Low Level (Below Cutoff) of Anti-Cyclic Citrullinated Peptide Test Results in Diagnosis of Rheumatoid Arthritis in a High-risk Population

To the Editor:

We read with interest the recent article by Chibnik, *et al*[1]. The authors stated that the lower values of anti-cyclic citrullinated peptide (anti-CCP) should be regarded as a probable sign of preclinical rheumatoid arthritis (RA) and could be used as an additional tool in determining the course of action in treating the earliest potential symptoms of RA, especially in a high-risk population.

The Hospital for Rheumatic Diseases was the first specialized rheumatic disease hospital established in Korea. The patients consist largely of a high-risk population for RA in contrast to those in other institutions. With easy access to such a risk group, we were able to observe that the performance of the anti-CCP test changed as the cutoffs were lowered in the high-risk group.

The 5980 anti-CCP test results obtained from January to December 2007 at the hospital were analyzed. We used the Diastat anti-CCP test kit (Axis-Shield Diagnostics Limited, Dundee, UK), the identical commercial kit used by Chibnik, *et al*[1]. The tests were performed according to the procedures recommended by the manufacturer. We observed the changes in sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio of anti-CCP tests in RA diagnosis at each descending cutoff level by 1 U/ml from 5 U/ml down to 1 U/ml. The performance of anti-CCP tests for each threshold level is stated in Table 1. According to our results, we could obtain 91% sensitivity when adjusting the cutoff level down to 1 U/ml. In other words, with the new cutoff level, 11% of additional RA patients can be detected. Such a correlation between anti-CCP and RA allows us to assume that the patients with overt RA may also present with anti-CCP values that are lower than the cutoff level provided by the manufacturer. The presence of anti-CCP in the preclinical stage of RA has been reported in many studies, as in this article[2,3]. Also, similar results are being reported in various autoimmune diseases other than RA[4,5].

We suggest a new adjustment of cutoff levels for positive anti-CCP results to be lower than the current cutoff level, since we now understand the possibility of underdiagnosing 11% of additional overt RA with the current cutoff level. We also insist on an important role of the anti-CCP results at below the cutoff level in reflecting preclinical stages of future RA patients who do not meet the American College of Rheumatology criteria. The reduced specificity may be compensated for with the aid of the antiperinuclear factor test or the autoimmune target test for RA-specific antibodies such as anti-MTOC and anti-GiM[6].

Table 1. Diagnostic performance of 5 cut-off levels of anti-cyclic citrullinated peptide test for the diagnosis of rheumatoid arthritis.

	Level (U/ml)				
	> 1	> 2	> 3	> 4	> 5
Sensitivity (%)	91	86	83	82	80
Specificity (%)	46	68	74	78	82
PPV (%)	44	55	59	63	67
NPV (%)	91	91	91	90	90
PLR	1.69	2.71	3.20	3.74	4.35
NLR	4.88	4.78	4.45	4.26	4.10

PPV: positive predictive value, NPV: negative predictive value, PLR: positive likelihood ratio, NLR: negative likelihood ratio.

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