

Chapter

Growing Need for Diagnostic Precision in Rheumatoid Arthritis: Proposal of MR Imaging Criteria for Early Diagnosis

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Abstract

The recent and revolutionary paradigm shift involving novel therapeutics for the treatment of rheumatoid arthritis (RA) has called for changes in the early diagnosis of RA. Physicians now need to diagnose RA earlier, and with greater accuracy, in order to initiate effective definitive treatment as early as possible. However, due to the complexity and diverseness of RA, we still do not have comprehensive diagnostic criteria for RA readily available. To find a solution to this challenge, we aimed to develop practically useful criteria which integrate gadolinium (Gd) contrast-enhanced magnetic resonance imaging (MRI) findings with clinical manifestations of the disease. These diagnostic criteria we propose, the “diagnostic criteria for early RA with MRI findings,” are composed of two domains. The first domain consists of clinical findings suggestive of RA, which include both entry criteria—i.e., polyarthralgia of hands (joint pain of three or more joint areas confirmed by a physician), and exclusion criteria—i.e., exclusion of other rheumatic conditions including systemic lupus erythematosus (SLE), dermatomyositis and polymyositis (PM/DM), mixed connective tissue disease (MCTD), primary Sjögren’s syndrome (SS), and Behçet’s disease (BD). The second domain constitutes MRI criteria, which represent Gd-enhanced MRI findings indicating bilateral synovial enhancement seen in any joints of the proximal interphalangeal (PIP), metacarpophalangeal (MCP), or wrist joints. RA is defined by fulfilling all conditions of both domains. Our prospective study demonstrated that these criteria for the diagnosis of early RA, incorporating MRI findings with physical manifestations, can successfully distinguish patients with RA from those with other mimicking conditions, showing a sensitivity of 96%, specificity of 86%, and accuracy of 92%. When a case does not meet the criteria, RA can be ruled out with a high negative predictive value of 95%. We believe our “diagnostic criteria for early RA with MRI findings” can greatly help to solve unmet diagnostic needs in the early treatment of RA.

Keywords: rheumatoid arthritis (RA), early RA, magnetic resonance imaging (MRI), gadolinium (Gd) contrast-enhanced MRI, diagnostic criteria

1. Introduction

Rheumatoid arthritis (RA), an autoimmune systemic inflammatory disease marked by progressive joint destruction, disability, and mortality, is the most

common connective tissue disease (CTD), occurring in 1–2% of the population, and more frequently in women. The disease is primarily characterized by synovial inflammation which leads to an erosive/destructive polyarthropathy, predominantly affecting the peripheral joints, but also with extra-articular manifestations including subcutaneous nodules, skin ulceration, scleritis/episcleritis, pericarditis, splenomegaly, and a variety of pleuro-pulmonary disorders which may develop during its clinical course.

1.1 Etiology

Although the etiology of RA has not yet been fully elucidated, it is recognized as a multifactorial disease associated with genetic susceptibility, environmental triggering, hormonal predisposition, and possibly infections. Genetic risk factors include human leukocyte antigen (HLA)-DR4, in particular, HLA-DRB1 alleles encoding a common amino acid sequence (the “shared epitope”) in the third hypervariable region of the DRB1 molecule [1]. The HLA-DRB1*04 alleles (HLA-DRB1*0401, *0404, *0408, and *0405) show the strongest association with RA, especially with anti-citrullinated protein antibody (ACPA)-positive RA [2]. These alleles have in common a highly conserved sequence between amino acids 67 and 74 along the α -helix derived from the DR β chain, which forms one side of the antigen-binding site of the DR molecule [3]. Studies have shown that the shared epitope alleles may preferably present citrullinated peptides [4]. In addition to the HLA locus, recent genome-wide association studies (GWAS) have revealed many high-risk RA susceptibility genes, such as *CD244*, *PADI4*, *SLC22A2*, *PTPN22*, *CTLA4*, and *STAT4* [5]. However, except for some loci, the function of most of these RA risk loci remains unclear.

Among multiple environmental and behavioral risk factors that have been studied, cigarette smoking is identified as the strongest trigger for RA, especially in populations with a genetic predisposition [6]. Smoking may induce citrullination of peptide antigens present in the lungs, and the shared epitope alleles interact with smoking in the triggering of anti-citrulline immunity that may lead to ACPA-positive RA [7–9]. Two risk factors for RA, HLA-DRB1 shared epitope alleles and smoking, are also linked to adult periodontitis [10, 11]. Periodontitis is mainly induced by *Porphyromonas gingivalis* (*P. gingivalis*) infection, which, by subverting host immune defenses, leads to overgrowth of oral commensal bacteria causing inflammatory tissue destruction [12, 13]. This condition is characterized by the accumulation of large amounts of citrullinated proteins with similar patterns of hypercitrullination found in RA synovial fluid [14].

Since the 1980s, a number of studies have shown a possible association between RA and periodontitis, suggesting pathological similarities [15]. However, significant advances were not made until 1999, when it was found that *P. gingivalis* secretes a peptidylarginine deiminase (PAD)-like enzyme [16]. This was followed by a hypothesis by Rosenstein that periodontitis drives RA through the production of citrullinated antigens by *P. gingivalis* [17]. A periodontal pathogen, *P. gingivalis*, expresses an enzyme with PAD activity that mediates citrullination, in which arginine residues are deiminated to citrulline residues. This process may produce antibodies involved in the etiology of RA by breakdown of immunological tolerance to citrullinated antigens. To date, four citrullinated autoantigens have been defined: citrullinated fibrinogen, vimentin, collagen type II, and α -enolase [10, 11].

Although ACPAs, the autoantibodies directed against citrullinated peptides and proteins, are highly specific for RA, it should be noted that the enzyme-linked

immunosorbent assay is based on synthetic cyclic citrullinated peptides (CCPs) and not equivalent to the detection of antibodies to citrullinated proteins *in vivo*. Currently, both smoking and *P. gingivalis* are plausible causative factors that warrant further investigation into the gene/environment/autoimmunity triad of RA etiology [18, 19].

1.2 Immunopathology of synovitis

The hallmark feature of arthritis in RA pathology is “synovitis,” the inflammation of synovial membranes lining the inner surface of joint cavities, tendinous sheaths, and bursae. An autoimmune-mediated inflammatory response in joints leads to the formation of abnormal synovial tissue growth, the “rheumatoid pannus,” which invades the joint space as well as adjacent components including bones and their protective layer of articular cartilage. The pathological milieu of the inflammatory synovial compartment, characterized by leukocyte infiltration comprising innate immune cells, e.g., monocytes, dendritic cells, mast cells, and innate lymphoid cells, as well as adaptive immune cells, e.g., Th1 and Th17 cells, B cells, plasmablasts, and plasma cells, is governed by a complex network of cytokines and chemokines. Dynamisation of this network leads to aggravation of the inflammatory response by activating endothelial cells and fibroblasts and ultimately triggering osteoclast generation through receptor activation of nuclear factor κ B ligand (RANKL) on T cells, B cells, and fibroblasts, with its receptor RANK on macrophages, dendritic cells, and preosteoblasts [20]. In the context of such inflammatory pathway, the key cytokines, i.e., tumor necrosis factor- α (TNF- α) and interleukin 6 (IL 6), play a critical role, as evidenced by therapeutic interventions targeting these factors resulting in remarkable clinical improvement in arthritis [21].

The recent work has shed light on a new scenario, in which the IL23/Th17 axis plays an essential role in bone loss, by favoring the generation of pathogenic ACPAs, via the secretion of IL-21 and IL-22, and by facilitating osteoclastogenesis, via the secretion of IL-17 [22]. As our understanding of molecular occurrence before the onset of RA has increased, it became evident that the interplay between mucosal events is relevant in the pathogenesis of the disease, in which oral and lung mucosa, under the stimuli of environmental factors, represents sites of ACPA production, while the intestinal dysbiosis increases the inflammatory state through increased Th17 polarization and IL-23/IL-17 axis activation (**Figure 1**) [23]. The recent discovery of the effect of ACPAs on osteoclastogenesis and on periarticular IL-8 production also suggests a mechanism that accounts for the transition from systemic autoimmunity to clinical manifestations [24].

1.3 Treatment of RA

Three decades ago, the treatment for RA was guided by a step-up approach, i.e., “the pyramid approach,” in which nonsteroidal anti-inflammatory drugs (NSAIDs) and other conservative measures constituted first-line treatment, subsequently moving to more potent and cytotoxic drugs for persistent symptoms or progressive structural damage [25] (see **Figure 2**). This approach is no longer valid as RA has been recognized as causing substantial morbidity and mortality among those on the pyramid approach. Since then, RA treatment strategy has advanced dramatically. The routine administration of conventional disease-modifying antirheumatic drugs (cDMARDs), such as the anchor drug methotrexate, enabled physicians to ease RA symptoms with substantially better control of cartilage and bone erosion [26, 27] (**Table 1**).

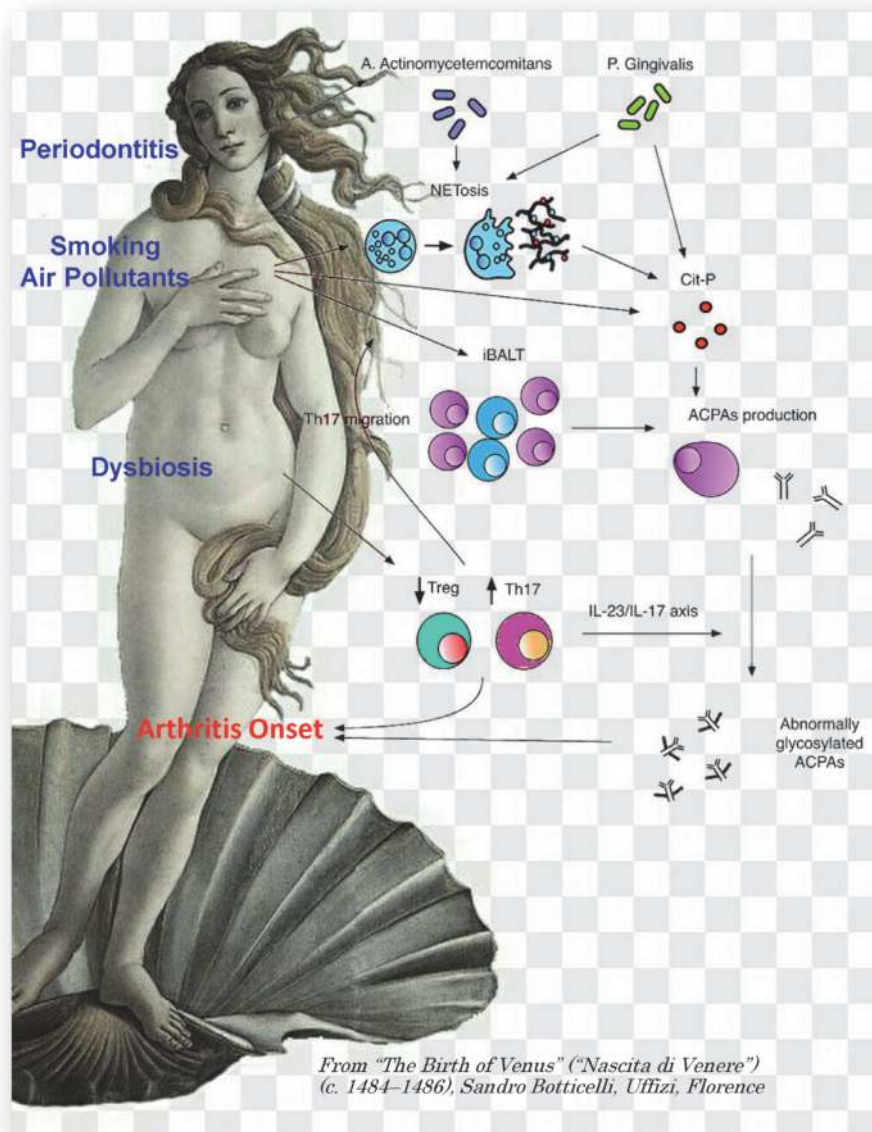


Figure 1.

Mucosa-environment interactions in the immuno-pathogenesis of RA. In the oral and lung mucosa, the stimuli of periodontal pathogens or environmental factors elicit production of citrullinated proteins, directly or through NETosis*, and consequently result in ACPA production in subjects at risk. (1) At the periodontal level, *Porphyromonas gingivalis* (*P. gingivalis*) generates citrullinated peptides through PPAD. Moreover, through gingipains (*Gp*) (a family of proteases secreted by *P. gingivalis*), *P. gingivalis* increases Th17 polarization and induces NETosis. *Aggregatibacter actinomycetemcomitans* (*A. actinomycetemcomitans*) can also elicit the formation of citrullinated peptides, through the production of leukotoxin A (*Lxt-A*) and the induction of NETosis. Citrullinated peptides (*Cit-P*), recognized by specific B cells, induce ACPA production. (2) In the lung mucosa, smoke and air pollutants generate the formation of citrullinated antigens and NETosis. Mucosa reacts through the formation of iBALT (inducible bronchus associated lymphatic tissue) and elicits the local production of ACPAs, which can be detected in local secretions. (3) In systemic circulation, there is an increase of circulating Th17 and a reduction of Treg. T cells present an abnormal hypoglycolytic and hyperproliferative phenotype, and show an increased production of pro-inflammatory cytokines, such as IL-17. (4) In gut mucosa, dysbiosis of the intestinal microbiota inhibits the normal induction of Treg. Pathobiont species stimulate the activation of dendritic cells (DC), macrophages and innate lymphoid cells 3 (ILC3), leading to the polarization towards Th17, and the activation of the IL-23/IL-17 axis. Locally-produced Th17 can migrate through systemic circulation to other sites, inducing inflammation, abnormal Ig glycosylation, and iBALT formation. Specific B cells directed against luminal antigens can be activated in Peyer's patches or in local lymph nodes, migrating back in lamina propria where they produce secretory immunoglobulins (sIgs). Some of these B cells recognize antigens that cross-react with self-antigens via molecular mimicry. Finally, inflammatory cells and ACPAs lead to the onset of arthritis. *Cit-p*: citrullinated proteins; PPAD pathogen PAD; *Gp*: gingipains;

Ltx-A: leukotoxin A; iBALT: inducible bronchus associated lymphatic tissue; sIgs: secretory immunoglobulins; ILC3: innate lymphoid cells 3; DC: dendritic cells; IL: interleukin.

***NETosis—the role in RA etiology:** neutrophil extracellular traps (NETs) are chromatin-derived extracellular “spider’s webs” that are expelled from neutrophils in response to infection or inflammatory stimuli. They were first described as an alternative defense mechanism by which neutrophils trap and kill microbes. NET-release represents a novel, unique form of cell death that is characterized by the discharge of decondensed chromatin and granular contents to the extracellular space, and is referred to as “NETosis”, distinct from apoptosis and necrosis. Afterwards, it has become clear that NETs also render autoantigens in autoimmune diseases. NETs have been implicated in the development of autoimmunity in certain conditions such as RA and SLE through an exposure of externalized intracellular neoepitopes e.g., citrullinated peptides in RA and dsDNA and nuclear proteins in SLE. Currently, emerging evidence implicates NETs as a source of citrullinated neoepitopes in RA, causing loss of immune tolerance and development of autoantibodies to citrullinated proteins (ACPA). Citrulline residues in aggrecan and vimentin are preferentially recognized by antigen-presenting cells in individuals who carry the HLA-DRB1*04:01/04 allele, providing a molecular explanation for the strong association between this allele and the development of RA. Modified from Lucchino et al. [23].

In addition, as the role of several key proinflammatory cytokines including TNF- α and IL-6, and cell-associated targets such as CD20 and co-stimulation molecules CD80/86, has been clarified, the treatment paradigm has changed with the advent of targeted biological therapies [28]. The emergence of a number of potent biological DMARDs (bDMARDs) has brought about a new therapeutic era that emphasizes the importance of early and aggressive treatment to prevent joint damage and induce remission [26, 29–32] (**Table 1**). It has become thoroughly evident that early suppression of disease activity is crucial. For instance, a large RA trial cohort study validated that early changes in MRI measures independently predicted X-ray and MRI progression, robustly suggesting the necessity of early intervention [33].

This conceptual trend in the treatment of RA was followed by new approval of the targeted synthetic DMARDs (tsDMARDs), such as small-molecule inhibitors of Janus kinase (JAK) enzymes [32, 34] (**Table 2**). The JAK family includes four members, JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). The different JAK isoforms, and the downstream signal transducer of activators of transcription

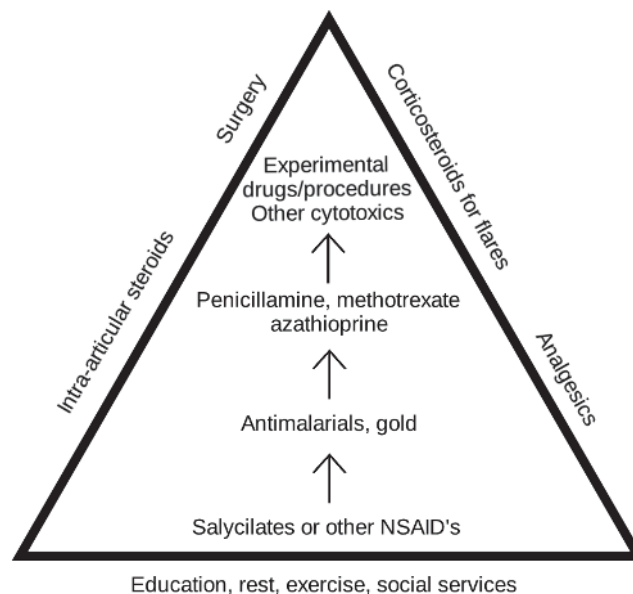


Figure 2.
The traditional treatment pyramid for RA, long since abandoned. Modified from Schumacher [62].

DMARD	Mechanism for rheumatoid arthritis	Adverse effects	Monthly cost [†]
Nonbiologic*			
More commonly used			
Methotrexate	Inhibits dihydrofolate reductase	Liver effects, teratogenesis, hair loss, oral ulcers	\$
Leflunomide (Arava)	Inhibits pyrimidine synthesis	Liver effects, gastrointestinal effects, teratogenesis	\$
Hydroxychloroquine (Plaquenil)	Antimalarial, blocks toll-like receptors	Rare ocular toxicity	\$\$
Sulfasalazine (Azulfidine)	Folate depletion, other mechanisms unknown	Anemia in G6PD deficiency, gastrointestinal effects	\$
Minocycline (Minocin)	Antimicrobial, other mechanisms unknown	Drug-induced lupus erythematosus, <i>Clostridium difficile</i> colitis	\$
Less commonly used			
Gold sodium thiomalate	Inhibits antigen processing, decreases cytokines (TNF, interleukin-6)	Skin, heme, renal effects	\$\$
Penicillamine (Cuprimine)	Chelates metal, other mechanisms unknown	Heme, renal effects	\$\$
Cyclophosphamide	Nitrogen mustard alkylating agent, cross-links DNA	Infertility, cancer, hemorrhagic cystitis	\$\$
Cyclosporine (Sandimmune)	Calcineurin inhibitor, decreases interleukin-2	Hypertension, renal effects, hirsutism	\$\$
Biologic*			
Anti-TNF agents			
Adalimumab (Humira)	Anti-TNF- α	TB, opportunistic infection	\$\$\$
Certolizumab pegol (Cimzia)	Anti-TNF- α , pegylated	TB, opportunistic infection	\$\$\$
Etanercept (Enbrel)	Anti-TNF- α , receptor	TB, opportunistic infection	\$\$\$
Golimumab (Simponi)	Anti-TNF- α	TB, opportunistic infection	\$\$\$
Infliximab (Remicade)	Anti-TNF- α	TB, opportunistic infection, infusion reaction	\$\$\$
Other biologic agents			
Abatacept (Orencia)	Costimulator blocker, cytotoxic T lymphocyte antigen 4	Opportunistic infection	\$\$\$
Anakinra (Kineret)	Anti-interleukin-1 receptor blocker	Opportunistic infection, injection site pain	\$\$\$
Rituximab (Rituxan)	Anti-CD20, eliminates B cells	Infusion reaction, opportunistic infection, progressive multifocal leukoencephalopathy	\$\$\$\$
Tocilizumab (Actemra)	Anti-interleukin-6 receptor blocker	Opportunistic infection	\$\$\$

G6PD = glucose-6-phosphate dehydrogenase; TB = tuberculosis; TNF = tumor necrosis factor.
Adapted from Wasserman [26].
*Nonbiologic drugs listed in approximate order of priority, biologic drugs listed in alphabetical order.
[†]\$ = \$30 to \$100; \$\$ = \$100 to \$1000; \$\$\$ = \$1000 to \$5000; \$\$\$\$ = more than \$5000.

Table 1.
Biologic and nonbiologic DMARDs.

(STAT) proteins, are expressed in synovial tissue and cells [35]. The JAK-STAT pathway is currently thought to be an evolutionarily conserved signaling pathway engaged by diverse cytokines, interferons, growth factors, and hormones, providing a simple and elegant machinery whereby extracellular molecules regulate gene expression [36]. Each JAK family member selectively binds different receptor chains (**Figure 3**).

Many proinflammatory cytokines involved in RA pathogenesis bind to a specific group of type I and type II cytokine-receptors, which are structurally distinct from

Synthetic DMARDs
<i>Conventional synthetic DMARDs</i>
<ul style="list-style-type: none"> • Unknown target: methotrexate, sulfasalazine, chloroquine, hydroxychloroquine and gold salts • Known target: that is, dihydroorotate-dehydrogenase for leflunomide
<i>Targeted synthetic DMARDs</i>
<ul style="list-style-type: none"> • Janus kinase 1 (JAK1) and JAK2: baricitinib • JAK1, JAK2 and JAK3: tofacitinib
Biological DMARDs
<i>Biological originator DMARDs</i>
<ul style="list-style-type: none"> • Tumour necrosis factor: adalimumab, certolizumab, etanercept, golimumab and infliximab • IL-6 receptor: tocilizumab and sarilumab • IL-6: clazakizumab, olokizumab and sirukumab • CD80 and CD86 (involved in T cell co-stimulation): abatacept • CD20 (expressed by B cells): rituximab
<i>Adapted from Smolen et al. [34].</i>

Table 2.
 Synthetic DMARDs and biologic DMARDs.

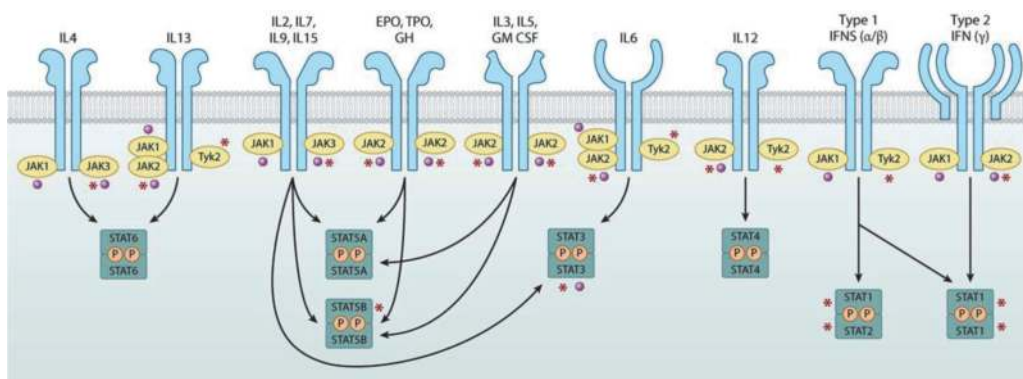
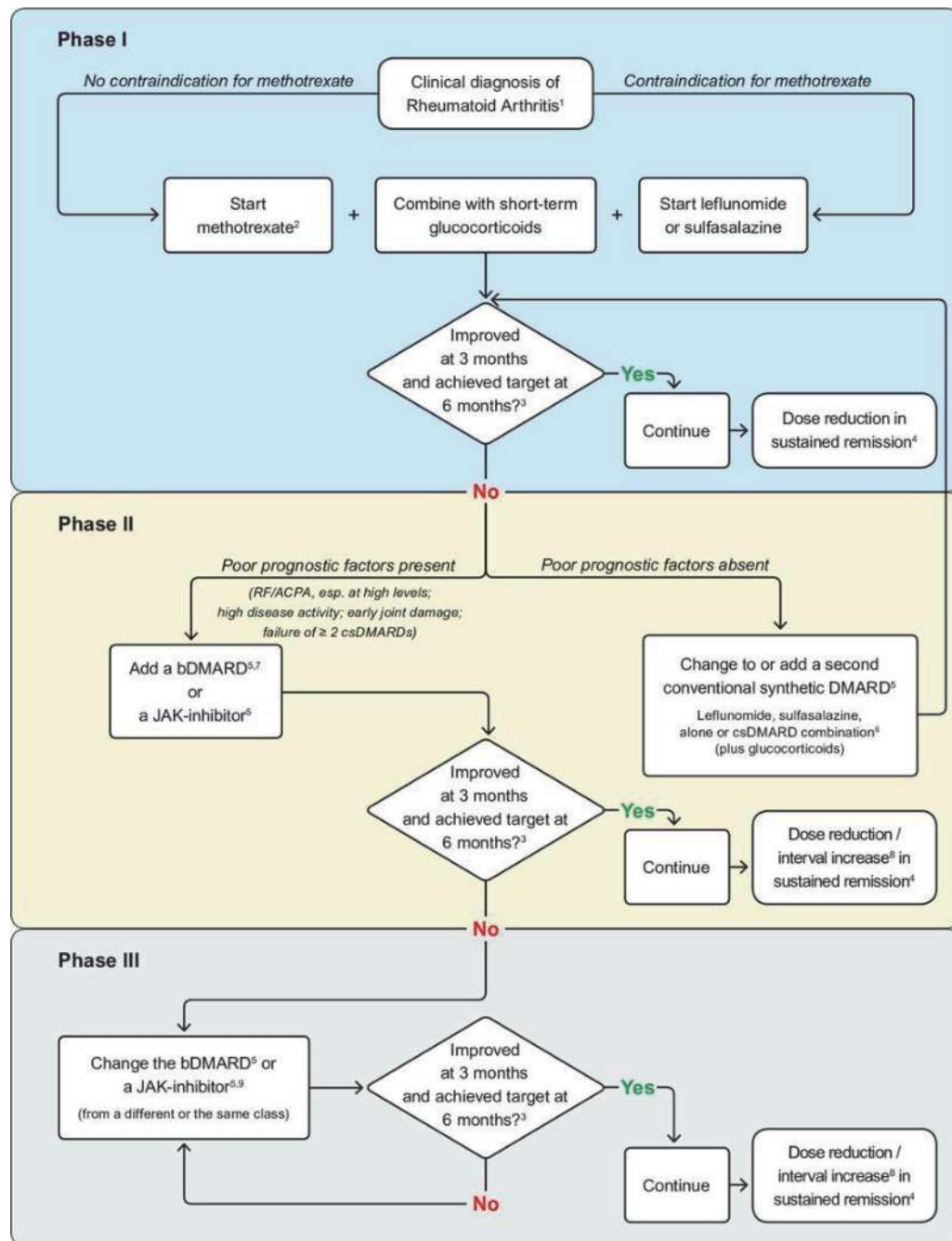


Figure 3.
 The JAK–STAT pathway. The four JAKs (JAK1, JAK2, JAK3, TYK2) are selectively bound to and therefore mediate signaling for various cytokine and hormone receptors. Different cytokines also have a propensity to activate certain STATs. Mutations in many of the gene encoding JAKs and STATs (indicated by an asterisk *) have been linked to human disease. A large number of medications targeting JAKs and, to a lesser degree, STATs (indicated by a ●) are being developed and used to treat human disease. Adapted from O’Shea et al. [36].

other receptors such as those that bind TNF and IL-1. Since cytokines binding type I and II receptors are dependent on the JAK–STAT pathway for signal transduction, several JAK inhibitors (“jakinibs”) with variable degrees of selectivity and specificity for the JAK enzymes have been tested in RA. Tofacitinib and baricitinib are the first orally available JAK inhibitors with selectivity for JAK 1 and 3 and JAK 1 and 2, respectively. Both have demonstrated rapid improvements in multiple outcome measures [37].

The latest 2019 update of the European League Against Rheumatism (EULAR) recommendations for the management of RA with synthetic and biological disease-modifying antirheumatic drugs provided consensus including the statement which elevated the JAK inhibitors (“tsDMARDs”), to the same recommendation level as bDMARDs [38]. The 2019 version of general overview of the RA management recommendations in form of an algorithm is depicted in **Figure 4** [32].



1. 2010 ACR-EULAR classification criteria can support early diagnosis.
 2. "Methotrexate should be part of the first treatment strategy". While combination therapy of csDMARDs is not preferred by the Task Force, starting with methotrexate does not exclude its use in combination with other csDMARDs although more adverse events without added benefit are to be expected, especially if MTX is combined with glucocorticoids.
 3. The treatment target is clinical remission according to ACR-EULAR definitions or, if remission is unlikely to be achievable, at least low disease activity; the target should be reached after 6 months, but therapy should be adapted or changed if insufficient improvement (less than 50% of disease activity) is seen after 3 months.
 4. Sustained remission: ≥ 6 months ACR/EULAR index based or Boolean remission.
 5. Consider contraindications and risks.
 6. The most frequently used combination comprises methotrexate, sulfasalazine and hydroxychloroquine.
 7. TNF-inhibitors (adalimumab, certolizumab, etanercept, golimumab, infliximab, including EMA/FDA approved biosimilars), abatacept, IL-6R-inhibitors, or rituximab (under certain conditions); in patients who cannot use csDMARDs as comedication, IL-6-inhibitors and tsDMARDs have some advantages.
 8. Dose reduction or interval increase can be safely done with all bDMARDs and tsDMARDs with little risk of flares; stopping is associated with high flare rates; most but not all patients can recapture their good state upon re-institution of the same DMARD/tsDMARD.
 9. Efficacy and safety of bDMARDs after JAK-inhibitor failure is not fully known; also, efficacy and safety of an IL-6 pathway inhibitor after another one has failed is currently unknown. Efficacy and safety of a JAK-inhibitor after insufficient response to a previous JAK-inhibitor is unknown.

Figure 4. Presentation of the 2019 update of the EULAR RA management recommendations in form of an algorithm. This is an abbreviated version aiming to provide a general overview, but it must be borne in mind that the algorithm cannot be separated from the details presented in the discussion of the individual recommendations in the paper which are part and parcel of these recommendations. ACPA, anti-citrullinated protein antibody; ACR, American College of Rheumatology; bDMARDs, biological DMARDs; bsDMARD, biosimilar DMARDs; csDMARDs, conventional synthetic DMARDs; DMARDs, disease-modifying antirheumatic drugs; EMA, European medicines agency; EULAR, European league against rheumatism; FDA, Food and Drug Administration; IL-6R, interleukin 6 receptor; JAK, Janus kinase; MTX, methotrexate; RA, rheumatoid arthritis; RF, rheumatoid factor; TNF, tumor necrosis factor; tsDMARDs, targeted synthetic DMARDs. Adapted from Smolen et al. [32].

1.4 Unmet diagnostic needs in RA

Given such revolutionary paradigm shift in the therapeutics for RA, it is warranted that we now readjust our focus towards innovative changes in the early diagnosis of RA. Today, physicians are required to diagnose RA earlier and with greater accuracy in order to start effective treatment as soon as possible and with greater confidence. Nonetheless, the reality in clinical practice is not simple at all. The diagnosis of RA continues to be mostly based on a combination of symptoms, signs, and results of investigations. However, because of the great variety of individual clinical presentations in RA, and since no single symptom or sign is specific for RA, accurate diagnosis may be hindered, especially in the early stages of disease when hallmark joint destruction may be absent or missed. Obviously, classification criteria for RA do exist, with a series of criteria having been created to define classic disease for clinical and both epidemiological studies. However, the application of classification criteria can give rise to both false-positive and false-negative classifications compared to the true clinical diagnosis [39]. In this context, we still do not have comprehensive diagnostic criteria of RA in the real clinical world.

Currently, among the clinically available imaging modalities, magnetic resonance imaging (MRI) is thought to be the most sensitive, and available evidence has led to its increasing use for assessing the active synovitis and bone damage central to many clinical RA studies including several of our previous reports [40–43].

Thus, to find a solution to the challenge of early diagnosis of RA, we aimed to develop practically useful diagnostic criteria which integrate gadolinium (Gd) contrast-enhanced magnetic resonance imaging (MRI) findings into clinical manifestations of the disease, which we will attempt to describe herein.

2. Attempts for accurate or earlier diagnosis of RA

2.1 The 1987 ACR classification criteria for RA: “old but gold” standard

As mentioned above, currently no validated diagnostic criteria exist for RA. By contrast, a few sets of classification criteria have been developed and modified over time. Classification criteria are standardized definitions that are primarily aimed to collect homogenous cohorts of patients with typical disease, primarily for clinical and epidemiological studies [44]. Although they are not intended to capture the entire universe of patients with the disease, they may provide some framework to support diagnosis and are often used in this way in daily practice.

The most historically notable classification criteria which have been used in RA are the American College of Rheumatology (ACR) criteria revised in 1987 by the American Rheumatism Association, published by Arnett et al. [45] (**Table 3**). At the time the 1987 criteria were presented, sensitivity and specificity were reported to be 91–94% and 89%, respectively. They have been widely applied for diagnosis, as well. However, the 1987 criteria, which were developed based on established patients with an average disease duration of 7.7 years, have come to be recognized as having poor performance for diagnosing early RA. A systemic literature review by Banal et al. of 138 publications comprising 7438 patients (including 3883 cases of RA) reported that the sensitivity and specificity of the 1987 criteria (in the list format) for early RA (<1 year) were 77% (68–84%) and 77% (68–84%), respectively, compared to 79% (71–85%) and 90% (84–94%), respectively, for established RA (>1 year) [46]. The Norfolk Arthritis Register report by Harrison et al. demonstrated that only 50% of RA patients fulfilled the 1987 criteria at 6 months and only

Criterion	Description
Morning stiffness	Morning stiffness in and around the joints that lasts at least 1 hour before maximal improvement
Arthritis in three or more areas	At least three joint areas that simultaneously have soft-tissue swelling or fluid (not bone overgrowth alone) observed by a physician (the 14 possible joint areas are the right and left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints)
Arthritis of hand joints	At least one of the following joint areas is swollen: wrist, MCP, or PIP joint (see description of second criterion)
Symmetric arthritis	Simultaneous involvement of the same joint areas listed for the second criterion on both sides of the body (bilateral involvement of PIP, MCP, or MTP joints is acceptable without absolute symmetry)
Rheumatoid nodules	Subcutaneous nodules over bone prominences or extensor surfaces or in juxtaarticular regions observed by a physician
Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor with any method that has yielded positive results in <5% of healthy control subjects
Radiographic changes	Changes typical of rheumatoid arthritis on posteroanterior radiographs of the hand and wrist; these must include erosions or unequivocal bone decalcification localized to or most marked adjacent to the involved joints (osteoarthritic changes alone do not qualify)

Note: For classification purposes, a patient is said to have rheumatoid arthritis if he or she has satisfied at least four of the seven criteria. The first four criteria must be present for at least 6 weeks. Patients with two clinical diagnoses are not excluded. MCP = metacarpophalangeal, MTP = metatarsophalangeal, PIP = proximal interphalangeal. Adapted from Arnett et al. [45].

Table 3.
The ACR 1987 revised criteria for the classification of rheumatoid arthritis.

80% even at 2 years after enrolment [47]. Thus, the 1987 criteria do not appear to be well-suited as a diagnostic measure of short-duration RA. Emerging evidence on the response of arthritis to early intervention with DMARDs indicates the existence of “a window of opportunity in RA,” a time during which aggressive treatment accounts for long-term benefits in outcome. Therefore, to meet clinical needs, better diagnostic measures are required to identify RA patients at the earliest stages of the disease.

2.2 The 2010 ACR/EULAR classification criteria for RA

Since 2007, the ACR and EULAR have been working collaboratively to create new classification criteria for RA, which were finally published in 2010 [48] (**Table 4**). The 2010 criteria are an effort to facilitate earlier diagnosis of RA in patients who may not meet the 1987 ACR criteria. For example, they do not include the presence of rheumatoid nodules or radiographic erosive changes, both of which are less likely in early RA. The 2010 criteria consist of a classification scoring system, laying emphasis on small joint involvement as well rheumatoid factor (RF) or ACPA seropositivity. It should be noted that RF is not specific for RA and can be detected in patients with other disorders, such as viral hepatitis C, and in healthy elderly individuals [49, 50] (**Table 5**). Although ACPA is more specific for RA, it may be present in other rheumatic diseases and some infectious diseases [51] (**Table 6**). We know approximately 50–80% of patients with RA have RF, ACPA, or both [52]. Acute-phase reactants such as C-reactive protein and erythrocyte sedimentation rate are also part of the criteria. As shown in **Table 4**, in the new classification criteria, the definition of RA requires at least a single clinically swollen joint for inclusion entry and the absence

	Score
Target population (Who should be tested?): Patients who	
1. have at least 1 joint with definite clinical synovitis (swelling) [*] 2. with the synovitis not better explained by another disease [†]	
Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of ≥6/10 is needed for classification of a patient as having definite RA) [‡]	
A. Joint involvement [§]	
1 large joint [¶]	0
2–10 large joints	1
1–3 small joints (with or without involvement of large joints) [#]	2
4–10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint) ^{**}	5
B. Serology (at least 1 test result is needed for classification) ^{††}	
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification) ^{‡‡}	
Normal CRP and normal ESR	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms ^{§§}	
<6 weeks	0
≥6 weeks	1

^{*}The criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of rheumatoid arthritis (RA) with a history compatible with prior fulfillment of the 2010 criteria should be classified as having RA. Patients with longstanding disease, including those whose disease is inactive (with or without treatment) who, based on retrospectively available data, have previously fulfilled the 2010 criteria should be classified as having RA.

[†]Differential diagnoses vary among patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnoses to consider, an expert rheumatologist should be consulted.

[‡]Although patients with a score of <6/10 are not classifiable as having RA, their status can be reassessed and the criteria might be fulfilled cumulatively over time.

[§]Joint involvement refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are excluded from assessment. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.

[¶]“Large joints” refers to shoulders, elbows, hips, knees, and ankles.

[#]“Small joints” refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

^{**}In this category, at least 1 of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (e.g., temporomandibular, acromioclavicular, sternoclavicular, etc.).

^{††}Negative refers to IU values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤3 times the ULN for the laboratory and assay; high-positive refers to IU values that are >3 times the ULN for the laboratory and assay. Where rheumatoid factor (RF) information is only available as positive or negative, a positive result should be scored as low-positive for RF. ACPA = anti-citrullinated protein antibody.

^{‡‡}Normal/abnormal is determined by local laboratory standards. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

^{§§}Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g., pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status. Adapted from Aletaha et al. [48].

Table 4.
 The 2010 ACR/EULAR classification criteria for rheumatoid arthritis.

of other diseases (alternative diagnoses) better explaining the clinical symptoms. Thereafter, the classification is based on a total score from individual items in four domains including the number of involved joints, serological abnormalities, elevated acute-phase reactants, and duration of symptoms.

Disease	RF frequency, %
Arthritis	
Rheumatoid arthritis	70–90
Juvenile idiopathic arthritis	5
Psoriatic arthritis	<15
Reactive arthritis	<5
Other connective tissue diseases	
Primary Sjögren's syndrome	75–95
Mixed connective tissue disease	50–60
Systemic lupus erythematosus	15–35
Systemic sclerosis	20–30
Dermatomyositis/polymyositis	20
Systemic vasculitides	5–20
Infectious diseases	
Bacterial infections	
Subacute bacterial endocarditis	40
Chlamydia pneumoniae infection	
Klebsiella pneumoniae infection	
Syphilis primary-tertiary	8–37
Tuberculosis	15
Viral infections	
Coxsackie B virus infection	15
Dengue virus infection	10
EBV and CMV infections	20
Hepatitis A, B and C virus infection	25
HCV infection	40–76
Herpes virus infection	10–15
HIV infection	10–20
Measles	8–15
Parvovirus infection	10
Rubella	15
Parasitic	
Chagas	15–25
Malaria	15–18
Onchocerciasis	10
Toxoplasmosis	10–12
Other diseases	
Mixed cryoglobulinemia type II	100*
Liver cirrhosis	25
Primary biliary cirrhosis	45–70
Malignancy	5–25
After multiple immunizations	10–15
Chronic sarcoidosis	5–30
Healthy individuals	
Healthy 50-year olds	5
Healthy 70-year olds	10–25

*Monoclonal IgM rheumatoid factors.
 RF: rheumatoid factor; CMV: cytomegalovirus; EBV: Epstein-Barr virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus.
 Adapted from Ingegnoli et al. [50].

Table 5.
 Rheumatoid factor frequency in different diseases and conditions.

The primary aim of creating the 2010 criteria was described as not for developing diagnostic criteria but rather to facilitate the study of patients with earlier stages of RA. However, they have become widely used as an aid in the diagnosis of RA in

	N	ACPA ⁺ positive, no. (%)
Psoriatic arthritis	1343	115 (8.6)
Systemic lupus erythematosus	1078	84 (7.8)
Sjögren's syndrome	609	35 (5.7)
Spondylarthropathy	431	10 (2.3)
Scleroderma/CREST syndrome	380	26 (6.8)
Hepatitis C/cryoglobulinemia	285	10 (3.5)
Osteoarthritis	182	4 (2.2)
Hepatitis B	176	1 (0.6)
Juvenile idiopathic arthritis	169	13 (7.7)
Polymyalgia rheumatica	146	0 (0)
Vasculitis/Wegener's granulomatosis	107	5 (4.7)
Tuberculosis	96	33 (34.3)
Polymyositis/dermatomyositis	75	0 (0)
Fibromyalgia	74	2 (2.7)
Gout and pseudogout	58	0 (0)

*ACPA = anti-citrullinated peptide antibody; CREST = calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias syndrome.
 Adapted from Aggarwal et al. [51].

Table 6.
 Detection of ACPAs in diseases other than rheumatoid arthritis.

clinical practice, resulting in helping clinicians and researchers to become aware of the 2010 criteria's strengths and limitations as well. First of all, regarding entry criterion of the target population, the sentence "patients who with the synovitis not better explained by another disease" is quite tricky. Annotation states that "Differential diagnoses differ in patients with different presentations, but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear about the relevant differential diagnosis to consider, an expert rheumatologist should be consulted." Most rheumatologists know that there are many mimicking conditions to be distinguished from RA. The easy "ask-the-expert" attitude may be paradoxical to the principle of having criteria. Furthermore, Kaneko et al. identified a problem with the scoring criteria, which weigh relatively heavily in favor of serology, reporting a sensitivity as low as 15.8% when both RF and ACPA are negative. For instance, a seronegative person having 10 swollen joints for >6 weeks, with elevated CRP and ESR and destructive joint disease, would not achieve a total score of 6 per the new criteria [53]. Thus, several limitations of the 2010 criteria have already been recognized which hinder their use in daily practice.

3. Notion of early RA

Since early diagnosis and treatment with newly developed antirheumatic drugs including bDMARDs and tsDMARDs have been advocated for patients with RA, the understanding of "early" RA has changed. Formerly, early RA denoted disease of less than 2 years, or used to be sometimes less than 12 months duration. However, today, many rheumatologists may even see patients with symptom duration of less than 6 weeks. While the definition of early RA is still heterogeneous, two-thirds of

rheumatologists use the term “early” for symptoms shorter than 3 months. Currently, in general, early RA patients are preferentially regarded as those with symptoms of less than 3 months duration [54].

Besides the notion of disease duration, clinical practice informs us that there are a number of existing clinical factors which may also suggest early RA. These may include persistent pain in multiple joints despite normal joint radiography without fulfillment of RA classification criteria. Similarly, because clinicians may care for RA patient longitudinally over time, they are more likely to appreciate early manifestations, even in hindsight, as exemplified by the following common clinical situations:

1. Patients in the early stage of RA may not manifest soft tissue swelling (arthritis) of three or more joints as described in the 1987 classification criteria.
2. Patients in the early stage of RA may not necessarily present with unequivocally symmetric swelling (arthritis).
3. Patients in the very early stage of RA may not demonstrate serological abnormalities such as elevated acute-phase reactants during which time CRP and ESR are often unremarkable.
4. Inclusion of the presence of autoantibodies as major criteria for diagnosis may not be fair, considering that a significant proportion of patients are seronegative. As evidence suggests that seronegative RA represents a disease entity clinically and immunogenetically distinct from seropositive RA, it may well be inappropriate to apply RF to a mixed population of seropositive and seronegative patients [55].
5. Almost all RA patients have joint symptoms in the hands; even though the knee, ankle, or foot joint symptoms may precede hand pain, most patients have some joint pain of the hands at the time of presentation.

On the basis of these fundamental understandings, we aimed to develop practically useful criteria for the early diagnosis of RA by integrating Gd contrast-enhanced MRI findings with clinical manifestations of the disease.

4. Benefits of MRI in diagnosing RA

Radiographs are the current gold standard for evaluating joint damage in RA, and it is likely that radiography will continue to be used in daily clinical practice for monitoring arthritis disease progression. However, conventional radiography is not sensitive enough for depicting bone damage in early disease and is also insufficient for assessing synovial inflammation. These limitations have led to emerging interest in the multiplanar imaging abilities of MRI in RA and to wider use of MRI for assessing synovitis and bone damage [56].

4.1 Basic principles of MRI and RA pathology on MRI

The principles of MRI are briefly explained here. Upon being placed in external magnetic fields, hydrogen protons in human tissue align. They acquire energy (resonance) when excited by an external electro-magnetic pulse at a characteristic resonance frequency, with a consequent decrease in longitudinal magnetization and increase in transverse magnetization. When the pulse is turned off, protons return

to their previous low-energy state. The net movement of hydrogen protons elicits an electric current that is measured as the MR signal [57]. The presentation of particular tissues depends on their hydrogen proton content. In common MRI sequences, a T1-weighted (T1W) image represents fat-containing tissues, for example, the high signal of the bone marrow. By contrast, on T2W images, not only fat but fluid demonstrates high signal. The available techniques of fat suppression eliminate high signal from fat, consequently making fluid and inflammation better evident.

MRI can be used to assess inflammation (synovitis and bone edema) and damage (bone erosion) in the joint. Synovitis is depicted as an area in the synovial compartment that shows enhancement (signal intensity increase) on T1-weighted images after venous injection of gadolinium contrast. MRI bone erosion is visualized as a sharply marginated bone lesion, with correct juxta-articular localization and typical signal characteristics, i.e., loss of normal low-signal intensity of the cortical bone and loss of normal high-signal intensity of the trabecular bone on T1-weighted images. MRI bone edema is visualized as a lesion within the trabecular bone, with ill-defined margins and signal characteristics consistent with increased water content, i.e., high-signal intensity on T2-weighted fat-saturated and STIR images and low-signal intensity on T1-weighted images. Bone edema may occur alone or surrounding an area of erosion or other bone abnormality. Outcome Measures in Rheumatology (OMERACT), an independent initiative of international health professionals serving for the validation of clinical and radiographic outcome measures, has iteratively developed an RA-MRI scoring system (RAMRIS) framework for the evaluation of inflammatory and destructive changes in RA hands (metacarpophalangeal, MCP, joints) and wrists (carpal bones, distal radius, distal ulna, metacarpal bases) [58].

4.2 MRI of synovitis

Since synovitis is the earliest abnormality to occur in RA, MR imaging of synovitis is currently the best way to identify the earliest changes critical for early diagnosis of RA. MRI signatures of synovitis include increased synovial volume, increased water content, and contrast enhancement, i.e., increased signal intensity after intravenous injection of contrast material.

Synovitis reveals intermediate-to-low-signal intensity on T1-weighted images, whereas due to the increased water content of synovitis, various signal intensities can be viewed on T2-weighted images including the high signal of hypervascular synovium, as well as the low-signal characteristic of fibrosis.

The use of intravenous Gd-based contrast material plays an important role in MRI identification of synovitis. A number of dynamic MRI studies have demonstrated a good correlation between MRI synovium volume estimates and arthroscopic and histological inflammation scores [59]. The most used contrast material for evaluating synovitis is the paramagnetic agent, gadolinium-diethylenetriamine penta-acid (Gd-DTPA). This agent shortens the relaxation time of adjacent tissues, thereby improving the contrast between tissues on imaging. Uptake of Gd-DTPA depends upon vascularity and capillary permeability of tissues, making it particularly useful in visualizing sites of inflammation.

Contrast-enhanced T1-weighted images are sensitive and specific in the assessment of acute synovitis. After intravenous administration of Gd-DTPA, acute synovitis enhances rapidly and intensely, unlike joint effusion, which does not enhance in the early phase. Early-phase enhancement lasts for approximately 5 min after contrast injection [60]. Since gadolinium may diffuse into the synovial joint fluid, images acquired more than 10 min after injection may not accurately depict the extent of synovitis. In contrast, joint fluid enhancement appears within minutes

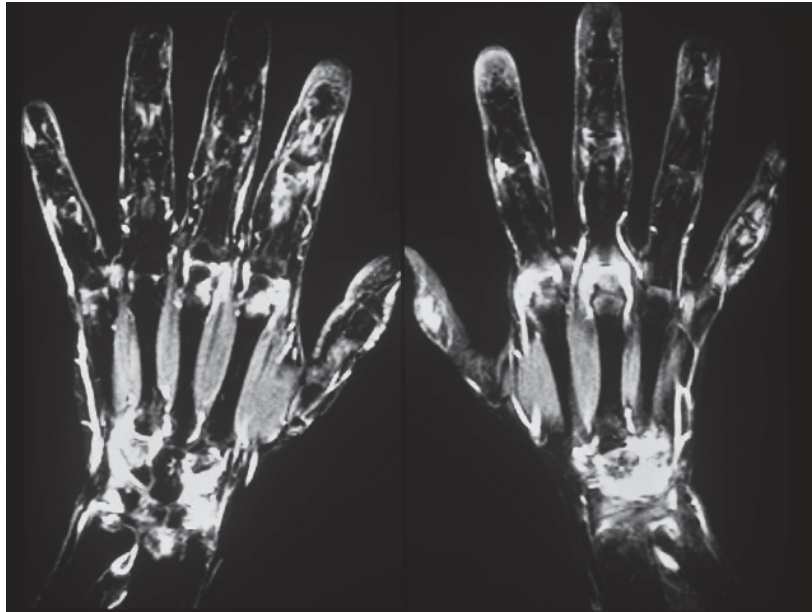


Figure 5. MR imaging signs of synovitis in our study. Fat-suppressed contrast-enhanced T₁-weighted coronal MR imaging from the volar aspect of the hand in a patient with early RA, in whom radiographic assessment was normal. There is marked synovial enhancement at the joints of PIP, MCP, as well as wrist joints.

and reaches a plateau after 30 min. The use of fat suppression increases visual contrast between the inflamed synovium and adjacent structures on contrast-enhanced T₁-weighted images [61]. OMERACT defines synovitis as an area in the synovial compartment with increased contrast enhancement whose thickness exceeds the width of normal synovium [58]. For the evaluation of synovitis in early RA, we used coronal Gd-enhanced fat-suppressed T₁-weighted MR images from both hands. The hand was chosen for MRI assessment given that is the most clinically affected area in RA. **Figure 5** represents fat-suppressed contrast-enhanced MRI from the volar aspect of the hand in a patient with early RA in our study, in whom radiographic assessment was normal. Remarkable synovial enhancement at the PIP, MCP, as well as wrist joints is noted.

5. Approach to the formulation of diagnostic criteria for early RA

5.1 Characteristics of contrast-enhanced MRI in active RA

First of all, we need to properly incorporate clinically significant MRI findings into our diagnostic criteria for early RA. Therefore, at the outset, preliminary studies of Gd-enhanced MRI were conducted to distinguish characteristics of synovial MR images in active RA, using 20 patients with definitive clinical diagnoses of RA (17 women, 3 men, ages 21–72 years, mean age 47.8 years), consisting of 17 active cases and 3 inactive cases in remission [40–43].

The MR imaging protocol we used is as follows: MR imaging of the hand was performed with a 1.5-Tesla superconducting magnet (MRT 200 FX/II, Toshiba) equipped with a circular surface coil 20 cm in diameter. Multiple coronal MR images of the hand were obtained using a fat-suppressed T₁-weighted spin-echo sequence (repetition time msec/echo time msec = 380/20, 4 mm section thickness with 1 mm intersection gap). Contrast-enhanced images were obtained after bolus injection of 0.1 mmol/kg gadopentetate dimeglumine (Magnevist, Schering) into a

vein in the arm. MR images were acquired within 5 min after injection to avoid diffusion of the contrast material into joints.

As a result, we found bilateral enhancement in the wrist joints (carpal bones, distal radius, distal ulna, metacarpal bases) in 17 cases of active RA and the metacarpophalangeal (MCP) or proximal interphalangeal (PIP) joints in 14 cases. By contrast, no enhancement was seen in any of the three inactive cases in remission. On the basis of these convincing results, we decided to focus on the bilateral enhancement of the synovia in the PIP, MCP, or wrist joints, which may best characterize the MRI findings of synovitis associated with active RA.

Thus, we established our preliminary criteria for the diagnosis of early RA using MR imaging. These preliminary criteria were comprised of two steps with the first requiring clinical findings suggestive of RA, including polyarthralgia of hands in three joints or more (“entry criteria”). The second step involved MRI findings indicating bilateral synovial enhancement seen in any PIP, MCP, or wrist joints on Gd-enhanced MRI (“MRI criteria”). Bilateral involvement of PIP, MCP, or wrist joints is acceptable though absolute symmetry is not required. RA was defined by fulfilling the both entry criteria and MRI criteria.

To evaluate the performance of these preliminary criteria, we conducted a provisional study to investigate the difference between the early RA and the other conditions than RA in Gd-MRI findings. We selected patients with early RA, defined as those carrying a definitive clinical diagnosis of RA made by a board-certified, trained rheumatologist, but without having radiographic changes. Sixteen patients (15 women, 1 man, aged 19–76 years, mean age 49.9 years) with early RA and 11 non-RA controls (9 women, 2 men, 19–52 years, mean age 41.7 years), who fulfilled the entry criteria, were enrolled. Non-RA controls consisted of patients with systemic lupus erythematosus (2 cases), Sjögren’s syndrome (one case), Behçet’s disease (one case), palindromic rheumatoid arthritis (one case), reactive arthritis (two cases), viral arthritis (one case), and nonspecific transient self-limiting arthritis (three cases). We evaluated the performance of the preliminary criteria among cases that fulfilled entry criteria, including sensitivity and specificity analyses. Our preliminary MRI criteria showed 100% sensitivity, 73% specificity, and 89% accuracy in differentiating RA from other conditions.

Since that study, from daily experience using contrast-enhanced MRI in a large number of clinical cases, we have found that enhancement in the synovium may also be observed occasionally in patients with systemic lupus erythematosus, dermatomyositis, polymyositis, mixed connective tissue disease, and Behçet’s disease.

5.2 Proposed “diagnostic criteria for early RA with MRI findings”

On the basis of our preliminary studies, we created provisional criteria under the title “diagnostic criteria for early RA with MRI findings” (Table 7).

These provisional diagnostic criteria comprise two domains. The first domain consists of clinical findings suggestive of RA and includes entry criteria requiring polyarthralgia of hands (joint pain of three or more joint areas confirmed by a physician) and exclusion criteria that exclude other rheumatic conditions, i.e., systemic lupus erythematosus (SLE), dermatomyositis and polymyositis (PM/DM), mixed connective tissue disease (MCTD), primary Sjögren’s syndrome (SS), and Behçet’s disease (BD). The second domain constitutes the MRI criteria, requiring Gd-enhanced MRI findings indicating bilateral synovial enhancement seen in any PIP, MCP, or wrist joints. Bilateral involvement of PIP, MCP, or carpal joints of wrists is acceptable, and absolute symmetry is not required to meet the domain criteria. Early RA is defined by fulfilling all conditions of both domains.

Diagnosis of RA is defined by fulfilling all conditions of following both domains
Clinical domain—clinical findings suggestive of RA:
1. Entry criteria: presence of polyarthralgia in hands (three or more joint areas)
2. Exclusion criteria: exclusion of other rheumatic conditions, i.e., systemic lupus erythematosus (SLE), dermatomyositis and polymyositis (PM/DM), mixed connective tissue disease (MCTD), primary Sjögren’s syndrome (SS), and Behçet’s disease (BD)
• If case meets entry criteria and does not meet any exclusion criteria, proceed to MRI criteria
MRI domain—MRI findings suggestive of RA:
3. MRI criteria: bilateral synovial enhancement on Gd-enhanced MRI [*] in the proximal interphalangeal (PIP), or metacarpophalangeal (MCP), or wrist joints
[*] <i>Symmetrical involvement in bilateral joints not required.</i>

Table 7.
The diagnostic criteria for early RA with MRI findings (proposal).

5.3 Validation of “diagnostic criteria for early RA with MRI findings” in prospective study

We evaluated our provisional diagnostic criteria for early rheumatoid arthritis with MRI findings in a prospective study, approved by our institutional review board. The validity of the diagnostic criteria was assessed by acquisition of final diagnoses at the end of the clinical follow-up of a certain duration. Final diagnoses were made comprehensively. Subjects included patients presenting with polyarthralgia who visited rheumatology clinic at our institution. At the end of recruitment, we enrolled 50 consecutive patients including 9 men and 41 women (mean age, 44 years; range, 19–74 years old). All enrollees met entry criteria defined as the presence of polyarthralgia in hands in three or more joint areas. The diagnosis of RA or non-RA was made after careful clinical follow-up by trained rheumatologists. The final diagnosis of RA was established according to physical

Subjects: 50 cases (41 women and 9 men, average age = 44 years old)	
Observation period: mean duration = 776 days	
Drop out: two cases	
Final diagnoses:	
Disease category	n
RA	26
Non-RA	22
Arthritis related to viral infection	3
Sjögren’s syndrome	2 [*]
Osteoarthritis	4
Reactive arthritis	1
Cryoglobulinemia	1
Palindromic rheumatism	1
Unclassified self-limited arthritis	10
[*] <i>Primary Sjögren’s syndrome diagnosed during the study period.</i>	

Table 8.
Demographic profiles of patients with RA and non-RA diseases.

Final Dx	No. of patients		True positive	True negative	False positive	False negative	Sensitivity (%)	Specificity (%)	Accuracy
	RA 26	Non-RA 22							
Proposed criteria	28	20	25	19*	3**	1	96%	86%	92%
ACR 1987 criteria	19	29	18	21	1	8	69%	95%	81%

*Predictive value of negative results: 95%.
 **False positive: cryoglobulinemia = 1; arthritis related to viral infection = 1, osteoarthritis = 1.

Table 9.
 Sensitivity, specificity, and accuracy of proposed criteria for rheumatoid arthritis.

findings compatible with RA or radiographic changes specific for RA and after ruling out other disease conditions. The average duration of follow-up from first visit was 776 days (range, 117–2161 days). Two of the 50 enrolled patients were lost to follow-up prior to diagnosis, and subsequent medical information was not available; they were excluded from the analysis.

After a thorough follow-up period of careful clinical observation, a final pool of 48 patients had confirmed diagnoses: 26 patients had RA, and 22 had non-RA conditions. Patient disease profiles are shown in **Table 8**. Statistics of diagnostic performance is presented in **Table 9**. The proposed diagnostic criteria for early RA with MRI findings was able to diagnose 25 of 26 patients with RA with high accuracy. False positives occurred in three patients, yielding a sensitivity of 96%, specificity of 86%, and accuracy of 92%, indicating high diagnostic performance. In particular, it should be noted that the criteria effectively ruled out RA with a high negative predictive value of 95%.

Thus, our study objectively demonstrated that the “diagnostic criteria of early rheumatoid arthritis with MRI findings” was clinically quite effective in making early diagnoses of RA, though there is a need to validate the criteria with a larger sample of patients.

6. Conclusions

The combined use of MRI measures and clinical findings for the diagnosis of early RA holds considerable promise for improving the accuracy of early diagnosis of RA and may be effective in facilitating earlier use of interventions for this progressive disease.

The increasing use of MRI for the diagnosis of RA may come at cost, and therefore inappropriate use and overuse should be avoided. Nonetheless, MRI provides a great advantage over conventional radiography in terms of quantitatively identifying inflamed synovium tissues with a high degree of sensitivity. The incorporation of MRI findings together with clinical findings into the criteria for the diagnosis of early RA demonstrates excellent diagnostic performance.

Early and accurate diagnosis, which can be achieved through the introduction of our proposed criteria, can prevent prolonged anxiety and suffering in RA patients who live with persistent joint pain and disability. Furthermore, early diagnosis may lead to a number of social benefits including enabling patients an earlier return to work and to active lives through early treatment.

We believe our novel diagnostic criteria for early RA integrated with MRI findings will contribute substantially to daily clinical practice as well as to the epidemiology and basic science of RA.

Disclosure statement

The authors have declared no conflicts of interest.

Patient consent

The authors have declared in the published articles that the informed consent was obtained from the patients.

Ethical approval

The authors have declared in the published articles that the protocols were approved by the institutional review board.

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