Anticitrullinated protein antibodies: taking into account antibody levels improves interpretation

Hensvold *et al*[1] reported on the discriminatory capacity of anticitrullinated protein antibodies (ACPA) for diagnosing rheumatoid arthritis (RA).[1] A major strength of the study is that it was performed in a population setting and that a large number of controls (n=12 434) were included, thereby allowing a reliable estimate of the specificity of ACPA. The authors give detailed information on the diagnostic performance of anti-CCP2 antibodies (Euro-Diagnostica) for two cut-off points, namely the cut-off point recommended by the manufacturer and a cut-off point that is three times higher than the manufacturer's cut-off point. The latter high cut-off was defined in accordance to the European League against Rheumatism/American College of Rheumatology 2010 RA classification criteria.[2] The authors show that the positive likelihood ratio (LR) was higher for the high cut-off (LR=74) than for the cut-off point recommended by the company (LR=33).

It is increasingly recognised that the likelihood for disease increases with increasing antibody levels. Nevertheless, most laboratories report results using a single cut-off value. Reporting test-result interval specific LRs can give additional diagnostic depth to a lab result.[3] The LR (probability of a specific result in patients divided by the probability of the same result in controls) is independent of prevalence or pretest probability and can be applied for test result intervals. An LR >10 or <0.1 indicates a clinically significant difference in pretest to post-test probability.

The unique and large dataset presented by Hensvold *et al*[1] allows to deduce test-result interval specific LRs. The LRs are 0.35 (95% CI 0.28 to 0.43), 3.4 (95% CI 1.5 to 7.5) and 73.6 (95% CI 58.7 to 92.3) for an anti-CCP2 test result <25 AU/mL, between 25 and 75 AU/mL and ≥75 AU/mL, respectively. Only a small fraction (4%) of the patients (in total 156 patients with RA were included) had a low positive anti-cyclic citrullinated peptide antibody (CCP). The data are for prevalent RA at inclusion (based on table 2 in Hesvold *et al*[1]).

LRs can be used to estimate post-test probabilities for any given pretest probability.[3] Figure 1 illustrates the post-test probability as a function of pretest probability for different anti-CCP test result intervals (<25 AU/mL, between 25 and 75 AU/mL and ≥75 AU/mL). For example, for a pretest probability of 1.2% (which corresponds to the prevalence of RA in the general population), the post-test probability for RA is estimated to be 0.4%, 3.9% and 47.2% for an anti-CCP2 test result of <25 AU/mL, between 25 and 75 AU/mL and ≥75 AU/mL, respectively. For a pretest probability of 10% (which corresponds to a clinical presentation of a 50-year-old women presenting with a slightly elevated C-reactive protein (CRP) (10 mg/L) and recent onset undifferentiated arthritis with intermittent asymmetric tender and swollen small joints (n=5) of the hands (deduced from Van der Helm-van Mil *et al*[4])), the post-test probabilities are 3.7%, 27.2% and 89.1% for an anti-CCP2 test result of <25 AU/mL, between 25 and 75 AU/mL and ≥75 AU/mL, respectively.

The 2010 RA classification criteria assign a score of 2 for a low-positive ACPA and of 3 for a high-positive ACPA. Our analysis revealed that the difference in pretest to post-test probability is clearly higher for a high positive ACPA than for a low-positive ACPA (LR 73.6 vs 3.4). Future refinements of the RA classification criteria might give a higher relative weight to a high-positive ACPA compared with a low-positive ACPA. Studies are needed to evaluate whether cut-off points or ACPA assays are aligned between different manufacturers.

In conclusion, interpretation of ACPA must be done in the clinical context and in function of pretest probability and test characteristics. The work presented by Hensvold *et al*[1] allows to deduce reliable estimates of test result interval specific LRs of ACPA for RA. A high ACPA has a higher LR for RA than a low ACPA. Such knowledge helps to better interpret ACPA test results.

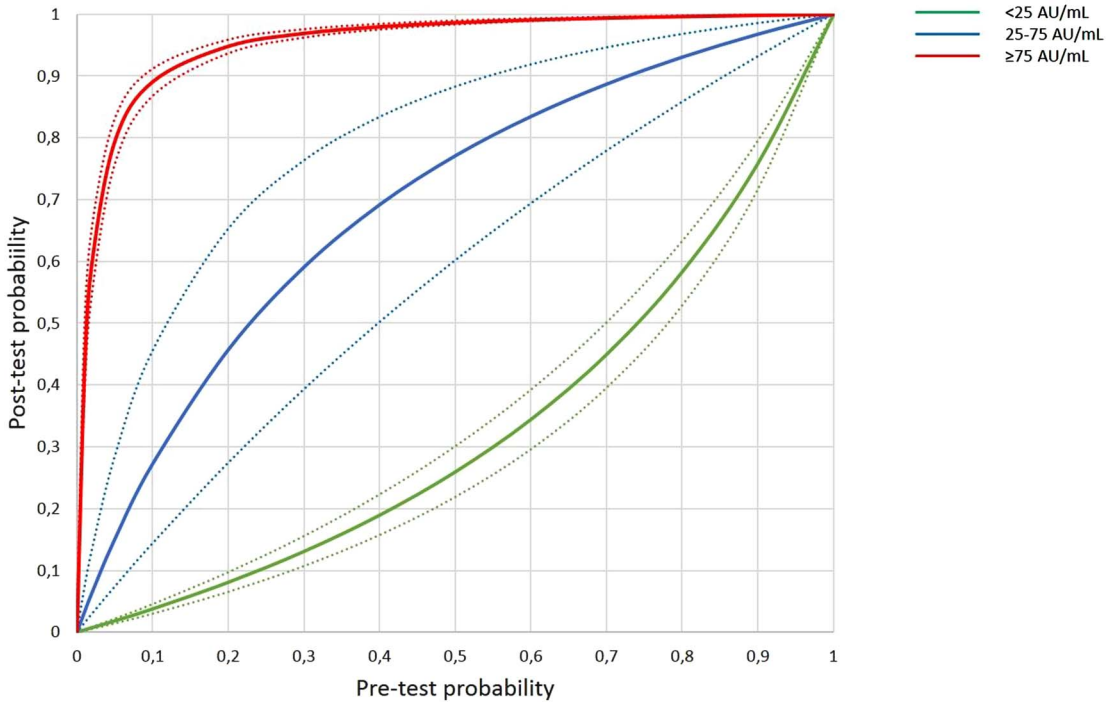

Figure 1 Post-test probabilities (with 95% CIs) as a function of pretest probability for different test result intervals (<25 AU/mL, between 25 and 75 AU/mL and ≥75 AU/mL).

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REFERENCES

1 Hensvold AH, Frisell T, Magnusson PK, *et al*. How well do ACPA discriminate and predict RA in the general population: a study based on 12 590 population-representative Swedish twins. *Ann Rheum Dis* 2017;76:119–25.
2 Aletaha D, Neogi T, Silman AJ, *et al*. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010;69:1580–8.
3 Bossuyt X. Clinical performance characteristics of a laboratory test. A practical approach in the autoimmune laboratory. *Autoimmun Rev* 2009;8:543–8.
4 van der Helm-van Mil AH, le Cessie S, van Dongen H, *et al*. A prediction rule for disease outcome in patients with recent-onset undifferentiated arthritis: how to guide individual treatment decisions. *Arthritis Rheum* 2007;56:433–40.