# Pre-clinical Rheumatoid Arthritis - Identification and Implication

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## INTRODUCTION

It is now abundantly clear that time is of utmost essence in Rheumatoid Arthritis (RA) since irreversible damage occurs within the first few years of disease onset. The rate of progression in the first year of disease is significantly higher than in later years. Patients with longer duration of disease do not respond as well to treatment compared with patients with early disease. Apart from the clinical and radiological benefits, early DMARD therapy also favorably influences mortality, which has been shown to be lower in patients who present early compared to those who present late.[1,2] This has led to the concept of 'window period' in RA- a period of time early in course of RA when the disease is more responsive to therapy. Other reasons that have been advanced in favour of early recognition and treatment of RA include:[3]

1. Nothing is gained by waiting. More than 90% of RA patients eventually receive a second line drug in the first 3 years. So deferring the decision on therapy does not lead to *avoidance* of drugs, it just *delays* the introduction.

2. The inflammation is at its peak at disease onset.

3. The final functional status is determined by the duration of symptoms before initiation of therapy.

4. Patients in early disease are relatively well and, therefore, more likely to better tolerate drugs.

In light of the arguments advanced above, the paradigm in RA has shifted to 'early' disease identification. I shall be discussing the concept of early RA before talking about pre-clinical RA. It is appropriate to add a caveat here- patients in India often present late. Treatment should not be denied to late presenters. It is never too late to start treatment, though earlier is better.

## EARLY RA- THE TRANSITION FROM 1987 CLASSIFICATION CRITERIA TO 2010 CRITERIA

The 1987 ARA criteria for RA were developed using cases and controls attending hospital clinics.[4] The patients included had longstanding disease (mean disease duration 7.7 years). These criteria (Table 1) incorporated the typical features of symmetric inflammatory polyarthritis and did away with the categories of definite, possible and probable. These criteria were simple to use and required only one laboratory test, rheumatoid factor, and only one set of radiographs, posteroanterior view of hands and wrists. The 1987 criteria were widely adopted all over the world and paved the way for uniformity in case inclusion. These criteria had a sensitivity of 91-94% and specificity of 89% when comparing RA with non-RA. These criteria served their purpose admirably well for several years. Over a period of time a few shortcomings became apparent. The first was the poor performance characteristics of 1987 criteria in early RA. This coincided with a shift in the focus in RA from 'established' to 'early disease'. Two things have fuelled interest in early RA: an explosion of targeted biologic therapies and the growing realization that time to treat is a key driver of outcome. When applied to early inflammatory polyarthritis, the 1987 ARA criteria for RA had a low ability to discriminate between patients who developed persistent, disabling, or erosive disease and those who did not.[5] Studies have shown that the 1987 ACR criteria, when applied to early RA, have a sensitivity ranging from 40 to 90% and specificity from 50 to 90%. The second drawback of 1987 criteria was the inclusion of radiographic features. The radiologic criterion of erosions is encountered in a very small proportion (~13%) of patients in the first 3 months of disease onset limiting its utility.[6] However, as many as 50-70% patients may have erosive disease by 2 years thereby underscoring the importance of early treatment.[7]

Over the past few years anti-citrullinated peptide antibodies (ACPA), also known as anti-cyclic citrullinated peptide antibodies (anti-CCP), have emerged as an important serologic marker for RA. These predict erosive disease and are poor prognostic markers.[8] These antibodies obviously do not find mention in the 1987 criteria which were formulated prior to the advent of ACPA. The latest attempt in classification, the 2010 criteria, aim to rectify many of these shortcomings.

The 2010 criteria emerged as a joint initiative of American and European workers and were published simultaneously in the ACR and EULAR journals.[9,10] The major aim was to permit early identification of poor prognosis arthritis much before the classic features of

| Table 1: The 1987 Criteria for RA |
|---|
| 1. Morning stiffness |
| 2. Arthritis in 3 or more joints |
| 3. Arthritis of hand joints |
| 4. Symmetric arthritis |
| 5. Rheumatoid nodules |
| 6. Rheumatoid factor |
| 7. Radiographic changes |

| Table 2: The 2010 ACR/EULAR classification criteria for rheumatoid arthritis | |
|---|---|
| **Domain: Joint involvement** | **Domain: Duration of synovitis** |
| 1 large joint (0 points) | Less than 6 weeks (0 points) |
| 2-10 large joints (1 point) | 6 weeks or longer (1 point) |
| 1-3 small joints (2 points) | |
| 4-10 small joints (3 points) | |
| >10 joints [at least 1 small joint] (5 points) | |
| **Domain: Serology** | **Domain: Acute phase reactants** |
| RF/CCP negative (0 points) | Normal ESR/CRP (0 points) |
| RF or CCP positive at low titer, <3 times ULN (2 points) | Abnormal ESR/CRP (1 point) |
| RF or CCP positive at high titer, defined as >3 times ULN (3 points) | |

ULN= upper limit of normal; 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; "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.

florid disease became apparent. These criteria, listed in Table 2, are meant to be applied to patients newly presenting with undifferentiated inflammatory synovitis. These incorporate factors that best discriminate between those patients who are and those patients who were not at high risk for persistent and/or erosive disease—this being the appropriate current paradigm underlying the disease construct 'RA'.[9,10] The gold standard for diagnosis of RA was methotrexate initiation by the physician. This was used to identify clinical and laboratory variables which were then subjected to consensus-based, decision science informed approach leading to the evolution of a scoring system. The criteria were satisfied in 87-97% of the patients where physicians instituted methotrexate.

In the new criteria set, classification as 'definite RA' is based on the confirmed presence of synovitis in at least one joint, absence of an alternative diagnosis better explaining the synovitis, and achievement of a total score of 6 or greater (of a possible 10) from the individual scores in four domains: number and site of involved joints (range 0–5), serological abnormality (range 0–3), elevated acute-phase response (range 0–1) and symptom duration (two levels; range 0–1). These criteria have done away with features that are typical of late disease, namely symmetry, rheumatoid nodules and radiographic changes. There is no longer insistence on a disease duration of 6 weeks. The criterion of morning stiffness has been dispensed with and the serologic marker of ACPA included. This practically means that a patient with 1 small joint involvement (2 points), high levels of RF/ACPA (3 points) and high ESR/CRP (1 point) can be classified as RA even on day 1 of symptoms. These criteria have a provision whereby some patients can be classified as RA even if they do not fulfill the criteria. These include patients with erosive disease typical of RA with a history compatible with prior fulfillment of the 2010 criteria and patients with long-standing disease, including those whose disease is inactive (with or without treatment) who, based on retrospectively available data, have previously fulfilled the 2010 criteria.

Over diagnosis, however, remains an area of concern with the 2010 criteria. More patients whose disease eventually resolved without ever requiring DMARD were classified at baseline as RA according to the 2010 criteria than with the 1987 criteria (8%) vs. 2%; p=0.01) in a study from UK.[11] Similar concerns have been voiced from India especially in context of infectious arthritis where patients with Chikungunya arthritis may easily satisfy the 2010 criteria.[12] Clearly, the quest for early detection and ideal classification criteria of RA is far from over. The 2010 criteria for RA represent a significant advance but may need refinement in different populations and as new knowledge becomes available.

## EARLY VERSUS ESTABLISHED RA
The cut offs between 'early' and 'established' RA have progressively decreased over the years. 'Early RA' is traditionally defined as a disease duration less that 1 year while 'established RA' refers to a disease duration >1 year. The recent ACR recommendations for management of RA, however, peg the limit for early RA as 6 months.[13]

## EARLY RA TO PRE-CLINICAL RA
Moving a step forwards, what is dubbed as 'early RA' by clinicians is actually an 'immunologically advanced' disease where immunological events precede clinical events by years to decades. The advent of clinical disease, even in early stages, represents the culmination and not the beginning of events. There is, thus, considerable interest in picking up RA in its pre-clinical stage when the disease is immunologically nascent. A plethora of terms have been used to describe the earliest phases of RA. These include pre-RA, preclinical RA, autoantibody positive arthralgia, early RA, very early RA, and extremely early RA. In order to develop and promote consistency in this field, the EULAR (European League against Rheumatism)
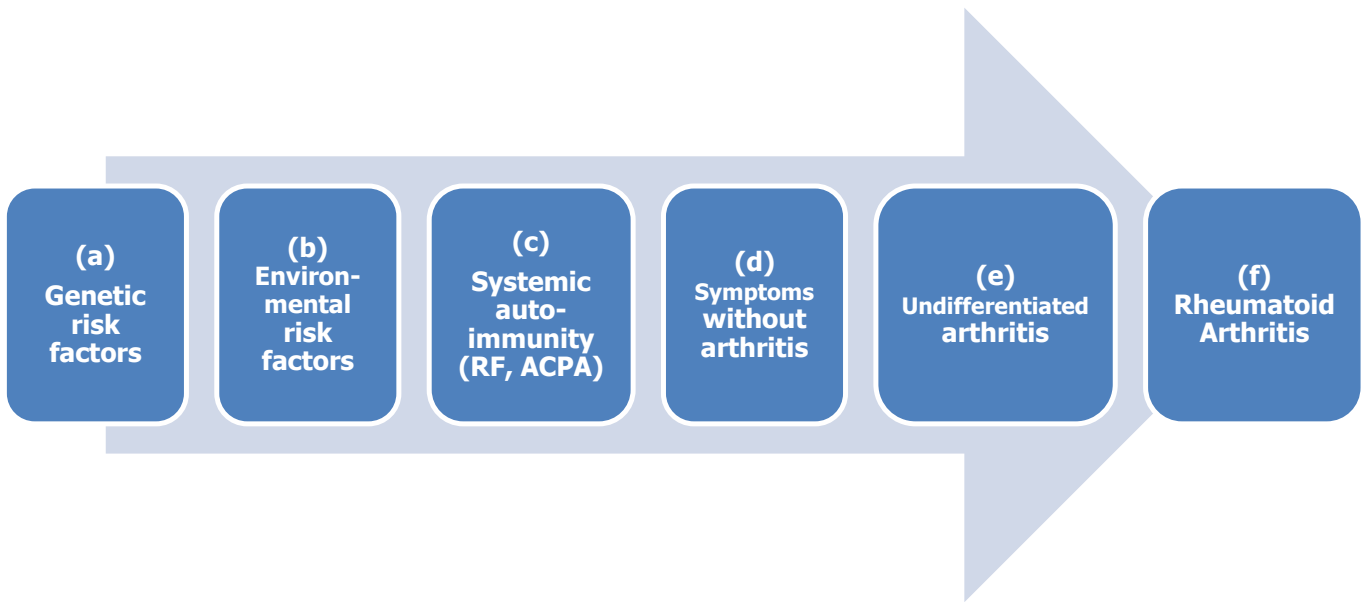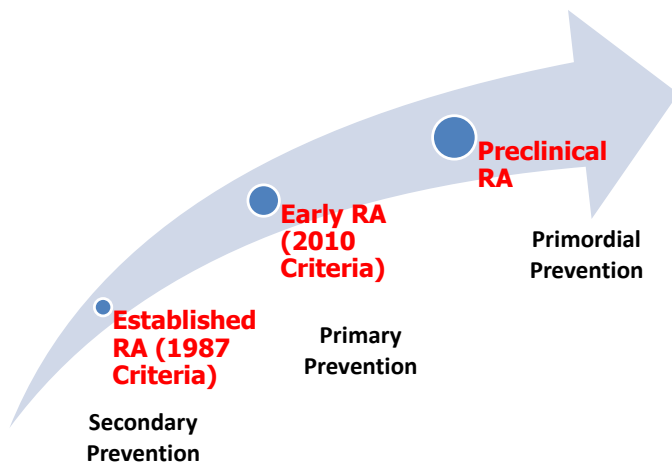
**Fig. 1: Pre-clinical RA to RA**



**Fig. 2: Evolution of concepts over time**

Standing Committee for Investigative Rheumatology established the Study Group for Risk Factors for RA.[14]

It was recommended (Figure 1) that, in prospective studies, individuals at risk of developing RA would be described as having:

a.  Genetic risk factors for RA

b.  Environmental risk factors for RA

c.  Systemic autoimmunity associated with RA

d.  Symptoms without clinical arthritis

e.  Unclassified arthritis

f.  RA

The term 'arthritis' is used to denote clinically apparent soft tissue swelling or fluid (not bony overgrowth alone). These phases can exist in combination as in some patients who have autoantibodies and arthralgia. Thus (a) to (e) can be used in a combinatorial manner for example, an individual may have (a)+(b), or (a)+(b)+(c) or (a)+(b)+(d), etc. The prefix 'pre-RA with:' can be used before any/

any combination of (a) to (e) but only to describe retrospectively a phase an individual was in once it is known that they have developed RA. Several variations are possible in the proposed schema. Not all individuals may pass through all phases. Seronegative patients may develop arthritis without autoantibodies. The order may also change like some patients develop rheumatoid factor after the onset of arthritis.[15]

It needs to be reiterated that pre-clinical RA is a retrospective label in a patient who has developed RA. For example a patient who tests positive for rheumatoid factor and anti-citrullinated peptide antibodies in the year 2012 but develops RA in 2016 would not be designated pre-RA in 2010. It is only in 2016 that one would apply the term pre-clinical RA to the period of 2010-2016. The term pre-clinical RA cannot and should not be used prospectively. Evolution is not inevitable and resolution is well known. Some patients may never progress to clinical disease.

Research is currently centring on genetic predisposition and environmental risk factors in RA- things that may lend themselves to manipulation and modulation.[16,17] Genome wide association study analyses have identified various RA-associated genes, such as HLA-DRB1, PADI4, PTPN22, TNFAIP3, STAT4 and CCR6.[16] However, the contribution of these individual risk loci to the development of RA is variable. Environmental risk factors include smoking which increases the risk of ACPA-positive RA. A detailed exposition of these is beyond the scope of this introductory article.

## CONCLUSIONS

RA is a 'time critical illness' where early treatment fetches the best dividends. Pre-clinical RA is an exciting concept that stimulates identification of preclinical disease. It cannot and should not be used as a prospective clinical label. It may only be applied as a retrospective designation. As our ability to predict disease improves, the pendulum

in future will likely shift from control to prevention in the disease that is RA.

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