Antibodies to citrullinated human fibrinogen (ACF) have diagnostic and prognostic value in early arthritis

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ANTIBODIES TO CITRULLINATED HUMAN FIBRINOGEN (ACF) HAVE DIAGNOSTIC AND PROGNOSTIC VALUE IN EARLY ARTHRITIS

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ABSTRACT

Objectives
The anti-cyclic citrullinated peptide (CCP) test has a high sensitivity and specificity for rheumatoid arthritis (RA), although CCP is not the physiological target of the autoantibodies. Since citrullinated fibrin is abundantly present in the inflamed synovium, we assessed the diagnostic and prognostic value of antibodies against citrullinated fibrinogen (ACF), a soluble precursor of fibrin, in comparison with IgM-Rheumatoid Factor (IgM-RF) and the second generation anti-CCP test.

Methods
In 379 early arthritis patients (258 RA and 121 undifferentiated arthritis) we calculated sensitivity, specificity and positive predictive value of ACF, anti-CCP and IgM-RF to diagnose RA. Multivariate logistic regression analysis was used to assess the diagnostic and prognostic value (radiographic progression after two years) of the tests.

Results
The sensitivities of the ACF, anti-CCP and IgM-RF test were 55.8%, 57.8% and 44.6% with specificities of 92.6%, 94.2% and 96.7%, respectively. Approximately 30% of the IgM-RF negative patients were positive for ACF and/or anti-CCP. The ACF and anti-CCP test had a high agreement in early arthritis (kappa 0.84). Of all baseline characteristics, the ACF test and the anti-CCP test were the best predictors for the diagnosis RA at one year (OR=10.3 and OR=10.6, respectively) and for radiographic progression after two years (OR=12.1 and OR=14.8).

Conclusions
The ACF test is as sensitive as the anti-CCP test and more sensitive than the IgM-RF test in diagnosing RA in an early arthritis cohort. The ACF test is also a good predictor of radiographic progression, with a performance similar to the anti-CCP test. The ACF test as well as the anti-CCP test are especially valuable in IgM-RF negative arthritis.

Key Words:
ANTIBODIES TO CITRULLINATED FIBRINOGEN
ANTI-CCP
IGM-RF
RHEUMATOID ARTHRITIS
Rheumatoid arthritis (RA) is a systemic autoimmune disease of unknown origin. To prevent joint destruction, early diagnosis and treatment of RA is required. The diagnosis of RA can be made by the 1987 classification criteria of the American College of Rheumatology (ACR) [1], but these criteria have a low sensitivity in early arthritis [2].

A few RA specific antibodies exist, the so-called antiperinuclear factor (APF), antifilagrin antibodies (AFA) and antikeratin antibodies (AKA). The epitopes recognized by APF, AFA and AKA were found to be generated by a posttranslational modification, namely deimination of the natural amino acid arginine to the amino acid citrulline by activity of peptidylarginine deiminase [3]. Based on that knowledge, Schellekens and co-workers developed an ELISA using a cyclic citrullinated peptide (CCP) derived from the sequence of human filagrin as substrate [4]. The assay has been improved (the second generation anti-CCP test) thereafter and sensitivities of 70-80% at specificities of 98-99% have been reported in established RA and controls [5, 6]. Sensitivity in early arthritis cohorts for the diagnosis RA varies between 40 and 70% [4, 7-11]. Although the anti-CCP ELISA has a reasonable sensitivity, the cyclic citrullinated peptide is not the physiological target of the autoantibodies.

Citrulline containing antigens are expressed in RA synovium [12, 13]. Moreover, B cells that actively secrete anti-CCP are specifically present in bone marrow and synovial fluid of anti-CCP seropositive RA patients [14, 15]. When searching for the nature of citrullinated proteins in RA synovial tissue, Masson-Bessière et al. identified citrullinated α- and β-chains of fibrin as the target for APF, AFA or AKA positive sera [16]. Subsequently, antibodies to in vitro citrullinated fibrinogen, a soluble precursor of fibrin, have been described as a serological criterion for the early diagnosis of RA when compared with rheumatoid factor (RF) and the first generation anti-CCP assay [17].

To study the diagnostic and prognostic value of anti-citrullinated fibrinogen (ACF) in early arthritis in comparison with IgM-RF and the second generation anti-CCP test, two studies were performed, including a cross-sectional analysis of patients with established RA and non-RA controls and a diagnostic and prognostic study on patients from an Early Arthritis Clinic (EAC).
PATIENTS AND METHODS

Patients. To calculate the cut-off values of the ACF test, anti-CCP test and the IgM-RF test at 99% specificity, the following groups of patients were tested: 239 established RA patients (53 active patients and 186 patients in clinical remission), 91 rheumatology clinic patients without arthritis and 91 healthy controls. The RA patients fulfilled the ACR criteria for RA [1]. These calculated cut-off values were then used to study the diagnostic and prognostic value of the ACF test in comparison with the IgM-RF test and the anti-CCP test in a study population.

This study population consisted of 379 consecutive patients aged ≥ 18 years, with peripheral arthritis of ≥ 2 joints and ≤ 2 years symptom duration, newly referred to the EAC of the Jan van Breemen Institute, a large rheumatology clinic in Amsterdam, between 1995 and 1998. Patients who were previously treated with a disease modifying anti-rheumatic drug (DMARD) or patients with spondylarthropathy, reactive arthritis, crystal-induced arthropathy, systemic lupus erythematosus, Sjögren syndrome, and osteoarthritis were excluded. In 258 patients the diagnosis of RA after 1 year follow-up was made by an experienced rheumatologist (BD), who was blinded for the results of the ACF test and the anti-CCP test. The remaining 121 non-RA patients were classified as undifferentiated arthritis (UA) (73 patients with polyarthritis and 48 patients with oligoarthritis).

Disease parameters. The following data were collected during the first visit: demographic characteristics, disease duration, disease activity by disease activity score (DAS28) [18], patient’s pain by Visual Analogue Scale (VAS) and functional status by the Health Assessment Questionnaire (HAQ) [19]. Laboratory assessments at baseline included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), IgM-RF, ACF and anti-CCP. Radiographs of hands and feet were obtained at baseline and after 2 years. The number of erosions and the joint space narrowing were scored according to the Sharp/van der Heijde method [20] by an experienced rheumatologist (DvS), who was blinded for all baseline variables.

Antibody measurements. Antibodies to CCP were measured using the second generation Immunoscan RA ELISA kit (Euro-diagnostica, Arnhem, the Netherlands, cut-off value 25 AU/ml). The assay was performed according to the manufacturer’s protocol. IgM–RF was measured on an ES300 immunochemistry analyser (Roche Diagnostics, Almere, The Netherlands) as described before [10].

IgG antibodies to citrullinated fibrinogen were detected by ELISA using citrullinated fibrinogen as immunosorbent [17]. Plasminogen free fibrinogen (Calbiochem, Breda, The Netherlands) was depleted of IgG using Protein G Sepharose. IgG free fibrinogen was citrullinated in vitro using rabbit skeletal muscle peptidylarginine deiminase (PAD) (Sigma, Zwijndrecht, The Netherlands): 7 U/mg fibrinogen in 0.1 M Tris-HCl (pH 7.4), 10 mM CaCl2 and 5 mM DTT for 2 hours at 37ºC [21]. Citrullination was controlled by a mobility shift of alpha and beta chain of fibrinogen detected by SDS gel electrophoresis followed by Western blotting with a positive serum [16]. Microtitre plates (MaxiSorp, Nunc, Roskilde, Denmark) coated with citrullinated fibrinogen (10 µg/ml PBS) were incubated for 1 h at room temperature with diluted sera in duplicate (1:50 in PBS, 0.2% gelatine, 0.05% (v/v) Tween 20). After incubation with horseradish peroxidase-conjugated mouse monoclonal anti-human IgG (MH16MIXME, Sanquin, Amsterdam, The Netherlands) for 1 h. at room temperature, 3,3’,5,5’ tetramethylbenzidine (10 mg/ml in DMSO) 1:100 diluted in 0.11 M acetate buffer pH 5.5 supplemented with 10 µl/10 ml of a 3% H2O2 solution was added. The reaction was stopped with 2M H2SO4 and absorbance at 450 nm was measured. All washing steps were performed with PBS, 0.1% Tween 20. The antibody titre is expressed in AU/ml using a pool...
of IgM-RF positive sera as calibrator in 8 dilutions. Coefficients of intra- and inter-assay variation were below 20% both for the same batch of citrullinated fibrinogen and for different batches of citrullinated fibrinogen.

Nissinen et al. reported that a majority of recent onset RA patients and 44% of SLE patients were positive in an anti-PAD ELISA [22]. Because the PAD enzyme used to citrullinate fibrinogen is not removed from the antigen preparation antibodies to PAD might influence the results. This is however unlikely, since we did not find positive reactions with SLE sera.

Data analysis. First, in the group of established RA patients and controls, the area under the receiver operating characteristic (ROC) curve of ACF, anti-CCP and IgM-RF was calculated and the sensitivities of the tests were compared at three specificities (95%, 98.5% and 99%). The cut-off value of the three tests was calculated at 99% specificity. These values were used in the other statistical analyses.

Second, sensitivity, specificity and positive predictive value (PPV) of ACF, anti-CCP and IgM-RF were calculated in the group of 379 early arthritis patients. Sensitivity expresses the percentage of RA patients that was positive for the test, whereas specificity is calculated from the percentage of test-negative UA patients. The baseline characteristics of the RA patients and UA patients were compared using Student’s t-test, the Mann-Whitney U test and the chi-square test, as appropriate.

Finally, multivariate logistic regression analysis was used to assess the diagnostic and prognostic value of the ACF test in early arthritis patients. The diagnostic value of the test was assessed by predicting the diagnosis RA or UA at one year follow-up, whereas the prognostic value was assessed by predicting radiographic progression at 2 years follow-up. Radiographic progression was defined as an increase of the Sharp/van der Heijde score of at least 5 after two years follow-up [23], the remainder was classified as not progressive. Variables that associated with the diagnosis RA in the univariate analysis (p<0.10) were entered into the models as independent variables. The analyses were carried out with a backward logistic regression analysis in SPSS 11.5.
RESULTS

The basic characteristics of the ACF test, the anti-CCP test and IgM-RF test in the group of established RA patients and controls are given in table 1. At a specificity of 99%, the sensitivities of the ACF test and the anti-CCP test were 67.8% and 71.1%, respectively. At this specificity, the IgM-RF test was only 41.8% sensitive. As a control for ACF, IgG-depleted fibrinogen was coated at 10 µg/ml and the ELISA was performed as described above. Subtracting the extinction obtained from the fibrinogen coat from that of citrullinated fibrinogen prior to calculation did not influence specificity and sensitivity (data not shown). Cut-off values of the tests at 99% specificity were 140 U/ml for ACF, 25 U/ml for anti-CCP and 45 IU/ml for IgM-RF. To compare all tests at the same specificity, these high cut-off values were chosen for further analysis in an early arthritis population.

Table 2 shows the baseline characteristics of that population. The group of RA patients was significantly older (p<0.01), had higher mean ESR and CRP levels (p<0.001), a higher mean DAS (p<0.001), a higher median radiographic damage score (p<0.01) and a worse mean HAQ (p<0.001) than the group of UA patients.

The sensitivity, specificity and PPV for the diagnosis of RA of the described tests are shown in table 3. Sensitivities varied between 44.6 and 57.8% and specificities between 92.6% and 96.7%. About 30% of the IgM-RF negative early arthritis patients were positive for ACF and/or anti-CCP. The ACF test and the anti-CCP test had a very high agreement in early arthritis. ACF and anti-CCP were single positive in 29 out of 379 patients (kappa 0.84, data not shown); 16 patients were single positive for anti-CCP (81.3% RA) and 13 patients were single positive for ACF (61.5% RA).

Complete two-year follow-up data were available from 296 of the 379 early arthritis patients (78.1%). These patients used a median of 1 DMARD (range, 1 to 5) during the period of follow-up; 62% of the patients used methotrexate. The reasons for loss to follow-up were: non-compliance (n=31), discharge from the clinic because of remission (n=17), moving home (n=10), death (n=9) and miscellaneous reasons (n=16). The group of patients that was lost to follow-up had similar baseline characteristics compared to the group of patients that completed the follow-up, except for the median baseline Sharp/van der Heijde score that was higher in non-completers compared to completers (6 vs. 1, p<0.001). Also, the non-completers were less often positive for IgM-RF (18.1% vs. 35.1%), anti-CCP (25.6% vs. 45.1%) and ACF (26.8% vs. 43.7%) (p<0.01 for all tests) than the completers.

In the univariate analysis, all baseline variables were statistically significantly associated with the diagnosis RA at one year (p<0.05, data not shown). Variables predictive for the diagnosis RA in the logistic regression analysis were anti-CCP, IgM-RF, ACF, DAS28 and VAS pain (Table 4). Because of the very high agreement of the ACF test and the anti-CCP test, two alternative predictive models were calculated with the same independent variables, but one without anti-CCP and one without ACF (data not shown). In the model without anti-CCP, the ACF test was the best predictor of diagnosis RA (OR = 10.3; 95%CI = 3.9 – 26.7) and in the model without ACF, the anti-CCP predicted diagnosis RA best (OR = 10.6; 95%CI = 4.1 – 27.8).

Baseline variables with a statistically significant association with radiographic progression at two years of follow-up were ACF, anti-CCP, IgM-RF, ESR, CRP, DAS28, HAQ and the Sharp/van der Heijde score (p<0.001, data not shown). Variables predictive for radiographic progression in the logistic regression analysis were anti-CCP, ESR and the Sharp/van der Heijde score at baseline with anti-CCP as the best predictor (OR = 14.8) (table 5a). The ACF test was removed by this model, due to the very high agreement of the ACF test and the anti-CCP test. Therefore, a second model for predicting radiographic progression was calculated without anti-CCP as independent variable (table 5b). In this model, ACF, ESR and
the Sharp / van der Heijde score at baseline were most predictive for radiographic progression with the ACF test as the best predictor (OR = 12.1).
DISCUSSION

The diagnostic and prognostic value of antibodies directed against citrullinated fibrinogen was compared with that of the second generation anti-CCP test in an early arthritis cohort. For diagnosing RA, the ACF test was as sensitive as the second generation anti-CCP test and more sensitive than the IgM-RF test. About 30% of the IgM-RF negative early arthritis patients were positive for the ACF test and therefore this test will be useful especially in IgM-RF negative early arthritis patients.

Despite the higher sensitivity of the ACF test and the second generation anti-CCP test compared to IgM-RF test for diagnosing RA, the specificity of the IgM-RF test was slightly higher. This is caused by a small percentage of patients diagnosed UA that have autoantibodies to citrullinated proteins. Those patients could eventually develop RA as has been suggested by the high positive predictive value of anti-CCP in a prospective study with early arthritis patients [24]. In an earlier study in the same cohort, Jansen et al found a sensitivity of 42.6% and a specificity of 97.5% for the first generation anti-CCP test [10]. In this early arthritis population, both the ACF test and the second generation anti-CCP test were more sensitive for the diagnosis RA. In an early RA population, Nogueira et al found a sensitivity for antibodies to citrullinated fibrinogen of 64.6% at 98.5% specificity [25], which is in line with the results of the present study. In multivariate analysis, we found that the anti-CCP test was the best predictor for the diagnosis RA, followed by the IgM-RF test and the ACF test (odds ratios around 4.5). Because of the high agreement of ACF and anti-CCP, it will not be useful to combine both tests to predict the diagnosis RA. Therefore, two other models were calculated with the same independent variables, but with only one of the two tests. In these models, baseline ACF and anti-CCP were similarly good predictors of the diagnosis RA one year later, with odds ratios of approximately 10.5.

The prognostic value of the ACF test was evaluated with multivariate logistic regression analyses using two year follow-up data. ACF was a good predictor of radiographic progression at two years follow-up, nearly as good as the anti-CCP test (OR 12.1 versus OR 14.8). Compared to previous reports on the prognostic value of citrulline specific autoantibodies, including the first and second generation anti-CCP test, an odds ratio of 12-14 is remarkably high [8, 11, 26-28]. The baseline characteristics of the non-completers were similar to those of the completers, except for the Sharp / van der Heijde score and the three antibody tests. The non-completers had a higher median Sharp / van der Heijde score than the completers at baseline, although they were positive less often for IgM-RF, anti-CCP and ACF. There may have been a coincidental selection of patients with a high Sharp / van der Heijde score at baseline, and a subsequent mild course of the disease, resulting in remission and loss to follow-up. Since the Sharp / van der Heijde score predicts radiographic progression, the selective loss to follow up may have led to an overestimation of the odds ratios of the anti-CCP test and the ACF test in predicting radiographic progression in our early arthritis population.

The results of this study underline the high disease specificity for antibodies to citrullinated proteins and peptides. Yet, the present data provide no explanation how the antibody response develops in RA patients. There was no difference in sensitivity between the anti-CCP test and the ACF test in early arthritis and established RA. In the vast majority of patients both ACF and anti-CCP were found. ACF and anti-CCP both were single positive in 8% of EAC patients. The agreement between the tests is surprising since citrullinated fibrin (fibrinogen is the soluble precursor of fibrin) has been described as a physiological substrate for antibodies recognizing citrulline-containing epitopes [16]. As has been shown for several other autoimmune disorders (reviewed in [29]), antibodies might preferentially recognize a modified physiological target, i.e. citrullinated fibrin, early in the disease. Later the antibody
response could spread towards less restricted epitopes [30]. Responses to uncitrullinated fibrinogen could be detected in our study population and were higher in patients compared to controls. However they never reached the degree of positivity that was found with citrullinated fibrinogen. It is known that RA specific antibodies can be detected several years before the onset of clinical symptoms [31-33]. Although the participants of the EAC in Amsterdam had a short disease duration at the time of testing for ACF and anti-CCP, differences between the two responses might be difficult to detect. The ACF response in patient samples taken before clinical signs of the disease could shed light on how the antibody response develops. Alternatively, other citrullinated proteins, e.g. vimentin, might trigger the initial immune response in RA [5]. Citrulline containing peptides derived from the sequence of vimentin have been shown to be efficiently presented by the RA-associated HLA-DRB1*0401 MHC class II molecule to T cells in a transgenic mouse model [34]. The data point towards an important role of citrulline as an anchor amino acid. Whether the overall sequence might be of less importance has to be elucidated in further studies.

In conclusion, the ACF test is useful for establishing the diagnosis of RA and is a good predictor of radiographic progression in early arthritis, comparable to the second generation anti-CCP test. Both tests are especially valuable in IgM-RF negative early arthritis.
ACKNOWLEDGEMENTS
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COMPETING INTEREST STATEMENT
None of the authors have competing interests

SPONSORS
This study was not sponsored
REFERENCES


**Table 1.** Sensitivity of IgM-RF, anti-CCP and ACF in established rheumatoid arthritis patients and controls
### Table 2. Baseline characteristics of the early arthritis population, separated into rheumatoid arthritis (RA) and undifferentiated arthritis (UA)

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Total group (n = 379)</th>
<th>RA (n = 258)</th>
<th>UA (n = 121)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years a</td>
<td>56.1 ± 15.6</td>
<td>57.6 ± 14.8</td>
<td>52.8 ± 16.6</td>
<td>*</td>
</tr>
<tr>
<td>Female, number (%) b</td>
<td>260 (68.6)</td>
<td>181 (70.2)</td>
<td>79 (65.3)</td>
<td>ns</td>
</tr>
<tr>
<td>Disease duration, years c</td>
<td>0.4 (0.3 to 0.7)</td>
<td>0.4 (0.3 to 0.7)</td>
<td>0.4 (0.3 to 0.6)</td>
<td>ns</td>
</tr>
<tr>
<td>ESR, mm/h a</td>
<td>31.8 ± 22.8</td>
<td>36.1 ± 23.2</td>
<td>22.8 ± 19.0</td>
<td>**</td>
</tr>
<tr>
<td>CRP, mg/dl c</td>
<td>15 (4 to 35)</td>
<td>18.5 (6.3 to 44)</td>
<td>6 (2 to 18)</td>
<td>**</td>
</tr>
<tr>
<td>DAS28-score a</td>
<td>4.8 ± 1.3</td>
<td>5.2 ± 1.2</td>
<td>4.1 ± 1.2</td>
<td>**</td>
</tr>
<tr>
<td>Sharp / van der Heijde score c</td>
<td>1 (0 to 6)</td>
<td>2 (0 to 6)</td>
<td>0 (0 to 4)</td>
<td>*</td>
</tr>
<tr>
<td>HAQ-score a</td>
<td>1.0 ± 0.8</td>
<td>1.2 ± 0.8</td>
<td>0.8 ± 0.6</td>
<td>**</td>
</tr>
</tbody>
</table>

Data are mean +/- SD or median (Interquartile range); *p<0.01; **p<0.001; ns = not significant.

a tested with Student’s t-test

b tested with Chi-square

c tested with Mann Whitney U-test
Table 3. Sensitivity, specificity and positive predictive value (PPV) of ACF, anti-CCP and IgM-RF for the clinical diagnosis of rheumatoid arthritis in early arthritis

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early arthritis (n=379)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgM-RF ≥ 45</td>
<td>44.6</td>
<td>96.7</td>
<td>96.6</td>
</tr>
<tr>
<td>ACF ≥ 140</td>
<td>55.8</td>
<td>92.6</td>
<td>94.1</td>
</tr>
<tr>
<td>Anti-CCP ≥ 25</td>
<td>57.8</td>
<td>94.2</td>
<td>95.5</td>
</tr>
<tr>
<td><strong>IgM-RF negative early arthritis (n=260)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACF ≥ 140</td>
<td>28.7</td>
<td>94.9</td>
<td>87.2</td>
</tr>
<tr>
<td>anti-CCP ≥ 25</td>
<td>30.8</td>
<td>96.6</td>
<td>91.7</td>
</tr>
</tbody>
</table>

Table 4. Results of logistic regression analysis of baseline variables to predict rheumatoid arthritis at one year in early arthritis

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>SE</th>
<th>Odds ratio (Exp(B))</th>
<th>95% CI</th>
<th>Accuracy</th>
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<tr>
<td>Constant</td>
<td>-3.355</td>
<td>0.622</td>
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<td></td>
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</tr>
<tr>
<td>anti-CCP ≥ 25</td>
<td>1.536</td>
<td>0.587</td>
<td>4.6</td>
<td>1.5 to 14.7</td>
<td></td>
</tr>
<tr>
<td>IgM-RF ≥ 45</td>
<td>1.521</td>
<td>0.662</td>
<td>4.6</td>
<td>1.3 to 16.7</td>
<td></td>
</tr>
<tr>
<td>ACF ≥ 140</td>
<td>1.443</td>
<td>0.614</td>
<td>4.2</td>
<td>1.3 to 14.1</td>
<td></td>
</tr>
<tr>
<td>DAS28</td>
<td>0.800</td>
<td>0.145</td>
<td>2.2</td>
<td>1.7 to 3.0</td>
<td></td>
</tr>
<tr>
<td>pain (VAS)</td>
<td>-0.014</td>
<td>0.007</td>
<td>0.99</td>
<td>0.97 to 0.99</td>
<td>78.0%</td>
</tr>
</tbody>
</table>

*Variables not in equation p-value*  
| Age       | 0.204 |
| ESR       | 0.484 |
| CRP       | 0.089 |
| HAQ       | 0.371 |
| Sharp / van der Heijde | 0.611 |
Table 5a. Results of logistic regression analysis of baseline variables to predict radiographic progression at two years in early arthritis

<table>
<thead>
<tr>
<th></th>
<th>B</th>
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<th>Odds ratio (Exp(B))</th>
<th>95% CI</th>
<th>Accuracy</th>
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<tbody>
<tr>
<td>Constant</td>
<td>-3.468</td>
<td>0.438</td>
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<td>80.2%</td>
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<tr>
<td>anti-CCP ≥ 25</td>
<td>2.694</td>
<td>0.364</td>
<td>14.8</td>
<td>7.2 to 30.2</td>
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<tr>
<td>Sharp / van der Heijde</td>
<td>0.102</td>
<td>0.029</td>
<td>1.1</td>
<td>1.0 to 1.2</td>
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<tr>
<td>ESR</td>
<td>0.024</td>
<td>0.007</td>
<td>1.02</td>
<td>1.01 to 1.04</td>
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Variables not in equation

<table>
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<tr>
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<tr>
<td>IgM-RF ≥ 45</td>
<td>0.376</td>
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<tr>
<td>ACF ≥ 140</td>
<td>0.099</td>
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<tr>
<td>DAS28</td>
<td>0.412</td>
</tr>
<tr>
<td>CRP</td>
<td>0.616</td>
</tr>
<tr>
<td>HAQ</td>
<td>0.481</td>
</tr>
</tbody>
</table>

Table 5b. Results of logistic regression analysis of baseline variables (without anti-CCP) to predict radiographic progression at two years in early arthritis

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>SE</th>
<th>Odds ratio (Exp(B))</th>
<th>95% CI</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>-3.239</td>
<td>0.403</td>
<td></td>
<td></td>
<td>81.7%</td>
</tr>
<tr>
<td>ACF ≥ 140</td>
<td>2.494</td>
<td>0.343</td>
<td>12.1</td>
<td>6.2 to 23.7</td>
<td></td>
</tr>
<tr>
<td>Sharp / van der Heijde</td>
<td>0.090</td>
<td>0.029</td>
<td>1.1</td>
<td>1.0 to 1.2</td>
<td></td>
</tr>
<tr>
<td>ESR</td>
<td>0.024</td>
<td>0.007</td>
<td>1.02</td>
<td>1.01 to 1.04</td>
<td></td>
</tr>
</tbody>
</table>

Variables not in equation

<table>
<thead>
<tr>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgM-RF ≥ 45</td>
<td>0.553</td>
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<tr>
<td>DAS28</td>
<td>0.291</td>
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<tr>
<td>CRP</td>
<td>0.955</td>
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<tr>
<td>HAQ</td>
<td>0.447</td>
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</table>
ANTIBODIES TO CITRULLINATED HUMAN FIBRINOGEN (ACF) HAVE DIAGNOSTIC AND PROGNOSTIC VALUE IN EARLY ARTHRITIS

Markus M.J. Nielen, Ann R van der Horst, Dirkjan van Schaardenburg, Irene E van der Horst-Bruinsma, Rob J van de Stadt, Lucien Aarden, Ben AC Dijkmans and Dörte Hamann

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