The new criteria for classification of rheumatoid arthritis: what we need to know for clinical practice

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A R T I C L E   I N F O

Article history:
Received 4 December 2010
Received in revised form 19 December 2010
Accepted 22 December 2010
Available online 26 January 2011

Keywords:
Rheumatoid arthritis
Classification criteria
Anti-citrullinated peptide autoantibodies
Bayesian reasoning
Likelihood ratio
Sensitivity and specificity

A B S T R A C T

The new criteria for classification of Rheumatoid Arthritis have been recently released. They incorporate the anti-Citrullinated Protein antibody testing and the other classic criteria in a score system (the diagnosis of definite rheumatoid arthritis is made by a total score ≥6). These criteria try to meet the pressing needs to gain sensitivity in early disease. Symptoms, elevated acute-phase response, serologic abnormality, joint involvement were all considered for scoring after confirming the presence of synovitis in at least 1 joint in the absence of an alternative diagnosis that better explains the synovitis. However, no sensitivity and specificity has been showed. Moreover, Area Under Curve of the Receiver Operating Characteristic curves (a measure of performance of the test) was not optimal in almost two of the three studied cohorts. On the contrary, the old criteria of the American College of Rheumatology had been tested to calculate sensitivity and specificity. Moreover, sensitivity and specificity of anti-citrullinated peptide auto-antibodies are available for clinical reasoning based on pre-test and post-test probabilities of the disease. The use of likelihood ratios applied to both the old criteria and anti-citrullinated autoantibodies could help clinicians to effectively manage early arthritis patients implementing Bayesian reasoning. Here, we tried to explain the methodology applied to the body of knowledge currently available about rheumatoid arthritis for diagnostic decision making based on the Bayesian approach.

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considered by the above-mentioned old American College of Rheumatology criteria. The importance of anti-Citrullinated Peptide autoantibodies consists in the best specificity in comparison with Rheumatoid Factor in patients affected by early Rheumatoid Arthritis [2,3]. Recently, a systematic review has been published on accuracy of anti-Citrullinated Peptide autoantibodies for diagnosing early RA [4].

This analysis of 151 studies showed that sensitivity and specificity were 57% (95% Confidence Intervals, 51% to 63%) and 96% (93% to 97%), respectively (analysis refers only to 15 relevant cohort studies). Thus, sensitivity and specificity of the old American College Rheumatoid arthritis criteria are available to us much the same data for anti-Citrullinated Peptide antibodies. How can this information be utilized for clinical practice? Sensitivity and specificity are stable characteristic of a test. The Bayes’ theorem demonstrates that the Likelihood Ratio of both a positive and negative test allows to compute posterior probability using different “a priori” probabilities [5]. In a few words Likelihood Ratios are sufficiently stable characteristics of a test with more informative power than sensitivity and specificity (usually cryptic information for the clinician). Indeed, sensitivity and specificity are useful parameters when they reach values near 100% (a negative result of a test with sensitivity of 100% permits to exclude a disease while a test with specificity of 100% is highly indicative of disease when it results positive). On the contrary, Likelihood Ratio of a positive test and of a negative one are always informative and easily usable. Generally, a positive Likelihood Ratio > 15 suggests a good probability to diagnose a disease while a negative Likelihood Ratio < 0.15 suggests a good probability to exclude a disease [6]. However, Likelihood Ratios have another very interesting characteristic: their values can be multiplied between or among Likelihood Ratios for different tests. For example, if we have two independent tests for a disease (anti-Citrullinated Peptide antibodies and the old American College of Rheumatology criteria are the case) we can multiply the positive Likelihood Ratios by themselves. The old American College of Rheumatology criteria have a positive Likelihood Ratio of 8.54 and a negative Likelihood Ratio of 0.07 (computed from the original sensitivity and specificity values of the American College of Rheumatology criteria). Anti-Citrullinated Peptide antibodies have a positive Likelihood Ratio of 14 and a negative Likelihood Ratio of 0.45 (data computed from the above-mentioned systematic review). It is obvious that none of the two diagnostic tests is easily usable in clinical practice for diagnosing or excluding Rheumatoid arthritis. However if we combine their values (positive Likelihood Ratios = 8.54×14 = 120; negative Likelihood Ratios = 0.07 × 0.45 = 0.031) Likelihood Ratios (positive and negative) became highly informative for an unexperienced physician as well. Even if we consider their 95% Confidence Intervals remain highly informative and usable in different clinical practice settings (e.g. general practitioner setting or a rheumatologic outpatient clinic). Moreover, the use of combined information simplifies diagnostic utilization of anti-Citrullinated Peptide autoantibody cut-off values. Indeed, Pietrapertosa et al [7], in another recent paper, have correctly pointed out the importance of different cut-off values to modify Likelihood Ratios according to Sackett lessons [6]. Indeed, different cut-off values can generate the so-called S’Pen (Sensitivity In: high values for the highest specificity, consequently to diagnose disease) and SNout (Sensitivity Out: low values for the highest sensitivity, consequently to exclude disease). Indeed, high anti-Citrullinated Peptide autoantibody cut-off value (>15.0 or >30.0 U/mL, that correspond to positive Likelihood Ratios of 42 and infinity, respectively) could became very useful to diagnose early RA much precociously, that is, when both American College of Rheumatology criteria cannot be applicable (onset of symptoms <6 week) or only one criterion is lacking to get a positive result.

However, as shown above, we can simply use two diagnostic test (anti-Citrullinated Peptide autoantibodies and the old American College of Rheumatology criteria) to easily reach diagnostic values of positive or negative Likelihood Ratios.

Archibald Cochrane claimed needs for synthesis caused by information overload [8]. The Cochrane network systematic reviews have become the standard to summarize information toward knowledge growth [9]. Now, we also need to organize information to generate usable knowledge using both the available methodology from clinical epidemiology and clinical research data [10]. We believe that what we have explained in this manuscript goes toward this direction. Scientific community and prominent journals oriented to readership of clinical practitioners must continue to provide knowledge support for ease clinical practice implementation. We strongly claim that scientific knowledge had to be based on facts and not on faith.

Learning points

- The new criteria for classification of Rheumatoid Arthritis incorporate the anti-Citrullinated Protein antibody testing and the other classic criteria in a score system. The diagnosis of definite rheumatoid arthritis is made by a total score ≥6. These criteria might be more useful for classification of patients with early arthritis disease. However, no sensitivity and specificity has been showed. Moreover, Area Under Curve of the Receiver Operating Characteristic curves (a measure of performance of the test) was not optimal in almost two of the three studied cohorts.
- On the contrary, the old criteria of the American College of Rheumatology had been tested to calculate sensitivity and specificity. Moreover, sensitivity and specificity of anti-citrullinated peptide auto-antibodies are available for clinical reasoning based on pre-test and post-test probabilities of the disease. The use of likelihood ratios (see the text) applied to both the old criteria and anti-citrullinated autoantibodies could help clinicians to effectively manage early arthritis patients implementing Bayesian reasoning.
- Less than four of the old classification criteria and negative anti-citrullinated peptide autoantibodies allow to exclude rheumatoid arthritis.
- Even If a patient had not sufficient probability of disease (below four of the old criteria) but the anti-citrullinated peptide autoantibodies >15 U/mL, the diagnosis of rheumatoid arthritis could be set.
References


