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Multiple Autoimmune Diseases after Autologous Stem-Cell Transplantation

TO THE EDITOR: Hematopoietic stem-cell transplantation can be an effective treatment in patients with refractory systemic sclerosis.[1] We report on a 19-year-old woman with systemic sclerosis who underwent CD34+-selected autologous hematopoietic stem-cell transplantation in March 2001. Before the transplantation, the physical and laboratory findings showed no evidence of any other autoimmune diseases. After written consent was obtained from the patient, CD34+ hematopoietic stem cells were transplanted according to a method used for systemic sclerosis.[1] The dermal sclerosis improved immediately after transplantation, but thrombocytopenia and Graves' disease developed.

In June 2005, the patient was admitted to the hospital because of fever and edema. Blood tests revealed proteinuria (11.4 g per day) and new autoantibodies in the serum (Fig. 1A). On the sixth hospital day, paralysis developed on the left side as the result of a right cerebral infarction. Systemic lupus erythematosus with membranous-type lupus nephritis (Fig. 2) and the antiphospholipid-antibody syndrome were diagnosed; the patient was treated with prednisolone, warfarin, and cyclosporine. She is currently in clinical remission and is back at work.

During the early phases of immune reconstitution, residual lymphocytes undergo proliferation and expansion, a process controlled by regulatory T cells.[2,3] These cells, defined by the phenotype CD4+CD25+FOXP3+, are important in the prevention of autoimmunity. Interleukin-17–producing helper T (Th17) cells may play a role in the induction of autoimmunity.[4,5] In our patient, the level of serum interleukin-17, released mainly by Th17 cells, was elevated at the onset of the systemic lupus (Fig. 1B). Levels of *FOXP3* messenger RNA, a marker of regulatory T cells, were reduced, suggesting a deficiency of such cells (Fig. 1C). The findings in our patient suggest a role of both regulatory T cells and Th17 in the development of systemic lupus.

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1. Farge D, Passweg J, van Laar JM, et al. Autologous stem cell

Figure 1 (facing page). Clinical and Laboratory Findings after CD34+-Selected Autologous Hematopoietic Stem-Cell Transplantation.
Panel A shows the association between clinical events (including the onset of autoimmune thrombocytopenia [AITP], Graves' disease, systemic edema, and cerebral infarction) and changes in titers of each autoantibody. At the onset of edema, a serum sample from the patient contained anti-Sm, anti-Scl70, and anticardiolipin IgG antibodies (IgG-aCL), in addition to anti-DNA autoantibodies and lupus anticoagulant. The solid line indicates the modified Rodnan total skin thickness score (ranging from 0 to 51, with higher values indicating more thickness). Normal ranges for these levels are as follows: anti-Sm, 0 to 5.9 U per milliliter, anti-Scl70, 0 to 18.9 U per milliliter; and IgG-aCL, <1.3 U per milliliter. Panel B shows serum levels of interleukin-17, transforming growth factor β1 (TGF-β1), and interleukin-6. Normal ranges for these levels are as follows: TGF-β1, 30.95 to 38.65 ng per milliliter; interleukin-6, 0.54 to 1.10 ng per milliliter; and interleukin-17, not detected. Panel C shows changes in T cells, including the ratio of interferon-γ–producing CD4+ T cells (Th1) and interleukin-4–producing CD4+ T cells (Th2) and FOXP3 messenger RNA (mRNA) on peripheral-blood mononuclear cells. The solid squares indicate levels of CD19+ cells, and the circles indicate levels of CD4+CD25+ cells. Normal ranges are as follows: ratio of Th1 to Th2, 7.22 to 47.52; FOXP3 mRNA, 57.10 to 175.19 copies per glyceraldehyde-3-phosphate dehydrogenase (GAPDH) standard; CD19+, 9.24 to 17.01%; and CD4+CD25+, 5.66 to 10.24%. Calculations were made with the JMP statistical software package, version 5.0 (SAS Institute).

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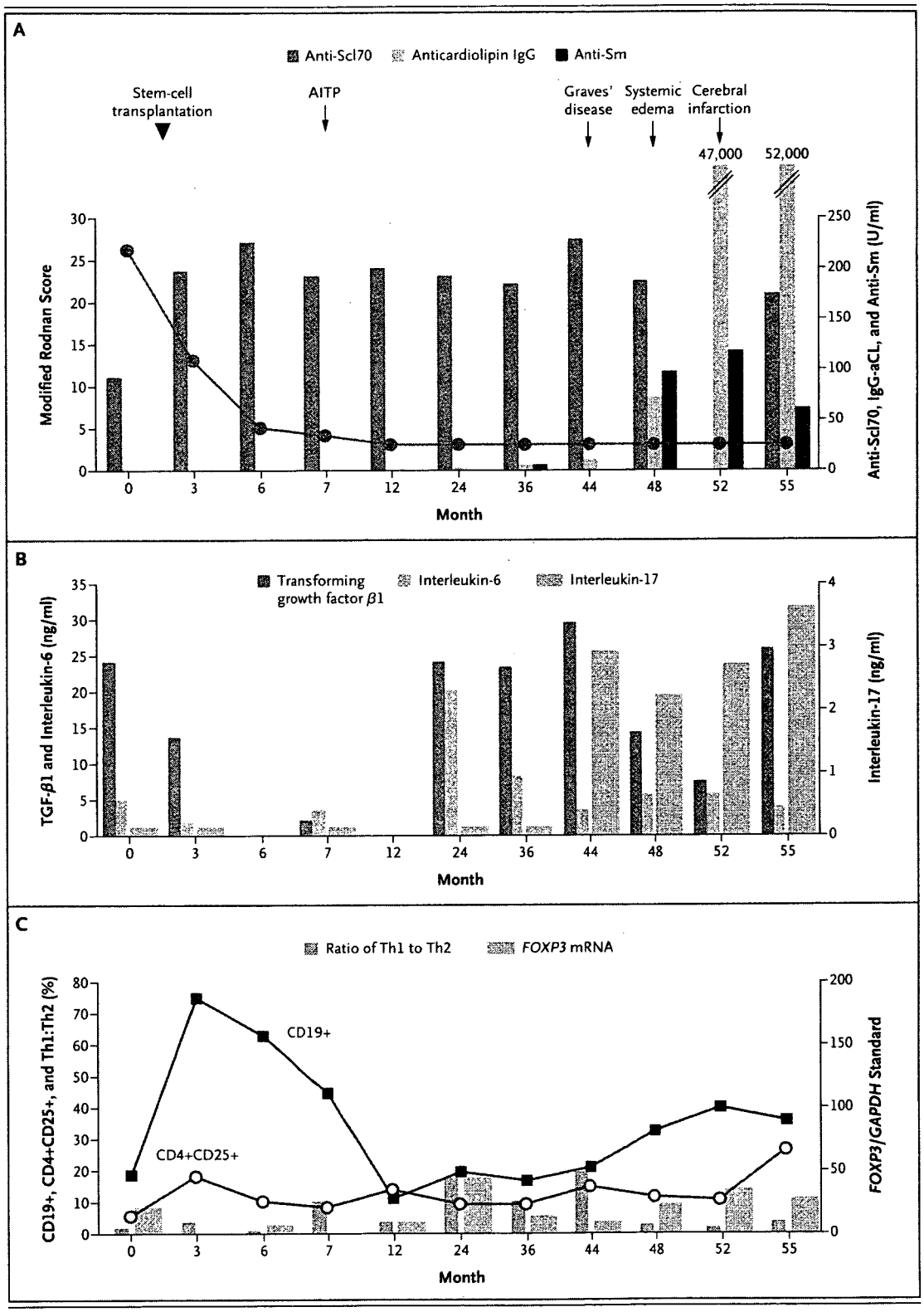
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Anti-Scl70
Anticardiolipin IgG
Anti-Sm
Stem-cell transplantation
AITP
Graves' disease
Systemic edema
Cerebral infarction
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Modified Rodnan Score
Anti-Scl70, IgG-aCL, and Anti-Sm (U/ml)
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B
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Interleukin-17
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Interleukin-17 (ng/ml)
Month
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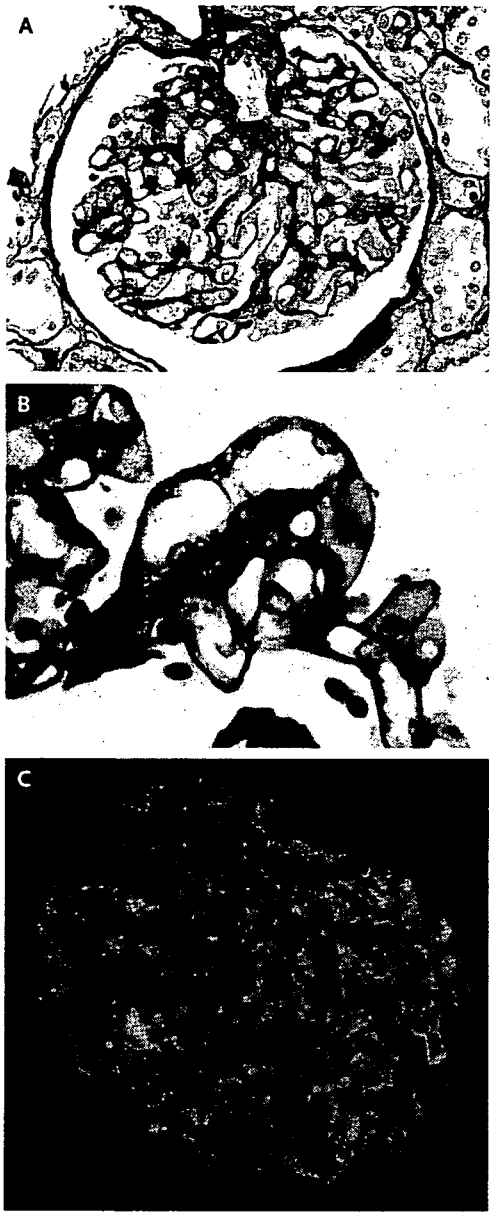

Figure 2. Renal-Biopsy Specimens Showing Representative Lesions at the Onset of Lupus Nephritis.

Renal-biopsy specimens show increased mesangial matrix (Panel A, periodic acid–Schiff staining), capillary-wall thickness and bubble appearance (Panel B, periodic acid–methenamine silver staining), and global granular immune deposits (Panel C, immunofluorescence staining).

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Annals of Internal Medicine | REVIEW

Meta-analysis: Diagnostic Accuracy of Anti–Cyclic Citrullinated Peptide Antibody and Rheumatoid Factor for Rheumatoid Arthritis

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Background: Rheumatoid factor (RF) and autoantibodies against cyclic citrullinated peptide (CCP) are markers that might help physicians diagnose rheumatoid arthritis.

Purpose: To determine whether anti-CCP antibody more accurately identifies patients with rheumatoid arthritis and better predicts radiographic progression than does RF.

Data Sources: MEDLINE through September 2006 and reference lists of retrieved studies and review articles.

Study Selection: Studies in any language that enrolled at least 10 participants and that examined the role of anti-CCP antibody and RF in the diagnosis or prognosis of known or suspected rheumatoid arthritis.

Data Extraction: Two authors independently evaluated studies for inclusion, rated methodological quality, and abstracted relevant data.

Data Synthesis: The DerSimonian–Laird random-effects method was used to summarize sensitivities, specificities, and positive and negative likelihood ratios from 37 studies of anti-CCP antibody and 50 studies of RF. The pooled sensitivity, specificity, and positive and negative likelihood ratios for anti-CCP antibody were 67% (95% CI, 62% to 72%), 95% (CI, 94% to 97%), 12.46 (CI, 9.72 to 15.98), and 0.36 (CI, 0.31 to 0.42), respectively. For IgM RF, the values were 69% (CI, 65% to 73%), 85% (CI, 82% to 88%), 4.86 (CI, 3.95 to 5.97), and 0.38 (CI, 0.33 to 0.44). Likelihood ratios among IgM RF, IgG RF, and IgA RF seemed to be similar. Results from studies of patients with early rheumatoid arthritis were similar to those from all studies. Three of 4 studies found that risk for radiographic progression was greater with anti-CCP antibody positivity than with IgM RF positivity.

Limitations: Many studies had methodological limitations. Studies of RF were heterogeneous and had wide ranges of sensitivity and specificity.

Conclusions: Anti-CCP antibodies are more specific than RF for diagnosing rheumatoid arthritis and may better predict erosive disease.

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Rheumatoid arthritis is the most common autoimmune disease, affecting approximately 1% of the world's population (1). It causes persistent synovitis, pain, joint destruction, and functional disability. Because irreversible joint destruction can be prevented by intervention during the first months of disease, early diagnosis of rheumatoid arthritis is important (2–4).

Rheumatoid factor (RF) is an antibody directed against the Fc region of IgG that has been used as a diagnostic marker for rheumatoid arthritis. However, it is nonspecific and may be present in healthy elderly persons or in patients with other autoimmune and infectious diseases (5). Other rheumatoid arthritis–associated autoantibodies known to be specific for rheumatoid arthritis include antiperinuclear factor and antikeratin antibodies (6, 7). Because of rigorous technical requirements for their detection, antiperinuclear factor and antikeratin antibodies have never been widely used as markers for rheumatoid arthritis, despite their high specificity. The epitopes of their antigens are arginyl residues citrullinated by peptidyl arginine deiminase (8–10). Some enzyme-linked immunosorbent assays (ELISAs) use linear citrulline-containing peptides that have similar sensitivity to and higher specificity than RF for diagnosing rheumatoid arthritis (11). To improve sensitivity, assays that use cyclic citrullinated peptide (CCP) were developed to detect anti-CCP antibody (12).

In this systematic review, we summarize published data on the sensitivity, specificity, and likelihood ratios of RF and anti-CCP antibodies for diagnosing rheumatoid arthritis. We also summarize results of studies that assessed the associations of these markers with development and radiographic progression of rheumatoid arthritis.

METHODS

Data Sources and Searches

We developed a protocol for the review and followed standard reporting guidelines (13, 14). We searched MEDLINE for studies published in any language through September 2006 that examined autoantibodies against citrullinated proteins, rheumatoid factor, or both for the diagnosis of rheumatoid arthritis. Our searches (available

See also:

Print
Editors' Notes 798
Editorial comment 816

Web-Only
Appendix Tables
Appendix Figure
Conversion of figures and table into slides

Context

Are autoantibodies against cyclic citrullinated peptide (CCP) better serum markers for rheumatoid arthritis than rheumatoid factor (RF)?

Contribution

This meta-analysis of 86 studies found that the positive likelihood ratio for anti-CCP antibody was greater than that for IgM RF for identifying patients with rheumatoid arthritis (12.5 vs. 4.9). Sensitivity was similar for the 2 tests, although specificity of anti-CCP antibody (95%) was higher than specificity of IgM RF (85%).

Cautions

Fewer studies evaluated anti-CCP antibody than RF. There was possible publication bias for reporting positive findings regarding anti-CCP antibody.

Implication

Anti-CCP antibody positivity seems to be more specific than IgM RF positivity for identifying patients with rheumatoid arthritis.

—The Editors

on request) were based on combinations of the following index terms: *rheumatoid arthritis, antiperinuclear factor, antikeratin antibody, citrullinated protein, anti–cyclic citrullinated peptide, rheumatoid factor, sensitivity, specificity, mass screening, predictive value of tests, receiver-operating characteristic curve,* and *accuracy.* We also reviewed reference lists of retrieved studies and review articles.

Study Selection

Two reviewers independently scanned abstracts that met the inclusion criteria. We included studies that evaluated the utility of assaying anti-CCP antibody or RF for diagnosis of known or suspected rheumatoid arthritis, enrolled at least 10 participants, were published after 1987, and provided enough data to allow calculation of sensitivity and specificity for diagnosis of rheumatoid arthritis. We used the 1987 revised American College of Rheumatology (ACR) criteria as the reference standard of rheumatoid arthritis (15). In general, we regarded reports of patients with symptom duration of less than 1 year as studies of early rheumatoid arthritis, although we also used the researchers' definitions of early rheumatoid arthritis.

Data Extraction and Study Quality Assessment

We extracted data by using a standard form that included the demographic characteristics of the participants, inclusion and exclusion criteria, number of participants who were evaluated with the index test, and methods of antibody testing. Two investigators independently assessed the design of the studies by using previously developed quality criteria for studies of diagnostic tests (16–18). These assessments addressed the technical quality of the anti-CCP antibody test, technical quality of the RF test, application of the reference or index test, blinding of observers, description of the study sample, and cohort assembly. We used κ coefficients to examine interrater agreement for our initial overall quality score (19) and resolved any item discrepancies through discussion.

Data Analysis

We used a random-effects model to combine estimates of sensitivity, specificity, and positive and negative likelihood ratios (19–21). We planned analyses that were stratified by generation of anti-CCP antibody assay (first [anti-CCP1] second [anti-CCP2]) and by RF subtype (IgA, IgG, and IgM). We analyzed subgroups of relevant studies that included patients with early rheumatoid arthritis and that evaluated combination testing for anti-CCP antibody and RF. We conducted a stratified analysis for different threshold and measurement methods when we suspected heterogeneity among studies. We also conducted threshold analyses and metaregression to assess whether the threshold effect and heterogeneity among studies existed (22).

We examined funnel plots for diagnostic odds ratios to explore the possibility of publication bias (23). For analyses, we used MetaDiSc, version 1.1.4 (Hospital Universitario Ramón y Cajal, Madrid, Spain); Stata, version 8.2 (Stata Corp., College Station, Texas); and R, version 2.21 (R Foundation for Statistical Computing, Vienna, Austria).

Role of the Funding Sources

This study was supported in part by a Grant-in-Aid for Young Scientists from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and a grant for Research on Allergic Disease and Immunology from the Ministry of Health, Labor and Welfare, Japan. The funding sources had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

RESULTS

Search Results and Characteristics of Studies

We identified 302 reports, of which 86 met the inclusion criteria (11, 12, 24–106) (**Appendix Figure**, available at www.annals.org). Thirty-seven studies in 14 949 patients (11, 12, 24, 26, 29–38, 40–42, 44, 45, 47, 48, 50, 52, 54, 56, 58, 60–62, 64, 66, 67, 70, 74, 76, 97, 99, 100) reported on the diagnostic accuracy of anti-CCP antibody, whereas 50 studies in 15 286 patients (12, 24, 27, 29, 30, 32–37, 39, 40, 42–44, 47, 48, 50, 52, 54, 55, 60–62, 64, 66, 70, 72–74, 76, 80–85, 88–98, 100) reported on the diagnostic accuracy of RF.

Appendix Table 1 (available at www.annals.org) (11, 24, 26, 29–38, 40–42, 44, 45, 47, 48, 50, 52, 54, 56, 58, 60–62, 64–67, 74, 76, 97, 99, 100) and **Appendix Table 2** (available at www.annals.org) (12, 24, 27, 29, 33–35, 37, 39–43, 45, 47, 48, 52, 65, 66, 72–74, 76, 80, 81, 88, 90–92, 94–98, 100) summarize the characteristics of the

included studies. In anti-CCP antibody and IgM RF studies, respectively, the median numbers of participants were 404 and 226, their median ages were 57 years and 53 years, and the median proportions of women were 59% and 68%. Studies of anti-CCP antibody that were published after 2000 usually addressed anti-CCP2 assays.

Characteristics of control groups varied. Among the anti-CCP antibody studies, 5 used patients with undifferentiated arthritis, 13 used patients with other rheumatic diseases, 1 used healthy persons, 1 used hepatitis C carriers, and 17 used a mix of healthy persons and patients with other diseases. Among the IgM RF studies, 5 used patients with undifferentiated arthritis, 16 used patients with other rheumatic diseases, 2 used healthy persons, 1 used hepatitis C carriers, 1 used patients with polymyalgia rheumatica, and 22 used a mix of healthy persons and patients with other diseases. Three studies did not report details on the control group.

Study Quality

Only 1 study satisfied all criteria on our quality checklist. Twenty-two studies (30%) met at least 70% of the criteria, and 9 studies (10%) met fewer than 50% of the criteria. The κ coefficient for interrater agreement was 0.92 on the quality score.

Most studies adequately described the technical aspects of assaying anti-CCP antibody and RF. In 86% (32 of 37) of anti-CCP antibody studies and 82% (41 of 50) of RF studies, the 1987 revised ACR criteria were used as the reference standard for rheumatoid arthritis. Most studies did not explicitly mention blinding of investigators to the clinical assessment or to the reference standard. Most studies (90%) enrolled patients with known or suspected rheumatoid arthritis. Characteristics of these patients were fully described in just over half of the studies. Enrollment was prospective in 18 of 37 anti-CCP antibody studies and 25 of 50 RF studies.

Studies of RF showed a wide range of sensitivities and specificities (**Appendix Table 1**, available at www.annals.org). One study (35) reported very low sensitivity and specificity. In this study, 57% of control patients had conditions that can present with RF-positive arthritis (primarily the Sjögren syndrome or Wegener granulomatosis).

Laboratory techniques for measuring RF varied across studies. Fifteen studies used nephelometry, 16 used latex agglutination, and 16 used ELISA. Twenty-two studies used less than 20 U/mL as the cutoff value for negative test results, 11 used less than 40 U/mL as the cutoff value, and 17 did not report cutoff values.

Diagnostic Accuracy of Anti-CCP Antibody and IgM RF, IgA RF, and IgG RF

The summary positive and summary negative likelihood ratios, respectively, were 12.46 (95% CI, 9.72 to 15.98) and 0.36 (0.31 to 0.42) for anti-CCP antibody and 4.86 (CI, 3.95 to 5.97) and 0.38 (CI, 0.33 to 0.44) for IgM RF (**Figure 1** and **Figure 2**). The pooled sensitivity and specificity were 67% (CI, 65% to 68%) and 95% (CI, 95% to 96%), respectively, for anti-CCP antibody and 69% (CI, 68% to 70%) and 85% (CI, 84% to 86%) for IgM RF. Data that were limited to studies of patients with early rheumatoid arthritis were similar to those from all studies (data available from the authors on request).

Studies published before 2000 tended to report high sensitivity and specificity for RF compared with studies published from 2000 onward. More recent studies reported favorable specificities for anti-CCP antibody. Summary likelihood ratios for studies that directly compared anti-CCP antibody and IgM RF (11, 12, 24, 26, 29–38, 40–42, 44, 45, 47, 48, 50, 52, 54, 56, 58, 60–62, 64, 66, 67, 70, 74, 76, 97, 99, 100) were similar to summary data from all studies. Positive likelihood ratios for anti-CCP antibody and IgM RF were 12.32 and 3.86, respectively. Negative likelihood ratios for anti-CCP antibody and IgM RF were 0.40 and 0.41, respectively. Positive and negative likelihood ratios for IgA RF and IgG RF seemed to be qualitatively similar to those for IgM RF (**Figure 3**). Stratified analyses for IgM RF showed no major differences for positive summary likelihood ratios or negative likelihood ratios across the strata of cutoff values and measurement methods (**Table**). The threshold effect for IgM RF is not statistically significant, and no covariate was statistically significant in the metaregression model.

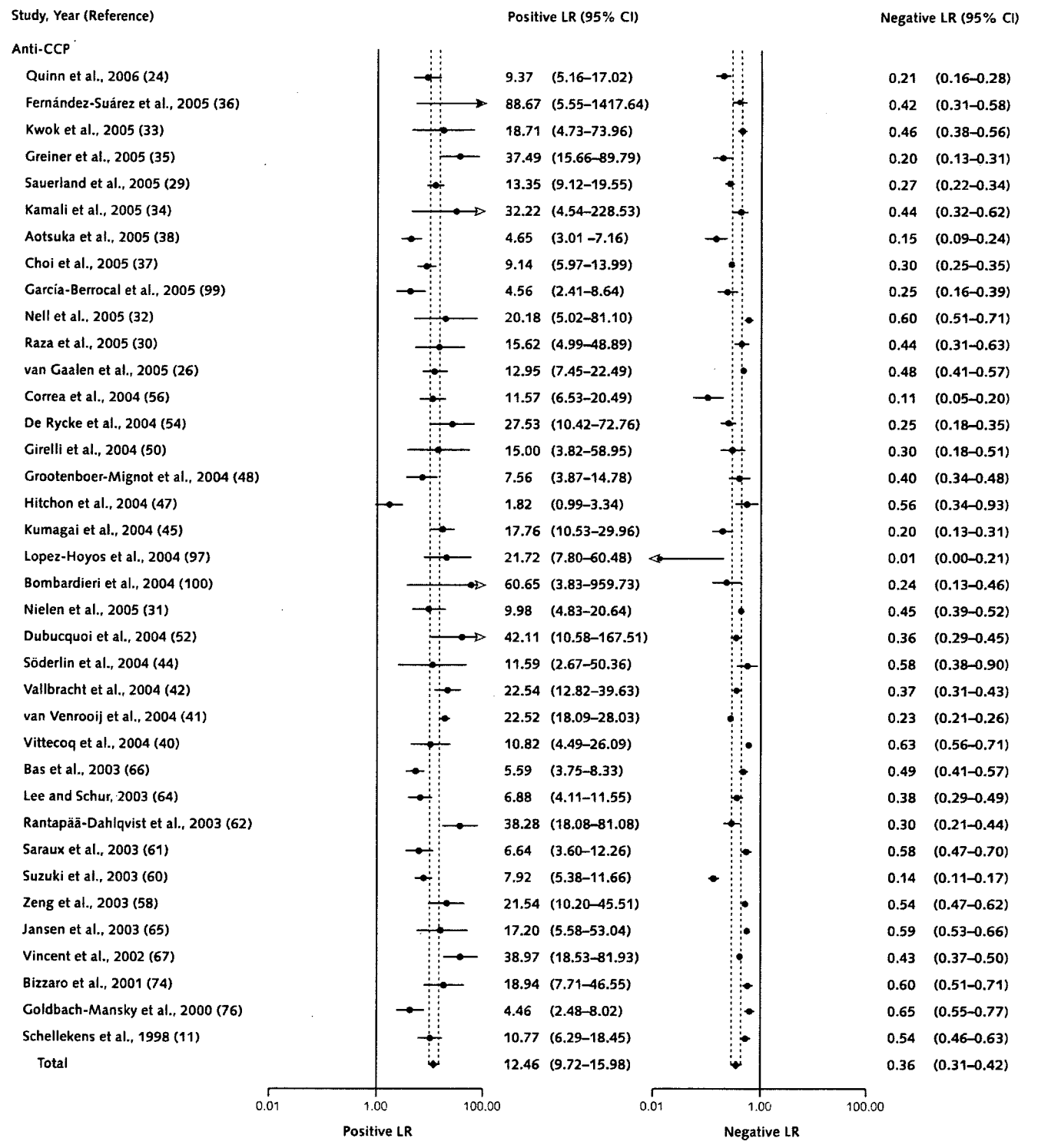
Diagnostic Accuracy of Anti-CCP1, Anti-CCP2, and Both Anti-CCP Antibody and IgM RF

Twenty-nine studies in 11 821 patients (24, 26, 29–38, 40–42, 44, 45, 47, 48, 50, 52, 54, 56, 60, 62, 64, 97, 99, 100) assessed anti-CCP2, whereas 5 studies in 2098 patients (61, 66, 67, 70, 74) assessed anti-CCP1.

Although the sensitivities and specificities were similar to those in the anti-CCP1 studies, 3 studies (12, 58, 76) that used an in-house ELISA were excluded because incorporating them introduced a positive threshold effect and caused heterogeneity among the studies. The summary positive and negative likelihood ratios were 12.77 (CI, 9.62 to 16.94) and 0.32 (CI, 0.27 to 0.38), respectively, for anti-CCP2 and 13.03 (CI, 5.74 to 29.04) and 0.53 (CI, 0.46 to 0.61) for anti-CCP1 (**Figure 4**).

Six studies in 1753 patients (12, 30, 37, 50, 64, 74) simultaneously measured anti-CCP antibody and RF, whereas 8 studies in 2837 patients (12, 30, 37, 42, 50, 64, 70, 74) performed 1 of the tests only when the results on the other test were positive. For studies that required the presence of both anti-CCP antibody and IgM RF for a positive result, the summary positive and negative likelihood ratios were 15.72 (CI, 8.30 to 29.75) and 0.46 (CI, 0.35 to 0.61), respectively. For studies that considered a result positive if either anti-CCP antibody or IgM RF was detected, the positive and negative summary likelihood ratios were 4.32 (CI, 2.71 to 6.90) and 0.32 (CI, 0.25 to 0.42), respectively.

Figure 1. Likelihood ratio *(LR)* for autoantibodies against cyclic citrullinated peptides *(anti-CCP)*.



Prognostic Value of Anti-CCP Antibody and IgM RF

Appendix Table 3 (available at www.annals.org) summarizes the results of 5 studies of the association between rheumatoid arthritis and anti-CCP antibody. The odds ratio for rheumatoid arthritis was 16.1 to 38.99 for anti-CCP antibody positivity and 1.2 to 8.7 for RF positivity.

Fifteen studies examined associations between marker positivity and radiographic progression (Appendix Table 4,

Figure 2. **Likelihood ratio *(LR)* for autoantibodies against IgM rheumatoid factor *(RF)*.**

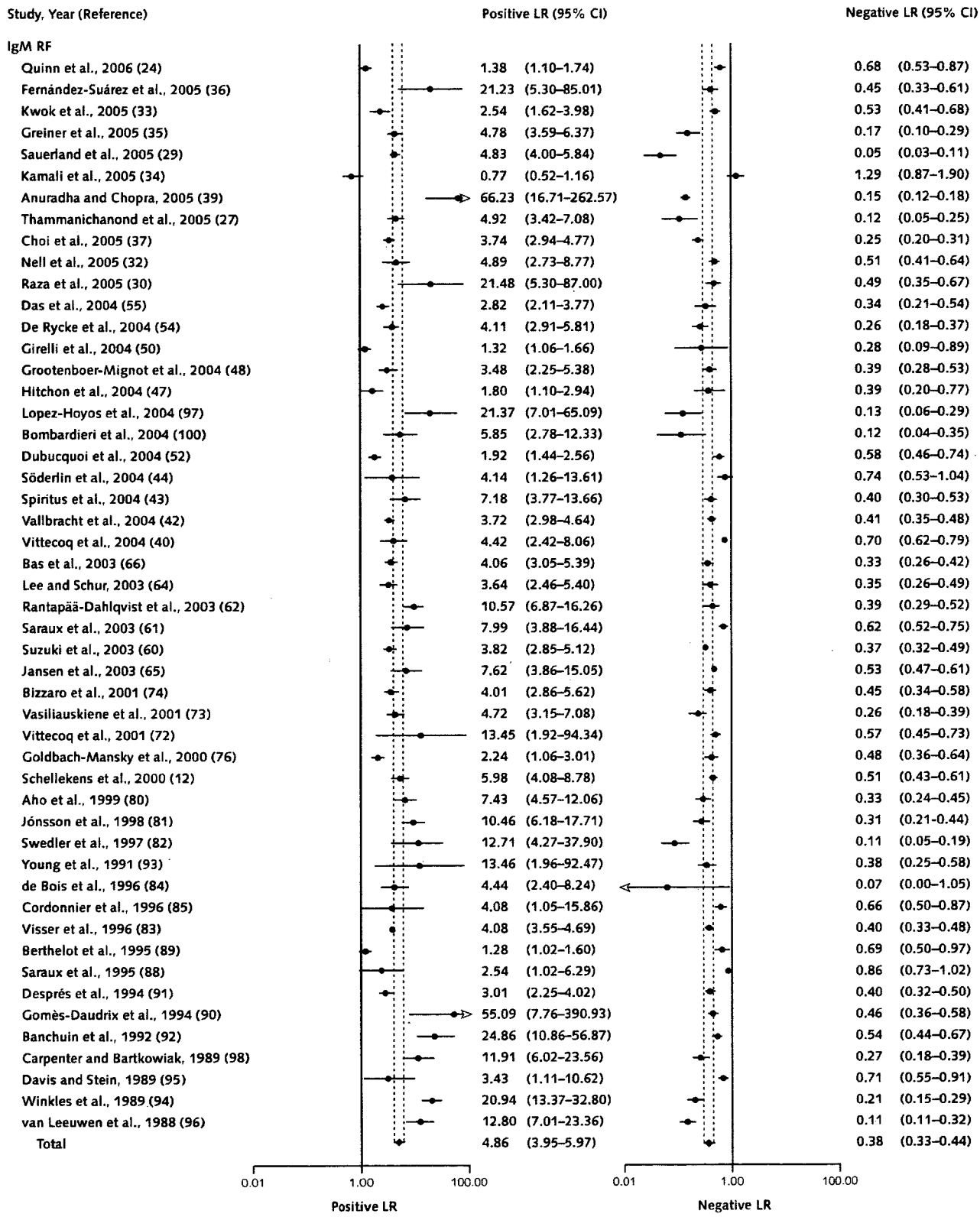
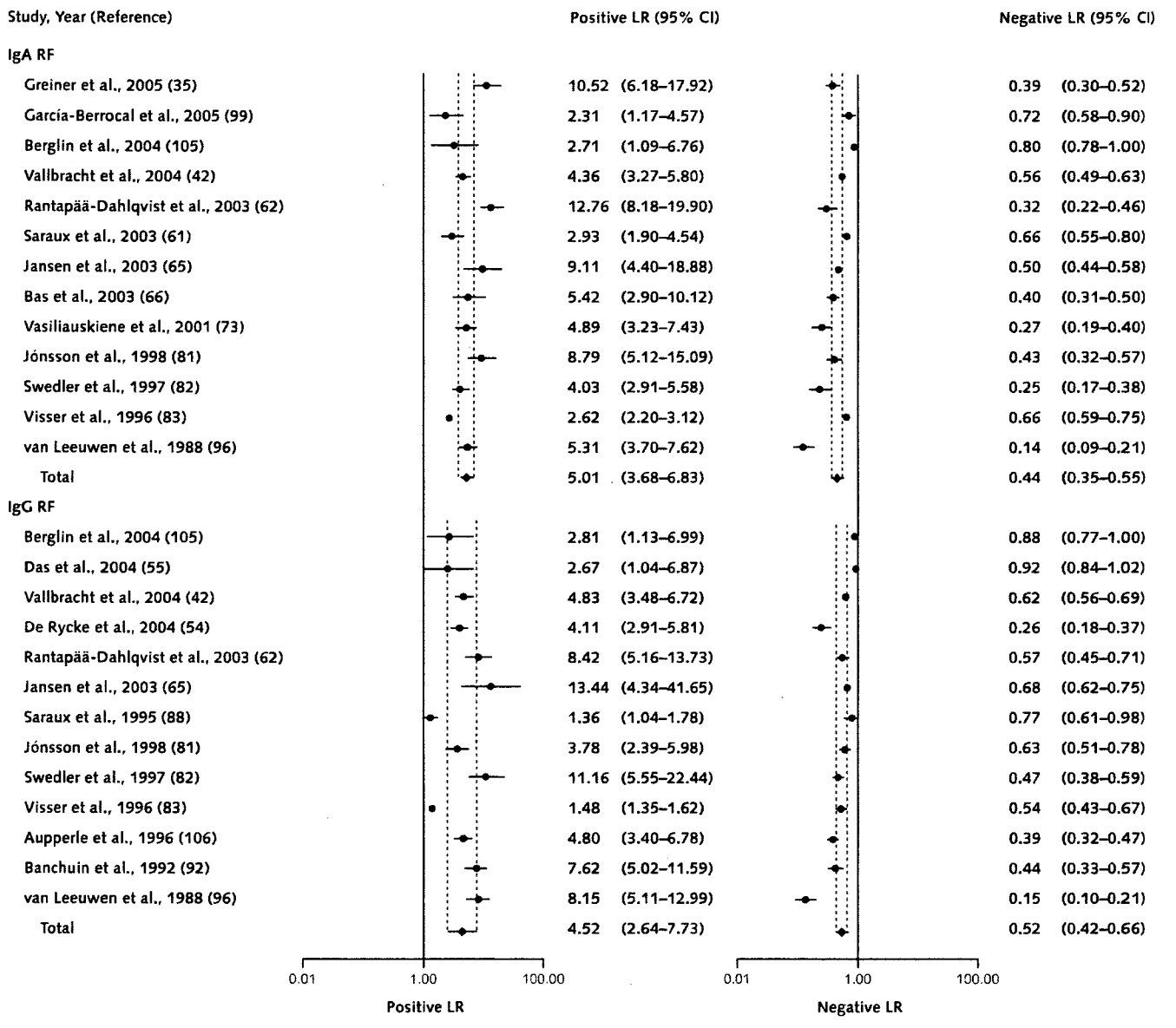


Figure 3. Likelihood ratio *(LR)* for IgA rheumatoid factor *(RF)* and IgG RF.



available at www.annals.org). Six studies assessed associations with anti-CCP antibody positivity; 3 of these studies used an anti-CCP1 assay. All 6 studies reported that anti-CCP antibody positivity was a statistically significant risk factor for radiographic progression. Of the 4 studies that examined anti-CCP antibody and RF, 3 reported that the risk for radiographic progression was greater for patients with anti-CCP antibody positivity than for those with IgM RF positivity.

Discussion

We identified several issues that had not been addressed systematically or quantitatively in past narrative reviews (107, 108). Anti-CCP antibody positivity was more specific than IgM RF, IgG RF, or IgA RF positivity for rheumatoid arthritis and was more specific than IgM RF for early rheumatoid arthritis. Because pooled sensitivities were similar for anti-CCP antibody and RF, the better diagnostic accuracy of anti-CCP antibody was mainly due to its higher specificity. Anti-CCP2 was a more sensitive marker than anti-CCP1. Assaying anti-CCP antibody alone and assaying combinations of anti-CCP antibody and IgM RF provided similar results. Anti-CCP antibody positivity, especially anti-CCP2, was superior to IgM RF positivity for predicting development of rheumatoid arthritis and radiographic progression.

Some experts believe that immunity against citrulline

plays a crucial role in the pathogenesis of rheumatoid arthritis (109). Anti-CCP antibodies and anticitrullinated filaggrin antibodies are locally produced in inflamed joints, and citrullinated fibrin is found in the synovia of patients with rheumatoid arthritis (110).

Anti-CCP antibody is present before symptoms develop, which suggests that citrullination and production of anti-CCP antibody are early processes in rheumatoid arthritis (62). As we show, anti-CCP antibody is highly specific for rheumatoid arthritis. However, the biological function of RF is unclear: It is found in some apparently healthy elderly persons and in persons who have conditions other than rheumatoid arthritis (111). Substantial differences exist among RF test kits, and the reliability of some RF assays is questionable (112). The varying techniques for measuring RF might partly explain the heterogeneous study results for RF.

Some studies have reported conflicting results on whether IgG RF and IgA RF are better diagnostic markers than IgM RF (82, 87, 92). We found no major diagnostic differences among IgG RF, IgA RF, and IgM RF, whereas anti-CCP antibody was a better diagnostic marker than all 3 RF subclasses. Our findings are compatible with those of earlier studies of the sensitivity of different generations of anti-CCP antibody assays. Filaggrin-derived cyclic peptide anti-CCP1 assays had very high specificity (98%) and moderate sensitivity that was lower than that of RF (12, 113). To overcome this problem, various cyclic epitopes that mimic true conformational epitopes were selected from libraries of citrullinated peptides to develop more sensitive anti-CCP2 assays (41, 62).

Some studies suggested that the diagnostic accuracy of both anti-CCP antibody and IgM–RF positivity was not markedly better than that of anti-CCP antibody positivity alone. The combination of anti-CCP antibody and IgM RF positivity improved specificity over RF positivity alone. Persons without rheumatoid arthritis who had false-positive results for RF did not have positive results for anti-CCP antibody and were regarded as healthy. The sensitivity, however, was reduced because positivity for anti-CCP antibody and RF is a more stringent criterion than is positivity for anti-CCP antibody or IgM RF alone. As a result, combining anti-CCP antibody and RF testing offered little improvement.

However, anti-CCP antibody positivity or IgM RF positivity is more permissive in terms of sensitivity because the antibodies complement each other in patients with false-negative results. In this case, specificity is reduced substantially because all persons with false-positive results for RF are counted as having positive results for rheumatoid arthritis. Because the improvement and deterioration of sensitivity were balanced, the overall diagnostic accuracy of RF is less than that of anti-CCP antibody alone. Together, these results show that anti-CCP antibody positivity is as effective a diagnostic indicator as anti-CCP antibody and RF positivity combined and is a less accurate indicator than positivity for either antibody alone.

In clinical practice, most rheumatologists recommend measuring anti-CCP antibody and RF because anti-CCP antibody has moderate sensitivity, and clinicians try to maximize sensitivities by combining the 2 markers, especially for early rheumatoid arthritis (32, 47, 48, 52, 59, 61, 63, 64, 66). Also, rheumatologists measure RF because it is included in the 1987 ACR criteria, and both anti-CCP antibody and RF are recommended screening tests for rheumatoid arthritis (114). In any case, comparison of anti-CCP antibody only with testing for anti-CCP antibody and RF involves a tradeoff between overall sensitivity and specificity. If we want to maximize sensitivity, then both tests are better, although this may prompt us to treat patients who are anti-CCP antibody negative but RF positive. Because it is harmful and costly to treat persons with false-positive results who do not have rheumatoid arthritis, we need to consider the risks and the benefits of such an approach. Clinical trials and cost-effectiveness studies of these tradeoffs are needed.

When should we measure both anti-CCP antibody and RF? If the prior probability of rheumatoid arthritis is relatively low, such as in patients who have knee pain only in primary care or those who meet no other ACR criteria, measuring anti-CCP antibody alone seems to be a reasonable strategy that avoids too many false-positive results. If, however, the prior probability of rheumatoid arthritis is relatively high, such as in patients seen in rheumatology clinics or those who meet other ACR criteria, measuring anti-CCP antibody or IgM RF seems to be a reasonable strategy that avoids missing potentially treatable patients.

We found that the presence of anti-CCP antibody is associated with development of rheumatoid arthritis and greater radiographic progression, and we confirmed that RF is a major predictor of bone damage (58, 88).

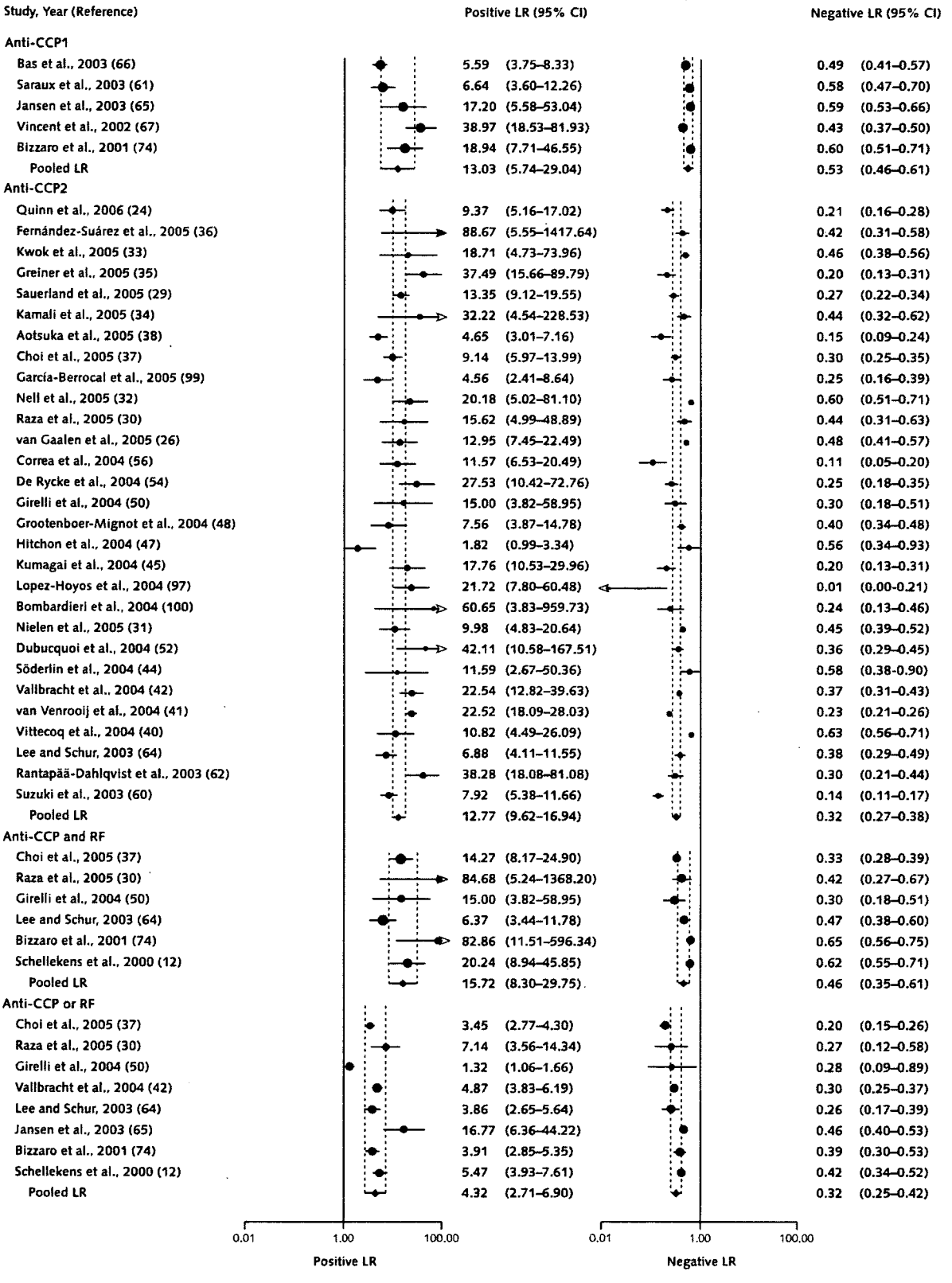
Our review has several limitations. We may have missed some pertinent studies, because we included only diagnostic studies that provided information on sensitivity

Table. **Summary Likelihood Ratios of IgM Rheumatoid Factor***

Variable	Positive LR (95% CI)	Negative LR (95% CI)
All studies	4.86 (3.96–5.97)	0.38 (0.33–0.44)
Cutoff value		
≥20 U/mL	4.42 (3.02–6.47)	0.39 (0.31–0.50)
≥40 U/mL	5.49 (2.25–13.38)	0.50 (0.37–0.69)
≥80 U/mL	4.57 (1.36–15.09)	0.44 (0.29–0.68)
Measurement method		
Nephelometry	4.15 (2.95–5.84)	0.32 (0.25–0.41)
Latex agglutination	5.05 (3.01–8.50)	0.39 (0.27–0.56)
ELISA	6.13 (4.60–8.17)	0.42 (0.34–0.51)

* ELISA = enzyme-linked immunosorbent assay; LR = likelihood ratio.

Figure 4. **Pooled likelihood ratio *(LR)* for first-generation assays for autoantibodies against cyclic citrullinated peptide *(CCP1)*, second-generation assays *(CCP2)*, anti-CCP antibody and rheumatoid factor *(RF)*, and anti-CCP antibody or RF.**



and specificity. Our funnel plots suggested some publication bias for favorable anti-CCP antibody studies (data not shown). Because RF is incorporated into the current diagnostic criteria of rheumatoid arthritis, diagnostic studies of IgM RF might have some incorporation bias that could have increased the apparent sensitivity of this marker (115).

In conclusion, anti-CCP antibody positivity is more specific than IgM RF positivity for diagnosing rheumatoid arthritis and early rheumatoid arthritis. Anti-CCP antibody positivity should be included among the diagnostic criteria of these 2 conditions.

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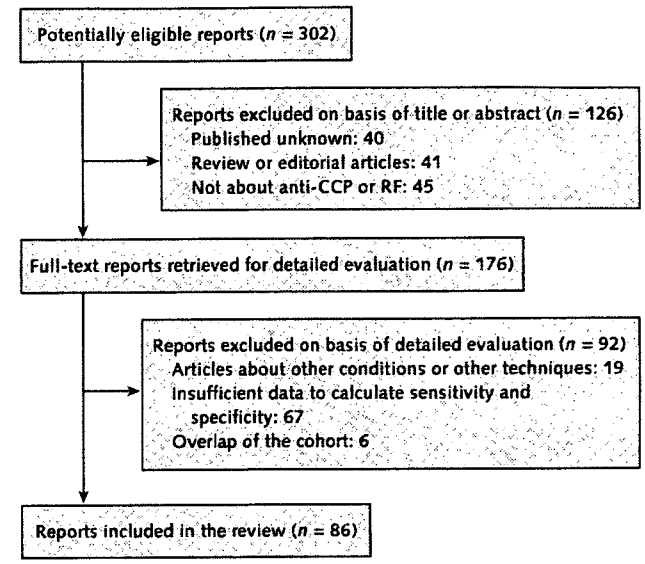
Appendix Figure. Study flow diagram. WEB-ON



CCP = cyclic citrullinated peptide; RF = rheumatoid factor.

Primary care	CCP2	Inova	ACR	Prospective	Not reported	Not reported	Yes	Yes	52	45.5	NA	Other rheumatic diseases (n = 25), healthy persons (n = 50)	31	0	22
Rheumatology clinic	CCP2	Inova	ACR	Retrospective	Not reported	NA	Yes	Yes	56	86.8	13.2	Other rheumatic diseases (n = 68), healthy persons (n = 60)	71	2	58
Teaching hospital	CCP2	Euro-Diagnostica	ACR	Not reported	Not reported	NA	Yes	Yes	54.8	NA	NA	Other rheumatic diseases (n = 233)	70	5	17
Teaching hospital	CCP2	Euroimmun	ACR	Prospective	Not reported	NA	Yes	Yes	NA	NA	NA	Other rheumatic diseases (n = 469)	171	26	60
Teaching hospital	CCP2	Euroimmun	ACR	Not reported	Not reported	Not reported	Yes	No	NA	NA	NA	Progressive systemic sclerosis (n = 32), Wegener granulomatosis (n = 22)	26	1	20
Teaching hospital	CCP2	Axis-Shield	ACR	Retrospective	Not reported	0–24 y	Yes	No	NA	NA	NA	Other rheumatic diseases (n = 90), healthy persons (n = 200)	115	17	16
Primary care	CCP2	Tosho	ACR	Not reported	Not reported	Not reported	Yes	Yes	NA	NA	NA	Other rheumatic diseases (n = 251)	236	20	88
Teaching hospital	CCP2	Euro-Diagnostica	ACR	Retrospective	Not reported	Not reported	Yes	Yes	NA	NA	NA	Other diseases (n = 49)	69	8	18
Cohort study	CCP2	Axis-Shield	ACR	Prospective	Not reported	<12 mo	Yes	No	NA	NA	0.125	UA (n = 98)	42	2	60
Rheumatology clinic	CCP2	Axis-Shield	ACR	Prospective	Not reported	<18 mo	Yes	Yes	59.5	53.7	0.1	Osteoarthritis (n = 10), hyperlipidemia (n = 20), other rheumatic diseases (n = 52)	24	3	18
Cohort study	CCP2	Euro-Diagnostica	ACR	Prospective	Not reported	<12 mo	Yes	Yes	49	0.55	3	UA (n = 107), other rheumatic diseases (n = 207)	82	13	71
Teaching hospital	CCP2	Inova Diagnostics	ACR	Retrospective	Not reported	Not reported	Yes	Yes	NA	NA	NA	Other rheumatic diseases (n = 131), healthy persons (n = 10)	74	11	8
Rheumatology clinic	CCP2	Euro-Diagnostica	ACR	Prospective	Not reported	Same period	Yes	Yes	63.5	34.7	5	Other rheumatic diseases (n = 146)	89	4	29
Rheumatology clinic	CCP2	Axis-Shield	ACR	Prospective	Not reported	Same period	Yes	Yes	62.9	0.779	NA	HCV infection (n = 14), other rheumatic diseases (n = 28)	25	2	10
Teaching hospital	CCP2	Euro-Diagnostica	Not reported	Not reported	Not reported	Not reported	Yes	No	NA	NA	NA	Other rheumatic diseases (n = 91)	167	8	98
Teaching hospital	CCP2	Inter-medico	ACR	Prospective	Not reported	Not reported	Yes	Yes	NA	NA	NA	UA (n = 23)	26	8	15
Teaching hospital	CCP2	Axis-Shield	ACR	Retrospective	Not reported	Not reported	Yes	No	NA	NA	NA	Other rheumatic diseases (n = 307)	64	14	15
Teaching hospital	CCP2	Euro-Diagnostica	ACR	Prospective	Not reported	Not reported	Yes	Yes	62.5	64.8	NA	Polymyalgia rheumatica (n = 48)	38	3	0
Teaching hospital	CCP2	Axis-Shield	ACR	Prospective	Not reported	Not reported	Yes	Yes	58.8	NA	10	HCV infection (n = 10)	23	0	7
Rheumatology clinic	CCP2	Euro-Diagnostica	ACR	Prospective	Yes	1 y	Yes	Yes	56.1	0.686	0.4	UA (n = 121)	149	7	109
Teaching hospital	CCP2	Axis-Shield	ACR	Retrospective	Not reported	6–18 mo	Yes	No	NA	NA	NA	Other rheumatic diseases (n = 98), healthy persons (n = 33)	90	2	50
Health care centers	CCP2	Euro-Diagnostica	Clinical diagnosis	Prospective	Yes	2 y	Yes	Yes	49.6	63.7	0.3	Reactive arthritis (n = 28), UA (n = 10), other arthritis (n = 15)	7	2	9
Teaching hospital	CCP2	Euro-Diagnostica	ACR	Not reported	Not reported	Not reported	Yes	Yes	56.8	0.712	8.3	Degenerative joint disease (n = 163), other rheumatic diseases (n = 103), healthy persons (n = 154)	190	12	105
Teaching hospital	CCP2	Not reported	Not reported	Not reported	Not reported	Not reported	No	Yes	NA	NA	NA	Other rheumatic diseases (n = 2297)	865	79	252
Cohort study	CCP2	Euroimmun	ACR	Prospective	Not reported	Not reported	Yes	Yes	51.7	10.5	0.33	Other rheumatic diseases (n = 225)	69	5	107
Teaching hospital	CCP1	Euro-Diagnostica	ACR	Cross-sectional	Not reported	Not reported	Yes	Yes	62	0.71	NA	Other rheumatic diseases (n = 160), spondyloarthropathies (n = 79)	110	24	86
Teaching hospital	CCP2	Axis-Shield	ACR	Retrospective	Not reported	Not reported	Yes	Yes	47.5	79.1	NA	Other rheumatic diseases (n = 113), noninflammatory arthritis (n = 23)	68	14	35

Teaching hospital	CCP1	In-house ELISA	ACR	Not reported	Not reported	Not reported	Yes	Yes	46.14	71.7	NA	Other rheumatic diseases (n = 132), nonrheumatic diseases (n = 98), healthy persons (n = 90)	90	7	101
Rheumatology clinic	CCP1	Euro-Diagnostica	Clinical diagnosis	Prospective	Not reported	Not reported	Yes	Yes	57	69	NA	UA (n = 121)	110	3	148
Rheumatology clinic	CCP1	Euro-Diagnostica	ACR	Not reported	Not reported	Not reported	Yes	Yes	58.06	79.6	NA	Other rheumatic diseases (n = 157), nonrheumatic arthritis (n = 314)	139	7	101
Rheumatology clinic	CCP1	Euro-Diagnostica	ACR	Prospective	Yes	Not reported	No	Yes	65	89.7	NA	Other rheumatic diseases (n = 174), healthy persons (n = 58)	40	5	58
Cohort study	CCP1	In-house ELISA	ACR	Prospective	Not reported	12 mo	Yes	Yes	42.1	0.66	NA	UA (n = 85), other rheumatic diseases (n = 57)	43	12	63
Teaching hospital	CCP1	In-house ELISA	ACR	Retrospective	Yes	Not reported	Yes	Yes	NA	NA	NA	Other rheumatic diseases (n = 329), infectious diseases (n = 366), healthy persons (n = 120)	72	14	77

CP = cyclic citrullinated peptide; ELISA = enzyme-linked immunosorbent assay; FN = false negative; FP = false positive; HCV = hepatitis C virus; LR = likelihood ratio; NA = not available; TN = true negative; TP = true positive; UA = undifferentiated arthritis.
: Axis-Shield (Dundee, United Kingdom), Euro-Diagnostica (Arnhem, the Netherlands), Euroimmun (Luebeck, Germany), Inova Diagnostics (San Diego, California), Intermedico (Markham, Ontario, Canada), and Tosho (Tokyo, Japan).