2.5), and 3.0 (3.7), respectively; a significant difference was found between the PsA and RA2 cohorts ($P = 0.028$)	Yes
			No difference in TJC was observed between the groups	
	Other	DAS28	Mean (SD) DAS28 scores for the PsA, RA1, and RA2 cohorts were 3.2 (1.3), 3.2 (1.5), and 3.8 (1.4), respectively; a significant difference was found between the PsA and RA2 cohorts ($P = 0.006$)	
Harter et al. [64]	Hip damage/ involvement	Fractures	Adjusted hazard ratios were calculated for each outcome	No
			Patients with RA had a significantly elevated risk of fracture: all (1.23), hip (1.55), and vertebral (1.53)	
			Those with mild psoriasis had significantly elevated risk of all (1.07) and hip (1.13) fractures	
			Patients with severe psoriasis had significantly elevated risk of all (1.26) and vertebral (2.23) fractures	
			Patients with PsA had a significantly elevated risk of all fracture (1.26)	

Table 3 continued

Study	Primary manifestation outcome(s)	Sub-outcome(s)	Results	Can SpA and RA be differentiated?
Illeez et al. [65]	Laboratory markers of inflammation	–	Hemoglobin values were significantly lower for patients with RA vs. controls ($P < 0.001$)	No
			ESR, CRP, NLR ($P < 0.001$ for all), and PLR ($P = 0.04$) values were significantly higher in patients with RA vs. controls	
			Patients with AS had significantly higher values for hemoglobin, ESR, CRP, and NLR ($P = 0.001$, $P = 0.001$, $P = 0.006$, and $P = 0.001$, respectively) vs. controls, whereas PDW values were significantly lower ($P < 0.05$)	
Ahmed et al. [66]	Peripheral arthritis	Joint effusion, synovitis	Ultrasound findings of synovitis and erosions at the distal interphalangeal joints were exclusively observed in PsA vs. RA ($P < 0.001$)	Yes
			Joint effusion was frequently seen at radiocarpal and midcarpal joints in patients with RA vs. PsA ($P = 0.047$ and 0.039, respectively)	
			Effusion at the third PIP joint was detected more significantly in PsA vs. RA ($P = 0.037$)	
	Enthesitis	Tenosynovitis	Tenosynovitis was observed more frequently at the extensor tendons among patients with RA vs. PsA ($P = 0.021$) and at the flexor tendons in patients with PsA vs. RA ($P = 0.022$)	
Ward et al. [67]	Entheseopathy	–	Higher rates of PTT fiber disruption, PTT tenosynovial effusion, and Doppler signal (all $P < 0.001$) were observed in RA and SpA vs. healthy controls	No
			Patients with RA and SpA were 5.1 and 3.6 times more likely to exhibit ultrasound-detected pathology, respectively, than healthy controls (both $P < 0.001$)	
Helenius et al. [68]	TMJ symptoms	–	Patients with rheumatic disease (RA, AS, and SpA) reported significantly more frequent severe TMJ symptoms vs. controls ($P < 0.001$)	No
			Mean (SD) maximum mouth opening was significantly less in patients with rheumatic disease (46.3 mm [8.6 mm]) vs. controls (55.0 mm [7.4 mm]; $P < 0.001$)	
			Erosions were observed in 4 patients with RA (17%), 7 with AS (37%), and 8 with SpA (38%)	

Table 3 continued

Study	Primary manifestation outcome(s)	Sub-outcome(s)	Results	Can SpA and RA be differentiated?
Milutinovic et al. [69]	Enthesitis	Enthesopathy	Using BUSES, authors distinguished 127 patients with enthesitis (76 with SpA, 26 with RA, and 25 with mechanically-related enthesitis) The mean (SD) BUSES was 9.9 (12.4) among those with SpA and 3.1 (4.2) among those without SpA ($P < 0.001$)	Yes
Aletaha et al. [70]	Comorbidity	–	Patients with AS, PsA, and RA had a 4.2%, 51.0%, and 3.4% 5-year cumulative incidence of psoriasis, respectively 5-year cumulative incidence of uveitis was 7.7% for patients with AS, 1.8% for those with PsA, and 1.5% for those with RA Patients with AS, PsA, and RA had significantly higher risk of developing any one or two of the six manifestations analyzed vs. controls ($P < 0.002$)	No
Smerilli et al. [71]	Enthesitis	Pulley inflammation	Inflammation of the A1 pulley was observed by ultrasound in 15 of 240 fingers (6.3%) of 8 of 30 patients with PsA (26.7%) vs. 1 of 240 fingers (0.4%) of 1 of 30 patients with RA ($P < 0.01$ and $P = 0.03$, respectively)	Yes
Tinazzi et al. [72]	Enthesitis	Tenosynovitis, enthesopathy, peritendon edema	Ultrasonographic findings of tenosynovitis, peritendinous soft tissue edema, and flexor tendon enthesopathy were more commonly observed in patients with PsA vs. RA ($P < 0.001$, $P = 0.003$, and $P = 0.001$, respectively), despite higher DAS28 score in RA When the three modifications of the flexor tendon were summed up per patient, the difference between PsA and RA remained significant ($P < 0.001$)	Yes
Rothschild et al. [73]	Dactylitis	–	Dactylitis was observed in 18 of 150 patients with SpA, 7 of 106 with undifferentiated SpA, 6 of 27 with PsA, 0 of 5 with AS, and 0 of 96 with RA	Yes

Table 3 continued

Study	Primary manifestation outcome(s)	Sub-outcome(s)	Results	Can SpA and RA be differentiated?
Matschke et al. [74]	PT physical function	PROs	PT stiffness was significantly reduced in patients with RA and AS vs. controls ($P = 0.04$ and $P = 0.01$, respectively) PT CSA was significantly larger leading to a reduction in YM in patients with AS ($P = 0.04$ and $P < 0.001$, respectively) Patients with RA and AS reported significantly lower scores for mHAQ ($P < 0.001$ and $P < 0.01$, respectively) and SF-36 PCS ($P < 0.001$ and $P = 0.04$, respectively) vs. controls, and SF-36 MCS score was significantly lower for patients with AS vs. controls ($P = 0.03$)	No
Grosse et al. [75]	RA serostatus comparison	CCP^+ and/or RF^+ (S^+) vs. CCP^- or RF^- (S^-)	Radiography (mean total modified Sharp erosion score) and ultrasonography (total ultrasonography score for erosions; presence of ≥ 2 eroded joint facets) were (OR) 4.4 and 3.7 times higher among patients with CCP^+ vs. CCP^- RA, respectively The most discriminating joint between the two groups was MTP5, especially in cases with bilateral erosion ($P < 0.001$); both radiography and ultrasonography findings of bilateral erosions in the MTP5 joints were highly discriminant for patients with CCP^+ RA ($P < 0.001$) CCP^+ RA was associated independently with more severe erosive disease vs. CCP^- RA on both radiography and ultrasonography	Yes
Mouterde et al. [76]	RA serostatus comparison	CCP^+ and/or RF^+ (S^+) vs. CCP^- or RF^- (S^-)	Compared with S^+ patients, S^- patients had lower DAS28 ($P = 0.002$) and modified total Sharp score ($P = 0.026$) at baseline At year 3 of follow-up, DAS28 remission was similar, but the radiographic progression rate was lower in S^- patients ($P < 0.001$)	Yes
Slimani et al. [77]	RA serostatus comparison	CCP^+ and/or RF^+ (S^+) vs. CCP^- or RF^- (S^-)	S^- patients were older at the time of inclusion in the study ($P = 0.03$) and at RA diagnosis ($P = 0.04$), with less severe disease (SJC, $P = 0.04$; ESR $P = 0.04$; HAQ, $P = 0.05$; and remission rate, $P = 0.04$) vs. S^+ patients	Yes
Liu et al. [78]	RA serostatus comparison	IA-irAE vs. RA serostatus	Mean (SD) CRP levels were 17.99 (21.90) and 27.93 (35.37) for patients with RA who were S^+ and S^-, respectively	No

Table 3 continued

Study	Primary manifestation outcome(s)	Sub-outcome(s)	Results	Can SpA and RA be differentiated?
Oprea et al. [79]	RA serostatus comparison	CCP^+ and/or RF^+ (S^+) vs. CCP^- or RF^- (S^-)	More patients with S^+ RA were associated with polyarticular damage vs. S^- patients (97.78 vs. 80.95%) MCP and PIP joints were more frequently involved in S^+ than S^- patients (88.89 vs. 38.09%) Patients with S^+ RA presented with more clinically active disease ($\geq$ 5 swollen joints) than S^- patients (33.33 vs. 23.81%)	Yes
Barra et al. [80]	RA serostatus comparison	CCP^+ and/or RF^+ (S^+) vs. CCP^- and RF^- (S^-)	S^- patients with RA were more likely to be older and male vs. those with S^+ RA ($P < 0.001$ for both) S^- patients were also less likely to meet the 1987 ACR and 2010 ACR/EULAR criteria for RA; however, at baseline they had higher SJC (9 vs. 6), more erosive disease (32 vs. 23%), and higher DAS28 scores (5.00 vs. 4.75; all $P < 0.05$) vs. those with S^+ RA Additionally, S^- patients had shorter duration of symptoms (166 vs. 192 days; $P = 0.007$) S^- patients had greater reductions in SJC (7 vs. 4) and similar DAS28 scores (2.97 vs. 2.83) at their 12-month follow-up vs. S^+ patients ($P = 0.0017$ and $P = 0.3$, respectively) Adjusted analyses showed that S^- patients were as likely to achieve DAS28 remission as S+ patients (OR, 1.18; 95% CI, 0.70 to 1.99); however, they were less likely to have erosive disease at follow-up (OR, 0.43; 95% CI, 0.19 to 0.95; $P < 0.04$)	Yes
Deveci et al. [81]	RA serostatus comparison	CCP^+ and/or RF^+ (S^+) vs. CCP^- or RF^- (S^-)	Included were 48 patients with RA (proportion of RF^+ patients, n = 27 [56.2%]) Anti-CCP antibodies were detected in 30.4% of RF^- patients (n = 15) CCP positivity was associated with higher DAS28 scores and RF positivity	Yes
Hamdi et al. [82]	RA serostatus comparison	CCP^+ and/or RF^+ (S^+) vs. CCP^- or RF^- (S^-)	No difference in ultrasound DAS28 scores was observed among patients with RA, regardless of CCP or RF status	No
Asikainen et al. [83]	RA serostatus comparison	CCP^+ and/or RF^+ (S^+) vs. CCP^- or RF^- (S^-)	Higher Larsen scores were observed in S^+ patients with RA than in S^- patients	Yes

Table 3 continued

Study	Primary manifestation outcome(s)	Sub-outcome(s)	Results	Can SpA and RA be differentiated?
Azuaga-Piñango et al. [84]	RA serostatus comparison	CCP^+ and/or RF^+ (S^+) vs. CCP^- or RF^- (S^-)	Globular synovitis was detected by ultrasound in 95.9% of S^+ patients with RA vs. only three patients with S^- RA ($P < 0.001$) Patients with globular synovitis had more erosions (72 vs. 33%; $P < 0.0001$), higher SJC, and higher synovial hypertrophy and power Doppler signal scores (all $P < 0.001$) than those without ultrasonographic globular synovitis	Yes
Azuaga-Piñango et al. [85]	RA serostatus comparison	CCP^+ and/or RF^+ (S^+) vs. CCP^- or RF^- (S^-)	Although no significant differences in disease activity was observed between S^+ or S^- patients, ultrasonographic proliferative synovitis was observed in 55.5% of S^+ patients (55.3% RF^+ and 58.2% CCP^+) vs. 16.1% S^- patients ($P = 0.0001$) Univariate analyses revealed that significantly more patients with proliferative synovitis had erosive disease, higher ultrasonographic scores, and were more likely to be treated with csDMARDs ($P = 0.0001$, $P = 0.0001$, and $P = 0.05$, respectively) Multivariate analyses revealed that erosions (OR, 4.5; 95% CI, 2.17 to 11.07; $P = 0.0001$) and CCP positivity (OR, 3.5; 95% CI, 1.39 to 10.7; $P = 0.09$), but not RF positivity (OR, 0.74; 95% CI, 0.31 to 1.71; $P = 0.483$), were independently associated with the presence of proliferative synovitis	Yes
Rauwel et al. [86]	RA serostatus comparison	$HCMV^+$ vs. $HCMV^-$	Patients who were $HCMV^+$ were less frequently CCP^+ (49.8 vs. 58.9%; $P < 0.0465$) and had higher mean (SD) DAS28-ESR (5.55 [1.24] vs. 5.20 [1.14]; $P < 0.0013$) vs. those who were $HCMV^-$ At 1 year, bone erosion progression was lower in patients who were $HCMV^+$ than those who were $HCMV^-$ (16.1 vs. 25.2%; $P = 0.0128$)	Yes

Table 3 continued

Study	Primary manifestation outcome(s)	Sub-outcome(s)	Results	Can SpA and RA be differentiated?
Hermosillo [87]	RA serostatus comparison	CCP^+ and/or RF^+ (S^+) vs. CCP^- or RF^- (S^-)	Among 64 patients with very early RA (< 3 months from time at onset of clinical manifestations), 20 (31.2%) had very early S^- RA Univariate analyses showed that those with very early S^- RA were more likely to have minor disease activity, better functional state at their 3-, 6-, 9-, and 12-month follow-up, lesser work disability, and lower comorbidities, and were less likely to use sulfasalazine, leflunomide, biologics, and corticosteroids than those who had very early S^+ RA	Yes
Morales-Arango et al. [88]	RA serostatus comparison	CCP^+ and/or RF^+ (S^+) vs. CCP^- or RF^- (S^-)	Among 430 participants in a Maya-Yucateco cohort, 28 were diagnosed with RA (S^+ RA, $n = 9$; S^- RA, $n = 17$) The level of pain/discomfort, as assessed by EQ5D-3L dimension, was significantly higher among those with S^+ RA than S^- RA	Yes
Shin et al. [89]	RA serostatus comparison	CCP^+ and/or RF^+ (S^+) vs. CCP^- or RF^- (S^-)	Among 109 patients analyzed, 64 (58.7%) had S^+ RA and 45 (41.3%) had S^- RA Those with S^+ RA had more frequent ankle joint involvement, as visualized by radiography, and ANA expression (all $P < 0.05$) than those with S^- RA Patients with S^+ RA had higher levels of ESR and CRP than those with S^- RA at initial diagnosis (all $P < 0.01$) and at their 2-year follow-up (all $P < 0.01$) DMARD combination therapy was more commonly used in the S^+ group ($P < 0.05$), especially triple DMARD combination	Yes
Sahatçiu-Meka et al. [90]	RA serostatus comparison	CCP^+ and/or RF^+ (S^+) vs. CCP^- or RF^- (S^-)	Patients with S^+ RA showed more inflammation of the peripheral joints of hand and foot, but only inflammation of PIP joints was statistically significant, compared with those with S^- RA ($P < 0.01$) With longer duration of disease, the "buttonhole" joint deformity was more prevalent among patients with S^+ RA than those with S^- RA ($P < 0.05$), and the "fibular deviation" joint deformity was more prevalent among those with S^- RA than those with S^+ RA ($P < 0.01$)	Yes

Table 3 continued

Study	Primary manifestation outcome(s)	Sub-outcome(s)	Results	Can SpA and RA be differentiated?
Sahatçiu-Meka et al. [91]	RA serostatus comparison	CCP^+ and/or RF^+ (S^+) vs. CCP^- or RF^- (S^-)	Inconclusive, no statistical differences found	No
Rajapaksa et al. [92]	RA serostatus comparison	CCP^+ and/or RF^+ (S^+) vs. CCP^- or RF^- (S^-)	Among patients with S^+ RA, the prevalence of erosions (38 vs. 21%) and nodules (16 vs. 4%) was significantly higher than in those with S^- RA ($P < 0.05$) Among patients with S^+ RA, levels of IgM-RF positively correlated with erosions ($P < 0.05$); among those with S^- RA, an inverse correlation was observed ($P < 0.01$)	Yes
Shin et al. [93]	RA serostatus comparison	CCP^+ and/or RF^+ (S^+) vs. CCP^- or RF^- (S^-)	CCP positivity was significantly associated with radiographic bony erosions (OR, 1.69; 95% CI, 1.13 to 2.52; $P = 0.0096$) vs. RF positivity (OR, 1.03; $P = 0.83$) or RF and CCP positivity (OR, 2.19; 95% CI, 1.19 to 4.01; $P = 0.012$) RF and CCP positivity were strongly associated with radiographic damage (OR, 4.93; 95% CI, 2.29 to 10.61; $P < 0.0001$) Multivariate analyses indicated that disease duration (estimate − 3.95; $P < 0.0001$) and RF titer (estimate + 0.0665; $P = 0.0157$) were associated with CCP titers	Yes
Modi et al. [94]	RA serostatus comparison	CCP^+ and/or RF^+ (S^+) vs. CCP^- or RF^- (S^-)	Of 884 patients with RA in the RACER registry, 60% were RF^+CCP^+, 12% RF^+CCP^-, 10% RF^-CCP^+, and 18% RF^-CCP^- Patients with RF and CCP positivity had longer disease duration compared with the other groups (median, 143 vs. 88 to 93 months; $P < 0.05$) Morning stiffness was most common in the RF^-CCP^- group (54 vs. 26% to 40%), and rheumatoid nodules were more common in the CCP^+ groups (12% to 15% CCP^+ vs. 5% to 6% CCP^-) (all $P < 0.05$)	Yes
Shankar et al. [95]	RA serostatus comparison	CCP^+ and/or RF^+ (S^+) vs. CCP^- or RF^- (S^-)	Among a cohort of 211 patients with established RA, anti-CCP2 positivity was a predictor of radiographic erosive disease in the hands ($P < 0.001$) Among patients with RF^- RA, anti-CCP2 antibodies were observed in > 50% of patients and were associated with a higher incidence of erosive disease ($P < 0.05$)	Yes

Table 3 continued

Study	Primary manifestation outcome(s)	Sub-outcome(s)	Results	Can SpA and RA be differentiated?
Fujinami et al. [96]	RA serostatus comparison	CCP^+ and/or RF^+ (S^+) vs. CCP^- or RF^- (S^-)	No differences in histology scores of features were observed between patients with RF^+ or RF^- RA	No
Othman et al. [97]	RA serostatus comparison	CCP^+ and/or RF^+ (S^+) vs. CCP^- or RF^- (S^-)	Among 80 adult patients with RA, authors observed a significant association between RF positivity and patients aged $\geq$ 50 years (P = 0.032)	Yes
Cappelli et al. [98]	RA serostatus comparison	CCP^+ and/or RF^+ (S^+) vs. CCP^- or RF^- (S^-)	Among 165 patients with RA, CCP negativity was significantly associated with greater fatigue (P = 0.03)	Yes
Choi et al. [99]	RA serostatus comparison	CCP^+ and/or RF^+ (S^+) vs. CCP^- or RF^- (S^-)	At baseline, patients with S^- RA had significantly higher mean (SD) TJC (4.7 [2.9] vs. 3.3 [2.7]; P = 0.004), SJC (4.3 [3.0] vs. 2.9 [2.3]; P = 0.001), and DAS28 (5.1 [1.0] vs. 4.7 [1.0]; P = 0.043) vs. those with S^+ RA	Yes
			After 2 years of similar treatment with DMARDs across both groups, the mean (SD) ΔDAS28 at 1 year was greater among patients with S^- RA than S^+ RA (–2.84 [1.32] vs. –3.70 [1.29]; P = 0.037) in the high disease activity population (DAS28-ESR > 5.1)	

ACR American College of Rheumatology, *ANA* antinuclear antibody, *AS* ankylosing spondylitis, *axSpA* axial spondyloarthritis, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *BMI* body mass index, *BUSES* Belgrade Ultrasound Enthesitis Score, *CCP* cyclic citrullinated peptide, *CDAI* Clinical Disease Activity Index, *CRP* C-reactive protein, *CSA* cross-sectional area, *csDMARDs* conventional synthetic disease-modifying antirheumatic drugs, *DAS28* Disease Activity Score in 28 joints, *DAS28-ESR* Disease Activity Score in 28 joints for RA with ESR, *DMARD* disease-modifying antirheumatic drug, *EQ5D-3L* EuroQoL 5-dimensional questionnaire-3 level, *ESR* erythrocyte sedimentation rate, *EULAR* European League Against Rheumatism, *GUESS* Glasgow Ultrasound Enthesitis Scoring System, *HAQ* Health Assessment Questionnaire, $HCMV^+$ human cytomegalovirus seropositive, $HCMV^-$ human cytomegalovirus seronegative, *IgM* immunoglobulin M, *irAE* inflammatory arthritis induced by immune checkpoint inhibitors, *IBP* inflammatory back pain, *LSC* least squares change, *MASEI* Madrid Sonographic Enthesitis Index, *MCP* metacarpophalangeal, *MCS* SF-36 mental component summary, *mHAQ* modified Health Assessment Questionnaire, *NLR* neutrophil–lymphocyte ratio, *OR* odds ratio, *PCS* SF-36 physical component summary, *PDW* platelet distribution width, *PGA* physician global assessment of disease activity, *PLR* platelet-lymphocyte ratio, *PIP* proximal interphalangeal, *PsA* psoriatic arthritis, *PtGA* patient global assessment of disease activity, *PT* patellar tendon, *PTT* posterior tibialis tendon, *RA* rheumatoid arthritis, *RF* rheumatoid factor, S^+ *RA* seropositive RA, S^- *RA* seronegative RA, *SF-36* Short-Form Health Survey, *SJC* swollen joint count, *SpA* spondyloarthritis, *TJC* tender joint count, *TMJ* temporomandibular joint, *VAS* visual analog scale, *YM* Young's modulus

Ankylosing Spondylitis Disease Activity Index and Bath Ankylosing Spondylitis Functional Index. Only one study evaluated IBP as a primary focus of the investigation (Table 3)—patients with axSpA had significantly higher Bath Ankylosing Spondylitis Disease Activity Index and Bath Ankylosing Spondylitis Functional Index scores than those with RA [38].

Dactylitis

A total of nine studies reported data on dactylitis (Fig. 2). Three studies focused their evaluation on dactylitis among patients with

PsA and RA; of these studies, the authors reported that dactylitis occurred exclusively in patients with PsA vs. RA (Table 3) [21, 33, 73].

Spinal Deformities

A total of seven studies reported data on spinal deformities (Fig. 2) [33, 37, 38, 43, 51, 64, 90]. Sub-outcomes included vertebral fractures and spinal pain and stiffness (Table 3). Overall, of three publications that evaluated spinal deformities as a primary focus of study, comparing this manifestation among patients with SpA and RA, only one study used imaging (computed tomography) and concluded that there were no differences between patients with SpA vs. RA [43].

Hip Involvement or Damage

A total of four studies reported data on hip involvement or damage (Fig. 2) [35, 47, 64, 90], two of which focused their evaluation on erosions and risk of fractures as a primary endpoint (Table 3). Neither study was able to differentiate between patients with SpA and RA with regard to this manifestation [47, 64].

PROs and Other Clinical Manifestations

Other manifestations evaluated included various PROs (pain, fatigue, PtGA, and Health Assessment Questionnaire), PGA, hand and grip strength, uveitis, CRP levels, erythrocyte sedimentation rate, DAS28, oligoarthritis, and body composition (Fig. 2). There were no studies that solely focused on differences in PROs between patients with SpA and RA; however, of the ten studies that incorporated PROs and other outcomes in their analyses among patients with SpA and RA, one concluded that there was no difference in PGA and PtGA among those with RA and AS (Table 3) [62]. Patients with PsA had significantly increased body mass index, waist circumference, and hip circumference vs. those with seropositive RA but not seronegative RA [35]. Anterior uveitis was exclusively observed in patients with AS vs. RA [53]. Patients with RA presented with worse mean hand grip strength than those with PsA [42, 58].

Clinical Manifestations and Outcomes in Seropositive and/or Seronegative RA vs. SpA

Of 25 studies comparing patients with seropositive and/or seronegative RA vs. SpA, only two studies concluded that no significant differences in RA disease activity can be delineated based on serostatus or in relation to SpA as measured by ultrasound, DAS28 [82], and histology [96] scores (Table 3). In general, although seronegative RA appeared to be milder in disease severity, pain, and discomfort than seropositive RA, Cappelli and colleagues reported that CCP^{-} was significantly associated with greater fatigue, which persisted after adjusting for age, sex, race, and swollen joints [98]. MCP, PIP [79], and ankle [89] joints were more frequently involved in seropositive than seronegative patients. In a cross-sectional study comparing patients with seronegative RA with those who had seropositive RA, patients with AS, or healthy controls, more patients with seronegative RA presented with enthesopathy findings than those with seropositive RA. However, patients with AS had significantly higher findings of enthesopathy (e.g., bone erosion at the common extensor tendon, calcification of the Achilles' tendon, and erosion at the triceps tendon) than those with seronegative RA [31]. In another cross-sectional study by Zabotti and colleagues, prevalence of peritendon inflammation indicative of enthesitis was significantly more common in patients with early PsA compared with those with seronegative RA (36 vs. 8%; $P = 0.006$) [23].

DISCUSSION

Various overlapping clinical characteristics, both temporary and persistent, occur in SpA and RA, including inflammation and destruction of joints, pain, diminished functional ability, and increased risk for comorbidities; these overlapping clinical manifestations are mainly related to peripheral—and not spinal—manifestations. While the ASAS axial and peripheral SpA classification criteria do attempt to make this distinction, classification is not

limited to those purely with axial or peripheral manifestations, which may contribute to likely reasons for misclassification of disease. Among patients with milder symptoms, negative serology, or those lacking definitive clinical signs, especially early in the disease course, determining the type of inflammatory arthritis may be challenging. In our analysis, we noted differences in the occurrence of SpA manifestations, not only among patients with SpA vs. RA, but also among those with early vs. late RA and by RA serostatus. Timelier and more comprehensive evaluation, especially aided by use of imaging techniques to evaluate peripheral manifestations such as enthesitis and peripheral arthritis, may reduce disease misclassification and inappropriate treatment.

The majority of the 79 studies reported on peripheral arthritis and enthesitis. Of 54 studies comparing SpA and RA study populations, only seven studies concluded that no distinction can be made between SpA and RA based on the SpA manifestations and outcomes examined [26, 32, 41, 43, 47, 62, 64]. Of 25 studies comparing patients with seropositive and seronegative RA, only two concluded that no significant differences in RA disease activity can be delineated based on serostatus [82, 96]. Although peripheral arthritis reportedly occurred at a similar frequency among patients with SpA and RA, distinct anatomical sites were involved [25, 27, 48, 66]. Two studies concluded that no distinction can be made between SpA and RA with regard to peripheral arthritis based on MRI [41] and ultrasonographic and MRI findings [47]. In their study, Cimmino and colleagues focused exclusively on the comparison of the degree of synovitis in the wrists of patients with PsA and RA using a low-field extremity-dedicated MRI device after accounting for disease activity [41]. The authors postulated that more sophisticated quantification tools may expose greater details of synovitis, allowing for better distinction of inflammation in SpA vs. RA; accordingly, in a later MRI study, they reported that the volume of inflammation was significantly higher in RA than PsA for two of three extensor compartments and in the joint synovial membrane [57]. In our analysis, enthesitis occurred almost exclusively among patients with SpA vs. those with RA, although three studies concluded that no distinction can be made between these two conditions based on ultrasonographic [26, 32] and both ultrasonographic and MRI findings [47]. As similar Madrid Sonographic Enthesitis Index [26] and Glasgow Ultrasound Enthesitis Scoring System [32] scores were noted among patients with RA and those with SpA, it may be interesting to follow up and observe the RA cohorts for the development of SpA because enthesopathy is a key SpA feature [100]. Psoriasis or nail psoriasis, IBP, dactylitis, and uveitis occurred exclusively among patients with SpA vs. RA. Based on PRO measures, the burden of disease was relatively equal between SpA and RA. While some studies did examine HLA-B27 as a laboratory measure in their patient population [24–26, 53, 55, 65, 69, 78], no comparisons were made between SpA and RA. As genetic and other biomarker assays become more validated as diagnostic tools to differentiate between specific disease states, this will hopefully address and potentially resolve some of the challenges associated with diagnosis highlighted here.

Technological advances in the development of more sophisticated imaging modalities and novel therapeutic interventions have greatly enhanced clinical practice with regard to disease detection, diagnosis, and management. The inclusion of imaging as a part of early diagnosis and differentiation of inflammatory arthritis underscores its significance, especially because similarities in synovitis and joint involvement and inflammation may be observed in SpA and RA [1, 17, 18]. In our analysis, ultrasonography and MRI were instrumental in detecting subclinical synovitis, entheseal inflammation, bone erosions, and bone marrow edema; in addition, two studies reported significant ultrasound findings that differentiated RA and SpA when routine clinical examinations could not [50, 55]. These reports may compel clinicians to pursue further investigation using advanced imaging modalities when presented with patients early in their course of inflammatory arthritis. Indeed, the role of imaging is multifaceted; in various clinical studies, imaging techniques may play a key role in ascribing the proper treatment course to

patients based on diagnostic or prognostic information and in tracking treatment effectiveness and complications. Accordingly, imaging features such as flexor tenosynovitis, bone erosion, and regional inflammation beyond the joint may be indicative of early SpA development and pathophysiology. Consequently, biologic interventions approved for SpA may be prescribed for these patients to address their symptoms. A delay in accurate diagnosis and initiation of appropriate treatment confers substantial burden on patients and may result in increased healthcare costs [4, 7, 10].

Limitations

Various diagnosis criteria and outcome measures were used to classify and assess patients with SpA and RA, which may contribute to the heterogeneity of study populations among the studies. As most of the studies included in this review were conducted across Europe and Asia, the results may not be representative of all patients or healthcare systems. Advanced imaging modalities may not be widely available for use in clinical practice, especially among rural practices or medically underserved populations. Along with the limited number of studies with higher methodological quality and small patient population, these limitations precluded meaningful meta-analysis for the outcome measures assessed; thus, the results of our systematic literature review are descriptive in nature.

CONCLUSIONS

Overall, SpA manifestations were observed among patients with RA, especially those with early or seronegative disease, suggesting that misclassification could occur. The use of imaging may allow for a timely and thorough assessment of subclinical manifestations in SpA and RA, thus reducing misdiagnosis and inappropriate treatment. As effective, but not always overlapping, therapies for SpA and RA are available, imaging tools can be critical for accurate diagnosis and subsequent appropriate disease management. As next steps, the improvement and standardization of imaging protocols and interpretation can be undertaken to positively impact clinical outcomes and quality of life.

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