Review

The performance of anti-cyclic citrullinated peptide assays in diagnosing rheumatoid arthritis: a systematic review and meta-analysis

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ABSTRACT

Objective. *We assessed the ability of anti-cyclic citrullinated peptide (CCP) tests to diagnose rheumatoid arthritis (RA), comparing the effect of manufacturer assay type, study design (single- and two- gated) and duration of disease (early vs. established).*

Methods. *We searched seven databases for relevant diagnostic studies containing data on CCP tests in known or suspected RA patients. We used a bivariate model to produce summary estimates for test sensitivity, specificity, and positive and negative likelihood ratios. Summary Receiver Operating Characteristic (sROC) curves were derived to compare early versus established RA.*

Results. *83 studies were identified and included. For individual manufacturer tests there was considerable variation in both pooled sensitivity (range 67–83%) and specificity (range 90–96%) estimates. This heterogeneity was also observed when grouping studies into two-gated and single-gated designs. Study design and disease duration impacted on sensitivity, with single-gated study designs and early RA patients resulting in lower estimates than two-gated and established disease, respectively.*

Conclusion. *This review highlights the large number of CCP tests that are now commercially available and the considerable variation in their diagnostic performance. This variation, although partly influenced in this analysis by the study design (single-gated vs. two-gated), seems to have different levels of impact depending on the manufacturers. The Thermo Fisher Scientific EliA and Inova Diagnostics Quanta Lite (CCP2) tests showed the least between-study variation in sensitivity and specificity suggesting they have the most consistent diagnostic performance overall.*

Introduction

Rheumatoid arthritis (RA) is a common, chronic autoimmune systemic inflammatory disease affecting between 0.5% and 1% of the adult population worldwide (1, 2). The prevalence of RA increases with age and is more common in women than men. Although the exact cause of RA remains unknown it is thought that it results from environmental exposure in genetically susceptible individuals (3). Specifically, a recent review has highlighted the importance of genetic loci and polymorphisms that impact upon the expression of human leukocyte antigen (HLA) molecules, lymphocyte activation, and protein citrullination pathways (4).

RA is characterised by chronic inflammation of the synovial joints and typically presents as stiffness, pain and swelling in one or more joints, usually the small joints of the hands and feet. If left untreated the chronic inflammation will induce the formation of pannus tissue, leading to joint, cartilage, and bone destruction. Patients with RA have significantly reduced health related quality of life caused by the pain, fatigue and loss of bodily function associated with disease progression (5), increased risk of lung and cardiovascular disease (4) and premature mortality (6). It is vital that RA is diagnosed early in order to ensure the disease is effectively treated; health outcomes have been shown to improve as patients receive early aggressive disease-modifying anti-rheumatic drugs (DMARDs) (*e.g.* methotrexate) (5).

The American College of Rheumatology (ACR) classification criteria is con-

sidered the gold standard and accepted method of diagnosing RA. In 2010 the ACR and European League against Rheumatism (EULAR) developed a new classification criteria for RA to facilitate the identification of patients at an earlier stage of the disease process (7). The 2010 ACR classification criteria for RA are based on the confirmed presence of synovitis in at least one joint, absence of an alternative diagnosis that better explains the synovitis, and achievement of a total score of 6 or greater (out of a possible 10) using an algorithm with four categories: joint involvement, serology, acute phase and duration of symptoms (8).

The ACR criteria utilise the presence or absence of rheumatoid factor (RF), a high-affinity autoantibody directed against the Fc portion of immunoglobulin (9), as well as antibodies against peptides and proteins containing citrulline, a modified form of the amino acid arginine (10). In recent years studies have indicated that anti-citrullinated peptide antibodies (ACPA) tests, including anti-cyclic citrullinated peptide (CCP) tests, are more specific than RF for the diagnosis of RA (11, 12). Furthermore, anti-citrullinated peptide antibodies are thought to anticipate the clinical manifestation of RA by many years and could be useful biomarkers for predicting RA development (7, 13).

Four systematic reviews have previously been published on anti-CCP tests for diagnosing rheumatoid arthritis (11, 12, 14, 15). However, there has been no recent comprehensive review of the literature, in all relevant databases, to assess the performance of the wide range of anti-CCP tests available on the market to diagnose RA. Therefore here, we performed a new systematic literature review of the diagnostic accuracy of anti-cyclic citrullinated peptide (CCP) tests for RA diagnosis. The primary analysis of this study focussed on the variation in the performance of CCP tests currently available. In light of recently published data we also performed subgroup meta-analyses to evaluate how manufacturer variability in diagnostic performance was impacted by study design (single *vs.* two gated), and the ability of CCP tests to diagnose early versus established RA.

Methods

We prepared a review protocol prior to the start of the study, which was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines for systematic review and meta-analysis (16).

Search methods for identification of studies

We conducted an electronic literature search from 2004 to March 2015 in Medline, Medline In-Process, Embase, PubMed, Cochrane Central Register of Controlled Trials, NIH Clinicaltrials.gov, and the WHO International Clinical Trials Registry Platform. The electronic search was supplemented by hand searching of reference lists of studies identified as eligible for inclusion, as well as several recently published systematic reviews. We applied no country limit. Language was limited to English. The search strategies focussed on terms associated with rheumatoid arthritis, autoantibodies and anti-citrullinated protein antibodies.

Study selection criteria

Studies were selected for inclusion based on pre-defined eligibility criteria. Diagnostic case-control (two-gate), cross-sectional and cohort studies (single-gate) using CCP diagnostic tests (index test) attributed to a named manufacturer were eligible. Study participants had suspected or known RA, and were diagnosed according to the 1987 or 2010 ACR criteria for diagnosing RA. Control participants could be healthy or affected by rheumatological diseases other than RA. Studies were required to report sensitivity and specificity using the manufacturers recommended cut-off threshold value. Reviews, discussion papers, non-research letters, editorials, qualitative studies and case studies were not eligible.

Two reviewers independently screened titles and abstracts and disagreements were resolved through consensus. The full texts of selected titles were reviewed and the inclusion criteria re-applied independently by two reviewers. Any disagreements were resolved through discussion until a consensus was reached. Where necessary, a third reviewer resolved disagreements.

Data extraction

Two reviewers independently extracted relevant data from eligible papers into a pre-defined data extraction table. For each study, the following items were extracted: (i) study characteristics (including study objective, setting, study design, reference standard); (ii) participant characteristics (including number of RA patients, number of control participants, age and gender); (iii) for RA patients, the RA status was recorded as either early (symptom duration <2 years), established (symptom duration >2 years) or mixed (combination of early and established); (iv) status of control participants (healthy, diseased or mixed); (v) index test characteristics (including test name, manufacturer, assay type, generation, and cut-off); and (vi) diagnostic performance of the index test (sensitivity and specificity, positive and negative likelihood ratios, positive and negative predictive values, and odds ratios).

We extracted data for all reported index tests. Where reported, we extracted data separately by RA type (early, established or mixed) and control type (healthy, diseased or mixed).

Assessment of methodological quality

The methodological quality of each study was assessed using the QUADAS-2 tool (17), as recommended by The Cochrane Collaboration. QUADAS-2 is designed to assess the quality of primary diagnostic accuracy studies. The tool has four domains: (i) patient selection; (ii) index test; (iii) reference standard; and (iv) patient flow. Two reviewers independently assessed the methodological quality of each study. Disagreements were resolved through discussion and consensus, with a third reviewer used as arbitrator where necessary.

Sub-analyses

Using sensitivity, specificity and likelihood ratio plots we visually compared the ability of single and two-gated study designs to accurately diagnose RA by calculating pooled estimates

Table I. Summary of the study characteristics.

Number of gates	RA type	Control type	Number of studies	Reference
Single-gated	Early	Non-RA	14	(22-35)
Single-gated	Mixed	Non-RA	2	(36, 37)
Single-gated	NR	Non-RA	6	(38-43)
Two-gated	Early	Diseased	1	(44)
Two-gated	Early	Healthy	4	(45-48)
Two-gated	Early	Mixed	3	(49-51)
Two-gated	Established	Diseased	3	(52-54)
Two-gated	Established	Healthy	3	(46, 53, 55)
Two-gated	Established	Mixed	4	(51, 56-58)
Two-gated	Mixed	Diseased	8	(59-66)
Two-gated	Mixed	Healthy	4	(60, 67-69)
Two-gated	Mixed	Mixed	6	(58, 70-74)
Two-gated	NR	Diseased	17	(75-91)
Two-gated	NR	Healthy	1	(92)
Two-gated	NR	Mixed	13	(44, 52, 86, 93-104)
Two-gated	NR	Non-RA	1	(104)

RA: rheumatoid arthritis; NR: not reported.

for each CCP test manufacturer. To investigate the ability of CCP tests to accurately diagnose early RA, we performed a second sub-analysis, pooling results from studies reporting the sensitivity and specificity of CCP in early and established RA patient subgroups. Where studies reported data on more than one index test for the same patient population, we selected a single set of sensitivity and specificity data for the meta-analyses using the following manufacturer hierarchy: Euro-diagnostica > Axis-Shield > Inova Diagnostics > Thermo Fisher Scientific > Euroimmun > Abbott > Roche Diagnostics. Additionally, we prioritised CCP2 tests over CCP3 tests for inclusion in the analysis. This selection method was applied to the analysis to avoid pseudo-replication. Where studies reported sub-group analyses for early and established patients using the same patient control group, both data-sets were included in the respective analyses.

Statistical analysis and meta-analysis

To produce summary estimates for test sensitivity and specificity, we employed a random effects bivariate model (18). CCP test threshold was set to the manufacturer's recommended cut-off. We constructed a 2x2 table for each study and populated it with values back-calculated from extracted sensitivity and specificity values (true-positive, false-positive, true-negative, false-negative). Where more than one study reported a CCP test, we calculated pooled estimates of sensitivity and specificity with 95% confidence intervals (CIs) and displayed them in forest plots. We derived summary positive and negative likelihood ratios from the summary estimates of sensitivity and specificity; likelihood ratios can be interpreted as follows: <0.1 often conclusive decrease in the likelihood of disease, =1 implies no change in the likelihood of disease, and >10 often conclusive increase in the likelihood of disease. For all analyses we used R software (www.R-project.org) and the package "mada" (meta-analysis of diagnostic accuracy), (cran.r-roject.org/web/packages/mada/mada.pdf).

For the sub-analyses of disease duration, we used the bivariate model to estimate summary sensitivity and specificity estimates, with 95% confidence and prediction regions, and derived summary receiver operating characteristic (ROC) curves. This approach allowed for assessment of between-study heterogeneity in sensitivity and specificity and for visualising the trade-off (negative correlation) between sensitivity and specificity commonly seen in diagnostic meta-analyses. The summary ROC curves were used to assess the heterogeneity between studies. The ROC graph plots sensitivity against the false-positive rate. The shape of the curve between these two fixed points depends on the discriminatory ability of the test. The area under the curve (AUC) equals 1 for a perfect test and 0.5 for a completely uninformative test. The AUC is the probability that a diseased individual will have a higher test result than a non-diseased individual, provided that all individuals are selected at random.

Results

Search results and characteristics of the studies

The flow of studies through the review process is shown in Supplementary Fig. S1. Our electronic search identified 3100 articles, of which 83 met the eligibility criteria and were included in the review. A single study reported data from a first generation CCP assay, 60 studies used second generation CCP2 assays, five studies used third generation CCP3 assays and 17 studies used both CCP2 and CCP3 assays. Twenty-two studies employed a single-gated study design in which a single group of patients suspected of RA were analysed. The remaining 61 studies adopted a two-gated (case-control) design. Amongst the single-gated studies, the majority focussed on early RA patients (14/22). Amongst the two-gated case control studies, eight had evaluable data-sets for early arthritis patients, ten for established arthritis patients, and 18 for mixed arthritis. Thirty-two two-gated studies did not report RA status or disease duration. A summary of study characteristics is shown in Table I.

Diagnostic performance of CCP tests

The pooled estimates for sensitivity, specificity, and positive and negative likelihood ratios for specific CCP tests are shown in Fig 1. We analysed 125 data-sets that reported diagnostic performance using 11 different index tests with a named manufacturer. We included data sets from 82 of the 83 studies: 77 CCP2 and 22 CCP3 data sets. One study was not included because it had assessed a first generation CCP test. There was considerable variation between the different tests for the pooled sensitivity estimates, which ranged

from 67% (Axis-Shield Diastat and EuroDiagnostica Immunoscan) to 83% (Abbott Architect). Despite this variation, with one exception, the observed differences in sensitivity between manufacturer tests were not found to be statistically significant. Only the Abbott Architect test was found to have a statistically superior pooled sensitivity estimate compared with another CCP test, namely the Inova Diagnostics Quanta Lite (CCP2) test. However, there was a corresponding trade-off in specificity as the Abbott Architect test was also the test with the lowest pooled specificity estimate. The pooled specificity estimates for all tests varied between 90% (Abbott Architect) and 96% (Euroimmun Anti-CCP ELISA and Thermo Fisher Scientific EliA). Both the Thermo Fisher Scientific EliA and Euroimmun Anti-CCP ELISA tests were found to have statistically higher specificity estimates than the Inova Diagnostics Quanta Lite 3.1 test. However, no other statistically significant differences in specificity were observed between the manufacturer tests. The pooled estimates for the positive likelihood ratios ranged from 7.24 (Abbott AxSYM) to 18.63 (Thermo Fisher Scientific and the negative likelihood ratios ranged from 0.19 (Abbott Architect) to 0.36 (Axis-Shield Diastat).

Sub-analysis: Diagnostic performance of manufacturer tests split by single and two-gated study design

Forest plots of pooled estimates for sensitivity and specificity for each manufacturer grouped by single-gated and two-gated study designs are shown in Fig 2. Forest plots of pooled estimates for positive and negative likelihood ratios grouped by single-gated and two-gated study designs are shown in Fig 3. For studies adopting a single-gated study design the highest pooled sensitivity estimate was observed for the Abbott AxSYM (84%) although there was a corresponding loss of specificity as a result compared to other manufacturers', with the test displaying the lowest specificity estimate of 91%. In the single-gated analysis the Thermo Fisher Scientific EliA and Inova Diagnostics Quanta Lite (CCP2) tests gave the high-

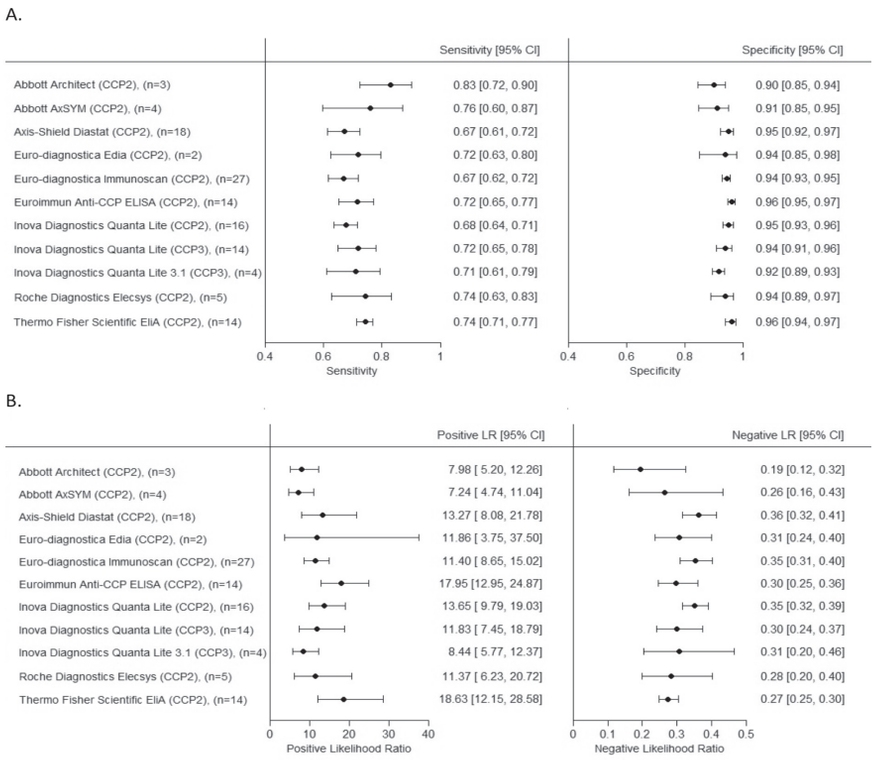

Fig. 1. The diagnostic accuracy of CCP2 and CCP3 index tests grouped by manufacturer.
Forest plots showing pooled estimates and 95% CI for (**A**) sensitivity and specificity, and (**B**) positive and negative likelihood ratios for each test manufacturer.

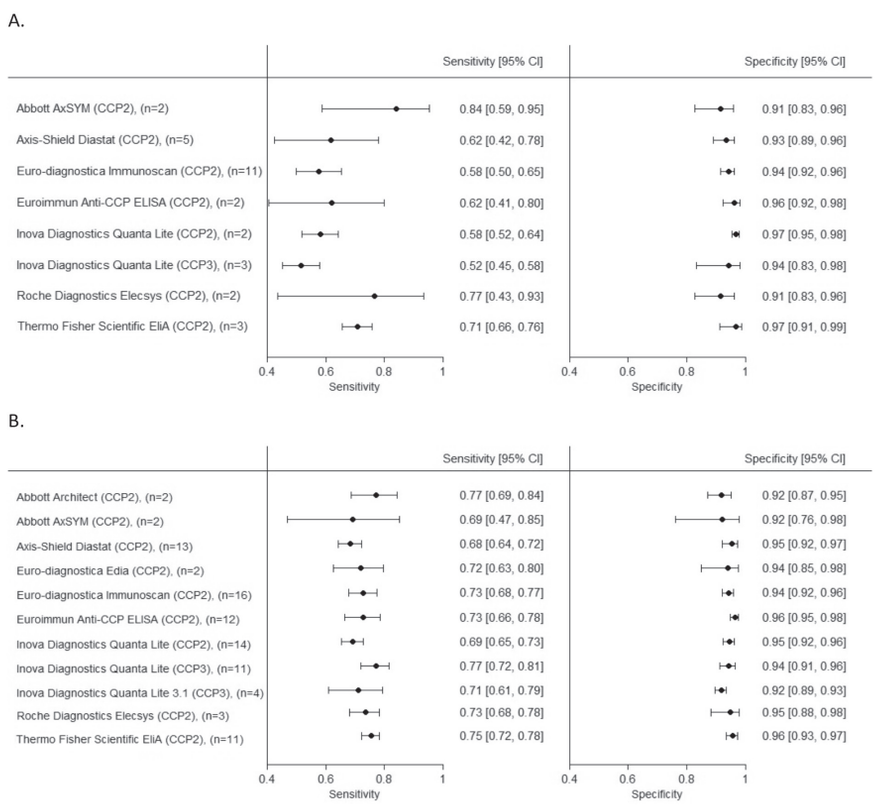

Fig. 2. The pooled sensitivity and specificity estimates of manufacturer tests used in single and two-gated study designs.
Forest plots showing pooled sensitivity and specificity estimates and 95% CIs for (**A**) single-gated study designs and (**B**) two-gated study designs for each test manufacturer.

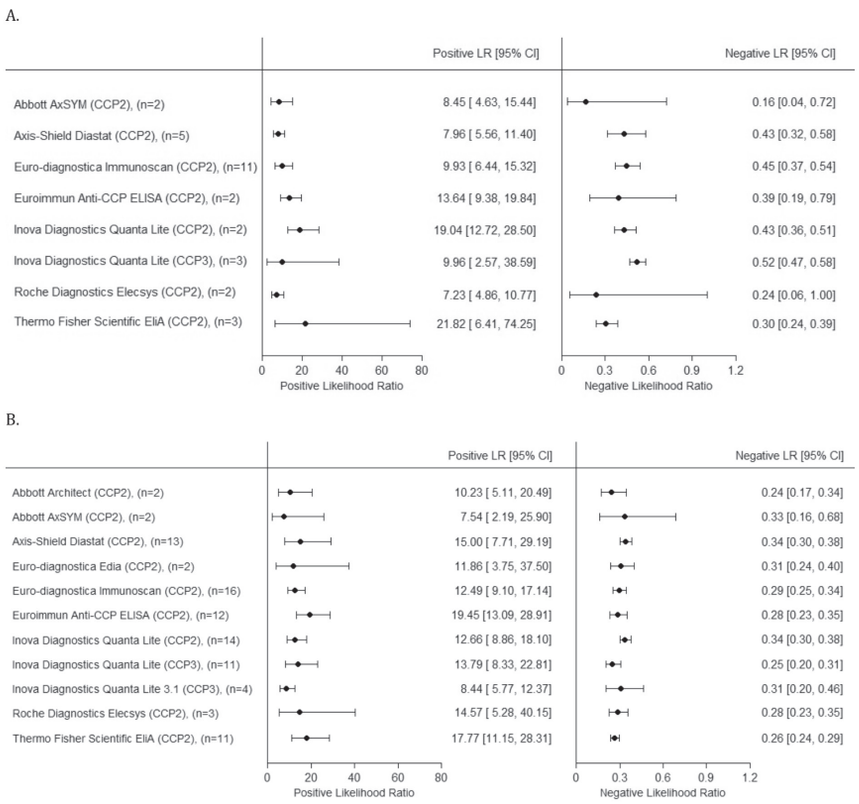

Fig. 3. The pooled positive and negative likelihood ratios of manufacturer tests used in single and two-gated study designs.
Forest plots showing pooled positive and negative likelihood ratios and 95% CIs for (**A**) single-gated study designs and **(B)** two-gated study designs for each test manufacturer.

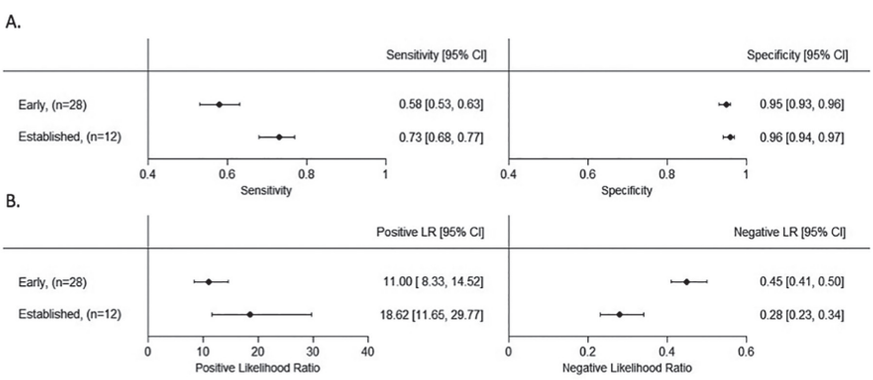

Fig. 4. The diagnostic performance of CCP tests in patients with established RA compared to early RA. Forest plots showing pooled estimates and 95% CIs for (**A**) sensitivity and specificity, and (**B**) positive and negative likelihood ratios in studies with established RA compared to early RA.

est specificities (both estimated at 97%). The single-gated studies produced both the lowest sensitivity estimates and the largest range of estimates (52%–84%) in comparison with the two-gated designs (68%–77%). Moreover, with regard to Thermo Fisher Scientific EliA test displayed the highest positive likelihood ratio of 21.8 (95% CI, range 6.4–74.2), while the other manufacturers' ranged between 7.2–19.0.

Sub-analysis: Diagnostic performance of CCP tests in early and established RA patients

Twenty-eight of the 83 studies included in the systematic literature review reported sensitivity and specificity data of CCP tests (all generations) in early RA, and 12 studies reported the sensitivity and specificity of CCP tests in established RA patients. Studies that reported on the diagnostic performance of CCP tests in mixed RA populations were not included in the analysis unless a sub-group analysis of either early or established patients was available. In early RA patients, the pooled CCP test sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio were 58%, 95%, 11.00, and 0.45, respectively (Fig. 4). In established RA patients, the pooled CCP test sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio were 73%, 96%, 18.62, and 0.28, respectively. The sROC analysis revealed non-overlapping 95% CIs between early and established RA patients, showing a trend that CCP testing has superior diagnostic performance in established RA patients compared to early RA patients (Fig. 5).

Study quality

The proportion of studies that fulfil each QUADAS-2 criterion is summarised in Supplementary Fig. S2. Of the 83 studies, only three satisfy all of the criteria in the QUADAS-2 check-list (17). In the patient selection domain, 71% of studies were classified at a high risk of bias for employing a case-control design. In the index test domain, 75% of studies were classified at a high risk of bias because CCP test results had been interpreted with knowledge of participant's RA status. In the reference standard domain, only 16% of studies were at a high risk of bias because, for the majority of studies, the diagnosis of RA by the ACR criteria (the reference standard) had pre-dated the CCP test. In the flow and timing domain, none of the studies were considered to be at high risk of bias. In all studies the same reference standard was applied (diagnosis of RA by the ACR criteria) as specified in the systematic review inclusion criteria. In terms of applicability no studies were considered to be at risk of bias for either patient selection, the reference standard or index test domains.

Discussion

In the last 10 years, five systematic literature reviews investigating the accuracy of ACPA and RF tests in the diagnosis of RA have been conducted (11, 12, 14, 15, 19). In 2007, the meta-analysis performed by Nishimura (10)

led to the conclusion that anti-CCP antibody positivity is more specific than IgM RF positivity for diagnosing RA and early RA. The increase in evidence supporting the value of ACPA testing for the diagnosis of RA led to the incorporation of ACPA testing in the updated ACR guidelines in 2010 (7). Moreover, the combination of anti-CCP positivity and RF positivity has been revealed to increase the probability of a true-positive result relative to either of the antibody tests in isolation (19). Recent systematic reviews investigating the effect of CCP generations by Whiting *et al*. (2010) (12) and Zhang *et al*. (2014) (15) found no significant differences between CCP2 and CCP3; therefore, we did not explore CCP generation. Our current systematic review is the first to perform a meta-analysis to investigate variation between manufacturer assays and, additionally, included analyses of study design (single- and two-gated), and duration of disease (early compared to established RA).

Overall, in this analysis using manufacturers recommended cut-offs we have demonstrated that the current commercially available CCP tests have high specificity and reasonable sensitivity for the diagnosis of RA. Despite no single test proving to be statistically superior to another in diagnostic performance, the analysis did reveal some differences in the pooled estimates of sensitivity and specificity between the commercially available CCP assays. Additionally, considerable within-assay variability was revealed, in particular for single-gated studies. Further studies are needed to establish what the clinical impact of such heterogeneity in diagnostic accuracy might be.

Among variables analysed, study design has been recognised as a potentially important source of bias in diagnostic accuracy studies (17). To accurately reflect diagnosing RA in clinical practice, a diagnostic study should adopt a single-gated consecutive or random patient flow with all patients suspected of RA, and ideally, showing early symptom duration. In the absence of single-gated design, the preferred design is two-gated (*i.e*. case-control studies). It is preferable that two-gated case-control studies use controls with non-RA rheumatology diseases, rather than a healthy control group because comparing confirmed diseased groups to healthy groups will likely exaggerate diagnostic accuracy (17). To prevent over-estimation of both sensitivity and specificity studies should ideally include difficult-to-diagnose patients and difficult-to-rule-out controls. The visual comparison of sensitivity estimates between single- and two-gate studies performed in this study does suggest that the performance of CCP test is influenced by study design as, on the whole, the single-gated designs result in lower sensitivities and higher within-assay variability.

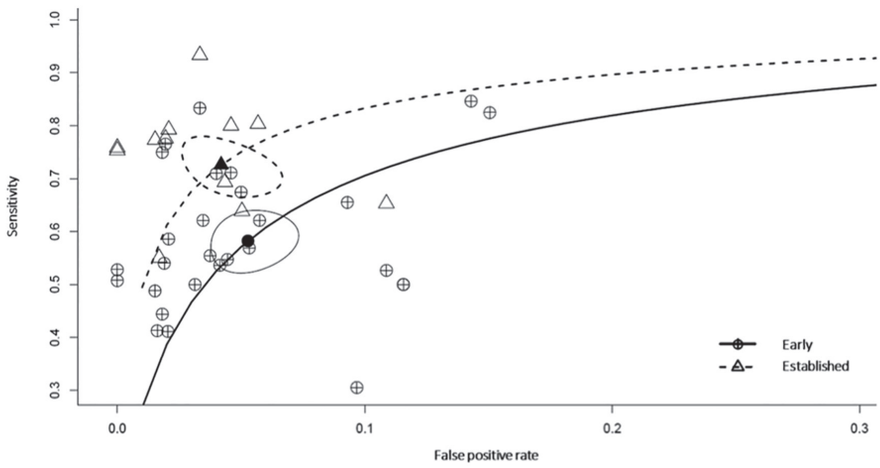

Fig. 5. Hierarchical summary receiver-operating characteristic (HSROC) curves for CCP test diagnostic performance in patients with established RA compared to early RA.

A comparison of manufacturers in the single-gate analysis, broadly representative of the scenario in which the test would be used in practice, revealed that based on the pooled positive likelihood ratios, the Thermo Fisher Scientific – EliA and the Inova Diagnostics Quanta Lite (CCP2) outperformed the other manufacturers (21.8 and 19, respectively *vs*. 7.2–13.6 for other manufacturers). The Thermo Fisher Scientific – EliA and the Inova Diagnostics Quanta Lite (CCP2) showed reliability for diagnosing suspected RA and implied that a positive result with these assays is often conclusive of the increase in the likelihood of disease. Overall, these tests showed lower between-study variations compared to other manufacturers, as demonstrated by the small confidence intervals on the pooled sensitivity estimates, thus showing reliability and consistency for ruling-in suspected RA. With regard to disease duration, our RA status sub-analysis suggests that patients with established RA are easier to detect using CCP testing than those with early disease. Nevertheless, there was a higher percentage of early RA studies that used a single-gated design (64% single-gated / 36% two-gated) compared to established RA studies (100% two-gated), which could explain the lower sensitivity observed in early RA diagnoses could be influenced by study design, in addition to physiological factors such as auto-antibody titres. It is well known that RA is difficult to diagnose at early onset, and although ACPAs add diagnostic value to the ACR criteria, the results of this study continue to demonstrate that there is still a need for novel biomarkers to further improve the diagnosis of RA. It is important to note that, as well as supporting the diagnosis of RA, CCP tests are also recognised as playing an important prognostic role since they often precede the onset of RA symptoms by years and are associated with significant and rapid radiographic progression (20, 21). Therefore, CCP tests can be used in cohort studies with long-term follow-up to identify patients who are at higher risk of developing RA.

Future studies need to evaluate antibody tests specifically in early and difficult-to-diagnose RA patients, utilising appropriate study designs and recruiting both patient and control groups that are relevant to a clinical setting.

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References

1. KVIEN TK: Epidemiology and burden of illness of rheumatoid arthritis. *Pharmacoeconomics* 2004; 222 Suppl 1: 1-12.
2. UHLIG T, MOE RH, KVIEN TK: The burden of disease in rheumatoid arthritis. *Pharmacoeconomics* 2014; 329: 841-51.
3. KLARESKOG L, PADYUKOV L, LORENTZEN J, ALFREDSSON L: Mechanisms of disease: Genetic susceptibility and environmental triggers in the development of rheumatoid arthritis. *Nat Clin Pract Rheumatol* 2006; 28: 425-33.
4. BELLUCCI E, TERENZI R, LA PAGLIA GM *et al*.: One year in review 2016: pathogenesis of rheumatoid arthritis. *Clin Exp Rheumatol* 2016; 345: 793-801.
5. BANSBACK N, MARRA CA, FINCKH A, ANIS A: The economics of treatment in early rheumatoid arthritis. *Best Pract Res Clin Rheumatol 2009*; 231: 83-92.
6. GONZALEZ A, ICEN M, KREMERS HM *et al*.: Mortality trends in rheumatoid arthritis: the role of rheumatoid factor. *J Rheumatol* 2008; 356: 1009-14.
7. 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; 699: 1580-8.
8. GIBOFSKY A: Overview of epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis. *Am J Manag Care* 2012; 1813 Suppl: S295-302.
9. WAALER E: On the occurrence of a factor in human serum activating the specific agglutination of sheep blood corpuscles. *Acta Pathol Microbiol Scand* 1940; 17: 172-88.
10. SCHELLEKENS GA, DE JONG BA, VAN DEN HOOGEN FH, VAN DE PUTTE LB, VAN VENROOIJ WJ: Citrulline is an essential constituent of antigenic determinants recognized by rheumatoid arthritis-specific autoantibodies. *J Clin Invest* 1998; 1011: 273-81.
11. NISHIMURA K, SUGIYAMA D, KOGATA Y *et al*.: Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. *Ann Intern Med* 2007; 14611: 797-808.
12. WHITING PF, SMIDT N, STERNE JA *et al*.: Systematic review: accuracy of anti-citrullinated peptide antibodies for diagnosing rheumatoid arthritis. *Ann Intern Med* 2010; 1527: 456-64.
13. RANTAPAA-DAHLQVIST S, DE JONG BA, BERGLIN E *et al*.: Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. *Arthritis Rheum* 2003; 4810: 2741-9.
14. RIEDEMANN JP, MUNOZ S, KAVANAUGH A: The use of second generation anti-CCP antibody (anti-CCP2) testing in rheumatoid arthritis - a systematic review. *Clin Exp Rheumatol* 2005; 235 (Suppl. 39): S69-76.
15. SUN J, ZHANG Y, LIU L, LIU G: Diagnostic accuracy of combined tests of anti cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis: a meta-analysis. *Clin Exp Rheumatol* 2014; 321: 11-21.
16. ZHANG WC, WU H, CHEN WX: Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide 2 antibody and anti-cyclic citrullinated peptide 3 antibody in rheumatoid arthritis. *Clin Chem Lab Med* 2014; 526: 779-90.
17. MOHER D, SHAMSEER L, CLARKE M *et al*.: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015; 4: 1.
18. WHITING PF, RUTJES AW, WESTWOOD ME *et al*.: QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011; 1558: 529-36.
19. REITSMA JB, GLAS AS, RUTJES AW, SCHOLTEN RJ, BOSSUYT PM, ZWINDERMAN AH: Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol* 2005; 5810: 982-90.
20. KLARESKOG L, WIDHE M, HERMANSSON M, RONNELID J: Antibodies to citrullinated proteins in arthritis: pathology and promise. *Curr Opin Rheumatol* 2008; 203: 300-5.
21. VAN VENROOIJ WJ, VAN BEERS JJ, PRUIJN GJ: Anti-CCP Antibody, a Marker for the Early Detection of Rheumatoid Arthritis. *Ann NY Acad Sci* 2008; 1143: 268-85.
22. ATES A, KARAASLAN Y, AKSARAY S: Predictive value of antibodies to cyclic citrullinated peptide in patients with early arthritis. *Clin Rheumatol* 2007; 264: 499-504.
23. FERNANDEZ-SUAREZ A, RENESES S, WICHMANN I, CRIADO R, NUNEZ A: Efficacy of three ELISA measurements of anti-cyclic citrullinated peptide antibodies in the early diagnosis of rheumatoid arthritis. *Clin Chem Lab Med* 2005; 4311: 1234-9.
24. HIURA K, IWAKI-EGAWA S, KAWASHIMA T *et al*.: The diagnostic utility of matrix metalloproteinase-3 and high-sensitivity C-reactive protein for predicting rheumatoid arthritis in anti-cyclic citrullinated peptide antibody-negative patients with recent-onset undifferentiated arthritis. *Rheumatology Int* 2013; 339: 2309-14.
25. KHAN AH, JAFRI L, HUSSAIN MA, ISHAQ S: Diagnostic utility of anti-citrullinated protein antibody and its comparison with rheumatoid factor in rheumatoid arthritis. *J Coll Physicians Surg Pak* 2012; 2211: 711-5.
26. NELL VP, MACHOLD KP, STAMM TA *et al*.: Autoantibody profiling as early diagnostic and prognostic tool for rheumatoid arthritis. *Ann Rheum Dis* 2005; 6412: 1731-6.
27. NELL-DUXNEUNER V, MACHOLD K, STAMM T *et al*.: Autoantibody profiling in patients with very early rheumatoid arthritis: a follow-up study. *Ann Rheum Dis* 2010; 691: 169-74.
28. NICAISE-ROLAND P, NOGUEIRA L, DEMATTEI C *et al*.: Autoantibodies to citrullinated fibrinogen compared with anti-MCV and anti-CCP2 antibodies in diagnosing rheumatoid arthritis at an early stage: data from the French ESPOIR cohort. *Ann Rheum Dis* 2013; 723: 357-62.
29. SAUERLAND U, BECKER H, SEIDEL M *et al*.: Clinical utility of the anti-CCP assay: experiences with 700 patients. *Ann NY Acad Sci* 2005; 1050: 314-8.
30. SILVEIRA IG, BURLINGAME RW, VON MUHLEN CA, BENDER AL, STAUB HL: Anti-CCP antibodies have more diagnostic impact than rheumatoid factor (RF) in a population tested for RF. *Clin Rheumatol* 2007; 2611: 1883-9.
31. VAN DER LINDEN MP, BATSTRA MR, BAKKER-JONGES LE *et al*.: Toward a data-driven evaluation of the 2010 American College of Rheumatology/European League Against Rheumatism criteria for rheumatoid arthritis: is it sensible to look at levels of rheumatoid factor? *Arthritis Rheum* 2011; 635: 1190-9.
32. VAN DER LINDEN MP, VAN DER WOUDE D, IOAN-FACSINAY A *et al*.: Value of anti-modified citrullinated vimentin and third-generation anti-cyclic citrullinated peptide compared with second-generation anti-cyclic citrullinated peptide and rheumatoid factor in predicting disease outcome in undifferentiated arthritis and rheumatoid arthritis. *Arthritis Rheum* 2009; 608: 2232-41.
33. VAN GAALEN FA, LINN-RASKER SP, VAN VENROOIJ WJ *et al*.: Autoantibodies to cyclic citrullinated peptides predict progression to rheumatoid arthritis in patients with undifferentiated arthritis: a prospective cohort study. *Arthritis Rheum* 2004; 503: 709-15.
34. VAN GAALEN FA, VISSER H, HUIZINGA TW: A comparison of the diagnostic accuracy and prognostic value of the first and second anti-cyclic citrullinated peptides (CCP1 and CCP2) autoantibody tests for rheumatoid arthritis. *Ann Rheum Dis* 2005; 6410: 1510-2.
35. YAMANE T, HASHIRAMOTO A, TANAKA Y *et al*.: Easy and accurate diagnosis of rheumatoid arthritis using anti-cyclic citrullinated peptide 2 antibody, swollen joint count, and C-reactive protein/rheumatoid factor. *J Rheumatol* 2008; 353: 414-20.
36. DE RYCKE L, PEENE I, HOFFMAN IE *et al*.: Rheumatoid factor and anticitrullinated protein antibodies in rheumatoid arthritis: diagnostic value, associations with radiological progression rate, and extra-articular manifestations. *Ann Rheum Dis* 2004; 6312: 1587-93.
37. DEJACO C, KLOTZ W, LARCHER H, DUFTNER C, SCHIRMER M, HEROLD M: Diagnostic value of antibodies against a modified citrullinated vimentin in rheumatoid arthritis. *Arthritis Res Ther* 2006; 84: R119.
38. DOGAN M, KUCUKSARAC S, TUFEKCI O *et al*.: Comparison of the diagnostic values in rheumatoid arthritis: Anti-CCP antibodies and other serological tests. *Biomed Res* (India) 2014; 253: 381-6.
39. HEROLD M, BOESER V, RUSSE E, KLOTZ W: Anti-CCP: history and its usefulness. *Clin Dev Immunol* 2005; 122: 131-5.
40. KIM S, KIM JH, LEE JH, KIM HS: Evaluation of three automated enzyme immunoassays for detection of anti-cyclic citrullinated peptide antibodies in qualitative and quan-

titative aspects. *Rheumatology* 2010; 493: 450-7.
41. LUIS CARO-OLEAS J, FERNANDEZ-SUAREZ A, RENESES CESTEROS S, PORRINO C, NUNEZ-ROLDAN A, WICHMANN SCHLIPF I: Diagnostic usefulness of a third-generation anti-cyclic citrulline antibody test in patients with recent-onset polyarthritis. *Clin Chem Lab Med* 2007; 4510: 1396-401.
42. PAYET J, GOULVESTRE C, BIALE L *et al*.: Anticyclic citrullinated peptide antibodies in rheumatoid and nonrheumatoid rheumatic disorders: experience with 1162 patients. *J Rheumatol* 2014; 4112: 2395-402.
43. VANDER CRUYSSEN B, NOGUEIRA L, VAN PRAET J *et al*.: Do all anti-citrullinated protein/peptide antibody tests measure the same? Evaluation of discrepancy between anti-citrullinated protein/peptide antibody tests in patients with and without rheumatoid arthritis. *Ann Rheum Dis* 2008; 674: 542-6.
44. WEBB T, LAKOS G, SWART A *et al*.: Clinical evaluation of a novel chemiluminescent immunoassay for the detection of anti-citrullinated peptide antibodies. *Clin Chim Acta* 2014; 437: 161-7.
45. EL-BARBARY AM, KASSEM EM, EL-SERGANY MA, ESSA SA, ELTOMEY MA: Association of anti-modified citrullinated vimentin with subclinical atherosclerosis in early rheumatoid arthritis compared with anti-cyclic citrullinated peptide. *J Rheumatol* 2011; 385: 828-34.
46. MANIVELAVAN D, VIJAYASAMUNDEESWARI CK: Anti-cyclic citrullinated Peptide antibody: an early diagnostic and prognostic biomarker of rheumatoid arthritis. *J Clin Diagn Res* 2012; 68: 1393-6.
47. MELGUIZO E, NAVARRO V, HERNANDEZ B *et al*.: Diagnostic utility of oxidative damage markers for early rheumatoid arthritis in non-smokers and negative anti-CCP patients. *An Sist Sanit Navar* 2014; 371: 109-15.
48. MIKULS TR, HOLERS VM, PARRISH L *et al*.: Anti-cyclic citrullinated peptide antibody and rheumatoid factor isotypes in African Americans with early rheumatoid arthritis. *Arthritis Rheum* 2006; 549: 3057-9.
49. HODKINSON B, MEYER PW, MUSENGE E *et al*.: The diagnostic utility of the anti-CCP antibody test is no better than rheumatoid factor in South Africans with early rheumatoid arthritis. *Clin Rheumatol* 2010; 296: 615-8.
50. INFANTINO M, MANFREDI M, MEACCI F *et al*.: Anti-citrullinated peptide antibodies and rheumatoid factor isotypes in the diagnosis of rheumatoid arthritis: an assessment of combined tests. *Clin Chim Acta* 2014; 436: 237-42.
51. MAKSYMOWYCH WP, NAIDES SJ, BYKERK V *et al*.: Serum 14-3-3 is a novel marker that complements current serological measurements to enhance detection of patients with rheumatoid arthritis. *J Rheumatol* 2014; 4111: 2104-13.
52. BESADA E, NIKOLAISEN C, NOSSENT H: Diagnostic value of antibodies against mutated citrullinated vimentin for rheumatoid arthritis. *Clin Exp Rheumatol* 2011; 291: 85-8.
53. DIAZ-TOSCANO ML, OLIVAS-FLORES EM, ZAVALETA-MUNIZ SA *et al*.: Comparison of two assays to determine anti-citrullinated peptide antibodies in rheumatoid arthritis in relation to other chronic inflammatory rheumatic diseases: assaying anti-modified citrullinated vimentin antibodies adds value to second-generation anti-citrullinated cyclic peptides testing. *Biomed Res Int* 2014; 2014: 198198.
54. EZZAT WM, RASLAN HM, ALY AA, EMARA NA, EL MENYAWI MM, EDREES A: Anticyclic citrullinated peptide antibodies as a discriminating marker between rheumatoid arthritis and chronic hepatitis C-related poly-arthropathy. *Rheumatology Int* 2011; 311: 65-9.
55. EL-BANNA H, JIMAN-FATANI A: Anti-cyclic citrullinated peptide antibodies and paraoxonase-1 polymorphism in rheumatoid arthritis. *BMC Musculoskelet Disord* 2014; 15: 379.
56. ALEXIOU I, GERMENIS A, ZIOGAS A, THEODORIDOU K, SAKKAS LI: Diagnostic value of anti-cyclic citrullinated peptide antibodies in Greek patients with rheumatoid arthritis. *BMC Musculoskelet Disord* 2007; 8: 37.
57. DAMJANOVSKA L, ATANASOVSKA V, GRUEV T: The diagnostic value of anti-cyclic citrullinated peptide antibodies (anti-CCP) in patients with rheumatoid arthritis. *J Med Biochem* 2007; 264: 285-8.
58. DOS ANJOS LM, PEREIRA IA, D'ORSI E, SEAMAN AP, BURLINGAME RW, MORATO EF: A comparative study of IgG second- and third-generation anti-cyclic citrullinated peptide (CCP) ELISAs and their combination with IgA third-generation CCP ELISA for the diagnosis of rheumatoid arthritis. *Clin Rheumatol* 2009; 282: 153-8.
59. COENEN D, VERSCHUEREN P, WESTHOVENS R, BOSSUYT X: Technical and diagnostic performance of 6 assays for the measurement of citrullinated protein/peptide antibodies in the diagnosis of rheumatoid arthritis. *Clin Chem* 2007; 533: 498-504.
60. DAMJANOVSKA L, THABET MM, LEVARTH EW *et al*.: Diagnostic value of anti-MCV antibodies in differentiating early inflammatory arthritis. *Ann Rheum Dis* 2010; 694: 730-2.
61. GUPTA R, THABAH MM, ANEJA R, KUMAR A, VARGHESE T, CHANDRASENAN PJ: Usefulness of anti -CCP antibodies in rheumatic diseases in Indian patients. *Indian J Med Sci* 2009; 633: 92-100.
62. SHARIF SK, EGHBAL S, GHARIBDOOST F *et al*.: Comparative study of anti-CCP and RF for the diagnosis of rheumatoid arthritis. *APLAR Journal of Rheumatology* 2007; 102: 121-4.
63. SWART A, BURLINGAME RW, GURTLER I, MAHLER M: Third generation anti-citrullinated peptide antibody assay is a sensitive marker in rheumatoid factor negative rheumatoid arthritis. *Clin Chim Acta* 2012; 414: 266-72.
64. VALLBRACHT I, RIEBER J, OPPERMANN M, FORGER F, SIEBERT U, HELMKE K: Diagnostic and clinical value of anti-cyclic citrullinated peptide antibodies compared with rheumatoid factor isotypes in rheumatoid arthritis. *Ann Rheum Dis* 2004; 639: 1079-84.
65. WAGNER E, SKOUMAL M, BAYER PM, KLAUSHOFER K: Antibody against mutated citrullinated vimentin: a new sensitive marker in the diagnosis of rheumatoid arthritis. *Rheumatology Int* 2009; 2911: 1315-21.
66. YOUSEFGHAHARI B, ALHOOEI S, SOLEIMANIAMIRI MJ, GURAN A: Comparison of sensitivity and specificity of anti-CCP and anti-MCV antibodies in an Iranian cohort of patients with rheumatoid arthritis. *Caspian J Intern Med* 2013; 43: 702-6.
67. AGHA S, LYKA H, KWATLI K: Sensitivity and specificity of anti-cyclic citrullinated peptide antibodies, compared to Rheumatoid factor in Syrian rheumatoid arthritis patients. *Int J Pharm Sci Rev Res* 2013; 202: 1-4.
68. EL SHAZLY RI, HUSSEIN SA, RASLAN HZ, ELGOGARY AA: Anti-mutated citrullinated vimentin antibodies in rheumatoid arthritis patients: Relation to disease activity and manifestations. *Egyptian Rheumatologist* 2014; 362: 65-70.
69. KORKMAZ C, US T, KASIFOGLU T, AKGUN Y: Anti-cyclic citrullinated peptide (CCP) antibodies in patients with long-standing rheumatoid arthritis and their relationship with extra-articular manifestations. *Clin Biochem* 2006; 3910: 961-5.
70. BIZZARO N, TONUTTI E, TOZZOLI R, VILLALTA D: Analytical and diagnostic characteristics of 11 2nd- and 3rd-generation immunoenzymatic methods for the detection of antibodies to citrullinated proteins. *Clin Chem* 2007; 538: 1527-33.
71. DUBUCQUOI S, SOLAU-GERVAIS E, LEFRANC D *et al*.: Evaluation of anti-citrullinated filaggrin antibodies as hallmarks for the diagnosis of rheumatic diseases. *Ann Rheum Dis* 2004; 634: 415-9.
72. KAMALI S, POLAT NG, KASAPOGLU E *et al*.: Anti-CCP and antikeratin antibodies in rheumatoid arthritis, primary Sjogren's syndrome, and Wegener's granulomatosis. *Clin Rheumatol* 2005; 246: 673-6.
73. MUTLU N, BICAKCIGIL M, TASAN DA, KAYA A, YAVUZ S, OZDEN AI: Comparative performance analysis of 4 different anti-citrullinated protein assays in the diagnosis of rheumatoid arthritis. *J Rheumatol* 2009; 363: 491-500.
74. VANICHAPUNTU M, PHUEKFON P, SUWANNALAI P, VERASERTNIYOM O, NANTIRUJ K, JANWITYANUJIT S: Are anti-citrulline autoantibodies better serum markers for rheumatoid arthritis than rheumatoid factor in Thai population? *Rheumatology Int* 2010; 306: 755-9.
75. CECCATO F, ROVERANO S, BARRIONUEVO A, RILLO O, PAIRA S: The role of anticyclic citrullinated peptide antibodies in the differential diagnosis of elderly-onset rheumatoid arthritis and polymyalgia rheumatica. *Clin Rheumatol* 2006; 256: 854-7.
76. CORREIA ML, CARVALHO S, FORTUNA J, PEREIRA MH: Comparison of three anti-CCP antibody tests and rheumatoid factor in RA and control patients. *Clin Rev Allergy Immunol* 2008; 341: 21-5.
77. DEBAUGNIES F, SERVAIS G, BADOT V, NOUBOUOSSIE D, WILLEMS D, CORAZZA F: Anti-cyclic citrullinated peptide antibod-

ies: a comparison of different assays for the diagnosis of rheumatoid arthritis. *Scand J Rheumatol* 2013; 422: 108-14.
78. ELREFAEI M, BOOSE K, McGEE M *et al*.: Second generation automated anti-CCP test better predicts the clinical diagnosis of rheumatoid arthritis. *J Clin Immunol* 2012; 321: 131-7.
79. GARCIA-BERROCAL B, GONZALEZ C, PEREZ M *et al*.: Anti-cyclic citrullinated peptide autoantibodies in IgM rheumatoid factor-positive patients. *Clin Chim Acta* 2005; 3541-2: 123-30.
80. GIRELLI F, FOSCHI FG, BEDESCHI E, CALDERONI V, STEFANINI GF, MARTINELLI MG: Is anti cyclic citrullinated peptide a useful laboratory test for the diagnosis of rheumatoid arthritis? *Eur Ann Allergy Clin Immunol* 2004; 364: 127-30.
81. HWANG SM, KIM JO, YOO YM *et al*.: Performance analysis of the ARCHITECT anti-cyclic citrullinated peptide antibody in the diagnosis of rheumatoid arthritis. *Clin Chem Lab Med* 2010; 482: 225-30.
82. KWOK JS, HUI KH, LEE TL *et al*.: Anti-cyclic citrullinated peptide: diagnostic and prognostic values in juvenile idiopathic arthritis and rheumatoid arthritis in a Chinese population. *Scand J Rheumatol* 2005; 345: 359-66.
83. LOPEZ-LONGO FJ, RODRIGUEZ-MAHOU M, SANCHEZ-RAMON S *et al*.: Anti-cyclic citrullinated peptide versus anti-Sa antibodies in diagnosis of rheumatoid arthritis in an outpatient clinic for connective tissue disease and spondyloarthritis. *J Rheumatol* 2006; 338: 1476-81.
84. LUTTERI L, MALAISE M, CHAPELLE JP: Comparison of second- and third-generation anti-cyclic citrullinated peptide antibodies assays for detecting rheumatoid arthritis. *Clin Chim Acta* 2007; 3861-2: 76-81.
85. NIKOLAISEN C, REKVIG OP, NOSSENT HC: Diagnostic impact of contemporary biomarker assays for rheumatoid arthritis. *Scand J Rheumatol* 2007; 362: 97-100.
86. PIETRAPERTOSA D, TOLUSSO B, GREMESE E *et al*.: Diagnostic performance of anti-citrullinated peptide antibodies for the diagnosis of rheumatoid arthritis: the relevance of likelihood ratios. *Clin Chem Lab Med* 2010; 486: 829-34.
87. RODRIGUEZ-MAHOU M, LOPEZ-LONGO FJ, SANCHEZ-RAMON S *et al*.: Association of anti-cyclic citrullinated peptide and anti-Sa/citrullinated vimentin autoantibodies in rheumatoid arthritis. *Arthritis Care Res* 2006; 554: 657-61.
88. SENE D, GHILLANI-DALBIN P, LIMAL N *et al*.: Anti-cyclic citrullinated peptide antibodies in hepatitis C virus associated rheumatological manifestations and Sjogren's syndrome. *Ann Rheum Dis* 2006; 653: 394-7.
89. SERDAROGLU M, CAKIRBAY H, DEGER O, CENGIZ S, KUL S: The association of anti-CCP antibodies with disease activity in rheumatoid arthritis. *Rheumatology Int* 2008; 2810: 965-70.
90. SOOS L, SZEKANECZ Z, SZABO Z *et al*.: Clinical evaluation of anti-mutated citrullinated vimentin by ELISA in rheumatoid arthritis. *J Rheumatol* 2007; 348: 1658-63.
91. ZAHRAN WE, MAHMOUD MI, SHALABY KA, ABBAS MH: Unique correlation between mutated citrullinated vimentine IgG autoantibodies and markers of systemic inflammation in rheumatoid arthritis patients. *Indian J Clin Biochem* 2013; 283: 272-6.
92. AL-SHUKAILI A, AL-GHAFRI S, AL-MARHOOBI S, ALKAABI J: Evaluation of anti-mutated citrullinated vimentin antibodies, anti-cyclic citrullinated Peptide antibodies and rheumatoid factor in Omani patients with rheumatoid arthritis. *Int J Rheumatol* 2012; 2012: 285854.
93. CAI B, WANG L, LIU J, FENG W: Performance evaluation of Elecsys analysis system for anti-cyclic citrullinated peptide detection in comparison with commercially available ELISA assays in rheumatoid arthritis diagnosis. *Clin Biochem* 2011; 4412: 989-93.
94. FAN LY, ZONG M, WANG Q *et al*.: Diagnostic value of glucose-6-phosphate isomerase in rheumatoid arthritis. *Clin Chim Acta* 2010; 41123-24: 2049-53.
95. KOCA SS, AKBULUT H, DAG S, ARTAS H, ISIK A: Anti-cyclic citrullinated peptide antibodies in rheumatoid arthritis and Behcet's disease. *Tohoku J Exp Med* 2007; 2134: 297-304.
96. LIMA I, OLIVEIRA RC, ATTA A *et al*.: Antibodies to citrullinated peptides in tuberculosis. *Clin Rheumatol* 2013; 325: 685-7.
97. LOUTHRENOO W, KASITANON N, WICHAINUN R *et al*.: Anti-agalactosyl IgG antibodies in Thai patients with rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis. *Clin Rheumatol* 2010; 293: 241-6.
98. MEHANOVIC-NIKOLIC J, LALOS-MILJUS J, STAJCIC-NALESNIK M *et al*.: The diagnostic value of anti-cyclic citrullinated peptide antibodies, adenosine deaminase activity and other potential biomarkers for predicting and monitoring rheumatoid arthritis. *J Med Biochem* 2008; 273: 383-8.
99. RIBEIRO SL, PEREIRA HL, SILVA NP, NEVES RM, SATO EI: Anti-cyclic citrullinated peptide antibodies and rheumatoid factor in leprosy patients with articular involvement. *Braz J Med Biol Res* 2008; 4111: 1005-10.
100. RYU HJ, TAKEUCHI F, KUWATA S *et al*.: The diagnostic utilities of anti-agalactosyl IgG antibodies, anti-cyclic citrullinated peptide antibodies, and rheumatoid factors in rheumatoid arthritis. *Rheumatology Int* 2011; 313: 315-9.
101. SANTIAGO M, BARON M, MIYACHI K *et al*.: A comparison of the frequency of antibodies to cyclic citrullinated peptides using a third generation anti-CCP assay (CCP3) in systemic sclerosis, primary biliary cirrhosis and rheumatoid arthritis. *Clin Rheumatol* 2008; 271: 77-83.
102. VAN CAMPENHOUT CM, VAN COTTHEM KA, STEVENS WJ, DE CLERCK LS: Performance of automated measurement of antibodies to cyclic citrullinated peptide in the routine clinical laboratory. *Scand J Clin Lab Invest* 2007; 678: 859-67.
103. YE H, CHEN F, YAN S *et al*.: Diagnostic utility of the Elecsys anti-CCP assay in patients with rheumatoid arthritis. Modern Rheumatology. 2014; 244: 580-4.
104. ABDUL WAHAB A, MOHAMMAD M, RAHMAN MM, MOHAMED SAID MS: Anti-cyclic citrullinated peptide antibody is a good indicator for the diagnosis of rheumatoid arthritis. *Pak J Med Sci* 2013; 293: 773-7.