

# Specificity versus sensitivity: how rheumatoid arthritis diagnosis has changed over the last 10 years

*“The diagnosis of rheumatoid arthritis is mainly clinical, supported by laboratorial and imaging findings. It is relatively easy to make a diagnosis of rheumatoid arthritis in the typical patient presenting with insidious onset symmetric polyarthritis ... However, in less characteristic presentations, the diagnosis of early rheumatoid arthritis can be challenging.”*

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Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that mainly affects diarthrodial joints. It is associated with significant morbidity and, in particular, irreversible joint damage and functional disability, and increased mortality. The diagnosis of RA is mainly clinical, supported by laboratorial and imaging findings. It is relatively easy to make a diagnosis of RA in the typical patient presenting with insidious onset symmetric polyarthritis, involving predominantly the wrists and small joints of the hands and feet with detectable rheumatoid factor (RF) in serum and with x-rays showing periarticular osteopenia with or without decreased joint space or erosions. However, in less characteristic presentations, the diagnosis of early RA can be challenging. This is true, for example, in older patients with a clinical picture of polymyalgia-type symptoms or remitting seronegative symmetrical synovitis with pitting oedema syndrome, in acute presentations with a predominance of systemic symptoms or in patients presenting with a monoarthritis or with an asymmetric oligoarthritis.

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Early diagnosis of RA and prompt initiation of standard disease modifying antirheumatic drugs and biologic agents has been shown to improve prognosis, by effectively controlling symptoms and slowing or halting the disease progression [1–3]. Thus, a new paradigm of aggressive treatment of early RA has been proposed, but the treatments available are not devoid of side effects. Therefore, there is a need to try to improve the

sensitivity and specificity of the tools used to make an early diagnosis of RA in clinical practice. The focus is on the ability to distinguish between patients with self-limiting, persistent nonerosive and persistent erosive arthritis.

There are no widely validated diagnostic criteria for RA to be used in clinical practice; a few sets have been proposed [4,5]. The main criteria used in RA are the American College of Rheumatology (ACR) or American Rheumatism Association 1987 revised criteria [6]. Although they were developed as classification criteria, they are widely used for diagnosis. However, classification criteria are developed for clinical research or for epidemiological studies; they are designed to distinguish a patient with RA from patients with other diseases in a rheumatology clinic or from a large population including healthy subjects. They allow classifying patients with established disease with high specificity but are not so frequently helpful in early disease classification. The 1987 revised ACR criteria for the classification of RA have high sensitivity and specificity in established RA but are less sensitive in early RA [7]. This is due, at least in part, to the fact that some of the criteria are rarely fulfilled in the first year after the onset of RA. A meta-analysis by Banal and colleagues, described a pooled sensitivity and specificity of the ACR set of criteria (when compared with expert opinion) of 77% (68–84%) and 77% (68–84%) in the list format versus 80% (72–88%) and 33% (24–43%) in the tree format in early arthritis (<1 year duration) [7]. In established disease, pooled sensitivity and specificity were 79% (71–85%) and 90% (84–94%) versus 80% (71–85%) and 93% (86–97%) respectively for list and tree format [7]. The authors concluded that the specificity of the classification criteria in early disease is low and this set of criteria should not be used as a diagnostic tool.

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In the last 10 years, early diagnosis of RA has been made easier by the use of tests to detect antibodies to cyclic citrullinated peptides (anti-CCP) in the serum and by increased usage of musculoskeletal imaging techniques, in particular, ultrasound (US) and MRI.

Anti-CCP have demonstrated good sensitivity (mean from various studies 68%) and high specificity (mean from various studies 95%) in the diagnosis of RA, including early disease [8]. They are also associated with bone erosions and influence prognosis, which helps in identify patients that will potentially benefit from early aggressive therapy [9,10]. Due to their high specificity, anti-CCP are useful in the diagnosis of early RA, both in patients seronegative and seropositive for RF. In one study, anti-CCP had a specificity of 92% and a sensitivity of 60% in RF-negative patients [10].

Several authors have called for the inclusion of anti-CCP in the revised classification criteria for RA. This addition may improve specificity owing to the fact that anti-CCPs predict the development of RA with a high probability [11,8,12]. Zhao and colleagues modified the ACR criteria by adding anti-CCP or substituting anti-CCP for rheumatoid nodules or both rheumatoid nodules and joint erosions [12]. Substituting anti-CCP for rheumatoid nodules increased sensitivity in the diagnosis of early disease without decreasing specificity (87 and 95.6%, respectively for early disease; 94.6 and 92.8%, respectively, for all patients). When both rheumatoid nodules and joint erosions were substituted by anti-CCP in the diagnosis of early RA, sensitivity was increased but specificity decreased [12,13].

Early RA is characterized by proliferative and hypervascularized synovitis, resulting in bone erosion, cartilage damage and irreversible joint destruction. Modern imaging modalities such as MRI and US have had major developments during the past 10 years in the musculoskeletal field. They allow more certainty in an early diagnosis of RA by documenting early joint damage (that may still not be detectable by conventional radiography) and by detecting subclinical disease in multiple joints. Bone erosions often develop during the first 2 years of the disease and within the first 6 months in patients with aggressive disease [14]. MRI is more sensitive than US in the detection of bone erosions and much more sensitive than conventional radiography. Both MRI and US are more sensitive than clinical assessment for detecting synovitis, even in small peripheral joints. They help in distinguishing patients with polyarthritis from those with oligoarthritis and, in cases of polyarthritis, they help in assessing whether the

typical joints are involved. Moreover, MRI has a strong negative predictive value in patients with a clinical suspicion of early RA when it shows no evidence of synovitis of the small peripheral joints [15]. Some data suggest that some alterations, in particular, bone marrow oedema (only detected by MRI), may predict future bone damage. Musculoskeletal imaging may also be useful in making the distinction between early RA and other joint diseases, including early psoriatic arthritis [15].

Abnormalities in early RA include synovitis, tenosynovitis, bone marrow oedema, bone erosions and bursitis [15]. The injection of gadolinium allows for distinction between synovial proliferation and joint effusion. Only MRI is able to identify the presence of bone marrow edema. These changes are thought to precede the development of bone erosions. Bone marrow edema strongly correlates with the erosive progression of the disease [16–18].

Sensitive US imaging using gray-scale and power Doppler is able to identify both subclinical synovitis and early erosive disease preceding changes seen on conventional radiography [19,20]. In contrast to MRI, there are no limiting factors such as the presence of pacemakers, metal or claustrophobia and all of the peripheral joints can be examined as often as necessary in a shorter period of time. US, including power Doppler, was found to have a major impact on the certainty of arthritis persistence at 12 months in seronegative patients presenting with an inflammatory arthritis with a duration of less than 12 weeks. In seronegative patients with one or more clinical conventional features of inflammatory arthritis (increased C-reactive protein, one or more swollen hand joint, x-ray erosion), US raised the probability of persistent arthritis at 12 months from 2–30 to 50–94%. It was of no value in patients with RF and/or anti-CCP as all these patients developed RA [21].

In conclusion, in the last 10 years, the development and increasing availability of tests for anti-CCP antibodies, together with musculoskeletal imaging techniques with increased sensitivity and specificity, have contributed to greater certainty in making a diagnosis of RA early in the disease course. These methods can also have a prognostic value and therefore help in choosing patients that will potentially benefit more from early aggressive treatment. In a joint European League Against Rheumatism (EULAR)–ACR initiative, new criteria for RA, which include more patients with early disease and anti-CCP antibodies as new markers, are being developed.

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**Bibliography**

- Lard LR, Visser H, Speyer L *et al.*: Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. *Am. J. Med.* 111(6), 446–451 (2001).
- Nell VP, Machold KP, Eberl G, Stamm TA, Uffmann M, Smolen JS: Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. *Rheumatology (Oxford)* 43(7), 906–914 (2004).
- Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF *et al.*: Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. *Arthritis Rheum.* 52(11), 3381–3390 (2005).
- Visser H, le Cessie S, Vos K, Breedveld FC, Hazes JMW: How to diagnose rheumatoid arthritis early: a prediction model for persistent (erosive) arthritis. *Arthritis Rheum.* 46(2), 357–365 (2002).
- Van de Helm-van Mil AHM, le Cessie S, van Dongen H, Breedveld FC, Toes REM, Huizinga TWJ: A prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: how to guide individual treatment decisions. *Arthritis Rheum.* 56(2), 433–440 (2007).
- Arnett FC, Edworthy SM, Bloch DA *et al.*: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum.* 31(3), 315–324 (1988).
- Banal F, Dougados M, Combescure C, Gossec L: Sensitivity and specificity of the American College of Rheumatology 1987 criteria for the diagnosis of rheumatoid arthritis according to disease duration: a systematic literature review and meta-analysis. *Ann. Rheum. Dis.* 68, 1184–1191 (2009).
- Avouac J, Gossec L, Dougados M: Diagnostic and predictive value of anti-cyclic citrullinated protein antibodies in rheumatoid arthritis: a systematic literature review. *Ann. Rheum. Dis.* 65, 845–851 (2006).
- Schellekens GA, Visser H, de Jong BAW *et al.*: The diagnostic properties of rheumatoid arthritis antibodies recognizing a cyclic citrullinated peptide. *Arthritis Rheum.* 43(1), 155–163 (2000).
- Quinn MA, Gough KS, Green MJ *et al.*: Anti-CCP antibodies measured at disease onset help identify seronegative rheumatoid arthritis and predict radiological and functional outcome. *Rheumatology (Oxford)* 45, 478–480 (2005).
- van Gaalen FA, Linn-Rasker SP, van Venrooij WJ *et al.*: Autoantibodies to cyclic citrullinated peptides predict progression to rheumatoid arthritis in patients with undifferentiated arthritis; a prospective cohort study. *Arthritis Rheum.* 50(3), 709–715 (2004).
- Zhao J, Liu X, Wang Z, Li Z: Significance of anti-CCP antibodies in modification of 1987 ACR classification criteria in diagnosis of rheumatoid arthritis. *Clin. Rheumatol.* 29, 33–38 (2010).
- Liao KP, Batra KL, Chibnik L, Schur PH, Costenbader KH: Anti-cyclic citrullinated peptide revised criteria for the classification of rheumatoid arthritis. *Ann. Rheum. Dis.* 67, 1557–1561 (2008).
- Combe B: Should patients with recent-onset polyarthritis receive aggressive treatment? *Joint Bone Spine* 71(6), 475–480 (2004).
- Boutry N, Moraes do Carmo CC, Flipo R-M, Cotton A: Early rheumatoid arthritis and its differentiation from other joint abnormalities. *Eur. J. Radiol.* 71, 217–224 (2009).
- McQueen FM, Benton N, Perry D *et al.*: Bone edema scored on magnetic resonance imaging scans of the dominant carpus at presentations predicts radiographic joint damage of the hands and feet six years later in patients with rheumatoid arthritis. *Arthritis Rheum.* 48(7), 1814–1827 (2003).
- Palosaari K, Vuotila J, Takalo R *et al.*: Bone oedema predicts erosive progression on wrist MRI in early RA – a 2-yr observational MRI and NC scintigraphy study. *Rheumatology (Oxford)* 45, 1542–1548 (2006).
- Haavardsholm EA, Boyesen P, Ostergaard M, Schildvold A, Kvien TK: Magnetic resonance imaging findings in 84 patients with early rheumatoid arthritis: bone marrow oedema predicts erosive progression. *Ann. Rheum. Dis.* 67, 794–800 (2008).
- Wakefield R, Gibbone WW, Conaghan PG *et al.*: The value of sonography in the detection of bone erosions in patients with rheumatoid arthritis: a comparison with conventional radiography. *Arthritis Rheum.* 43(12), 2762–2770 (2000).
- Wakefield RJ, Green MJ, Marzo-Ortega H *et al.*: Should oligoarthritis be reclassified? Ultrasound reveals a high prevalence of subclinical disease. *Ann. Rheum. Dis.* 63, 382–385 (2004).
- Freeston JE, Wakefield RJ, Conaghan PG, Hensor EMA, Stewart SP, Emery P: A diagnostic algorithm for persistence of very early inflammatory arthritis: the utility of power Doppler ultrasound when added to conventional assessment tools. *Ann. Rheum. Dis.* 69, 417–419 (2010).