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Letter to Editor

# Pre-Rheumatoid Arthritis State

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## LETTER TO EDITOR

Rheumatoid arthritis (RA) is the most common inflammatory arthritis which presents itself as a chronic progressive systemic autoimmune disease with the hallmark of chronic erosive polyarthritis [1]. We introduced a new set of criteria for early diagnosis of RA, called Iran criteria [2]. The main purpose of developing such criteria is to begin RA treatment before irreversible changes in the joints are established. But here, we would like to explain and do define individuals who are not affected by RA currently, but are vulnerable to progress to RA in the future; this condition is called pre-RA state. Hence, based on documented risk factors for RA we designed a scoring system to characterize subjects with the pre-RA state (Table 1). We believe that using this scoring system would result in less aggressive treatments and better outcomes, as well as avoidance of unnecessary administration of potentially toxic medications for those at lower risk of pre-RA state.

The following terms are used in the literature to explain different aspects of RA which need further clarification [3-6]:

- Subclinical RA
- Early RA
- Atypical RA
- Pre-RA

Subclinical RA is a type of RA in which articular synovitis is subclinical. In other word, physician cannot clinically detect synovial swelling by just physical examination and MRI or ultrasound is required to find pathological changes of the synovium. Early RA refers to the status of disease detected within the first 6 months from initial clinical presentation. Atypical RA has, as its name implies, unusual or atypical clinical pictures such as palindromic rheumatism, adult-onset Still's disease, arthritis robustus and chronic monoarthritis. Finally, pre-RA is a state of "nodisease". It is a state in an individual that has the potential of progression to frank RA. However, pre-RA state is sometimes mistaken by clinicians with the other above mentioned items.

The most important serologic markers of RA are rheumatoid factor (RF) and anti-citrullinated protein antibody (anti-CCP, ACPA). High titer of each one or positivity of both (RF and ACPA) are all serologoic hallmarksin the diagnosis of RA; however, the specificity of ACPA for RA is more than 95% [7,8]. It is well documented in the literature that the serum levels of RF andACPA increase years prior to establishment of RAdiagnosis [9,10]. For example, in a study by Nielen *et al*, RF and ACPA were positive for a median of 2 years and 4.5 years respectively prior to the time when diagnosis of RA was made[10]. Also, simultaneous presence of RF and ACPA in the serum of an individual was highly specific for development of future RA [9]. As a result, in the serologic subset of this scoring system, RF and ACPA were included.

Considering the genetic background, it is estimated that the genetic contribution to RA ranges between 30% and 60% [1,12]; the presence of HLA-DR4 allele in Caucasians is associated with a relative risk of almost 4 for RA[13]. Silman *et al* [14] studied the incidence of RA among individuals from multi-case RA families and showed that a positive family history of RA is associated with higher risk of future RA. Hence, in genetic background we included HLA-DR4 positivity and positive family history of RA.

Smoking, as the most important environmental factorfor RA, is associated with the risk of developing RA with an odds of 3 times for future RA in smokers compared with non-smokers [15,16].

**Table 1:** Proposed scoring system for pre-rheumatoid arthritis state.

| **Pre-Rheumatoid Arthritis State** [a, b] | **Points** |
|---|---|
| **Genetic background** | **Up to 2 points** |
| Positive HLA-DR4 | 1 point |
| Positive family history | 1 point |
| **Serology markers** | **Up to 2 points** |
| Positive RF or ACPA | 1 point |
| Positive RFand ACPA | 2 points |
| High titer RF or ACPA | 2 points |
| **Smoking** | **1 point** |

[a] At least 2 points out of 5 is required to define pre-RA state

[b] Entry criteria:

- No history of articular inflammatory pain and/or swelling
- No history of prolonged morning stiffness (i.e., ≥ 1 hour)
- No arthritis (synovitis) on physical examination

HLA: human leukocyte antigen; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibody.

As presented in Table , pre-RA state is a condition when an individual satisfies two points out of the total5 points while simultaneously the entry criteria are fulfilled. The target population to be assessed for pre-RA state is individuals with at least one of the above mentioned risk factors (positive HLA-DR4, positive family history for RA, positive RF, positive ACPA, and smoking); every person of this target population can be eligible forscoring system of pre-RA state. However, this understanding must be taken into consideration that it is possible that a person with pre-RA state does not progress to RA while a person without pre-RA state progresses to RA; though, a higher score can be associated with a higher risk of developing future RA.

The main purpose of this letter is to propose a guideline for predicting the risk of developing future RA, based on our experience and the findings in the literature. This guideline may power-up the Iran criteria for early diagnosis of RA by defining pre-RA state individuals who may further satisfy Iran criteria.

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