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ORIGINAL RESEARCH

Refining serological scores in rheumatoid arthritis classification: an international study

Lieve Van Hoovels ,[1,2] Christos Chatzichristos,[3] Juan Irure-Ventura,[4] Daphné Vandebeek,[5] Elke Lodewijckx,[6] Bert Vander Cruyssen,[7] Daniela Sieghart,[8] Carolien Bonroy,[9,10] Eszter Nagy,[11] Rille Pullerits,[12,13] Saša Čučnik,[14,15] Charlotte Dahle,[16] Ingmar Heijnen,[17] Luca Bernasconi,[18] Farid Benkhadra,[19] Laura Bogaert,[2] Stefanie Van Den Bremt,[2] Ann Van Liedekerke,[20] Geert Vanheule,[21] Johan Robbrecht,[22] Claudine Wirth,[23] Rüdiger B Mueller,[24] Diego Kyburz,[25] Christopher Sjöwall ,[16] Alf Kastbom ,[16] Rok Ješe,[14] Boja Jovancevic,[13] Emese Kiss,[26] Peggy Jacques ,[27] Maarten De Vos,[3,28] Marcos López-Hoyos,[4,29] Günter Steiner ,[8,30] Patrick Verschueren ,[6,28] Xavier Bossuyt [1,5]

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For numbered affiliations see end of article.

Correspondence to
Dr Günter Steiner; Guenter.steiner@meduniwien.ac.at

Dr Xavier Bossuyt; xavier.bossuyt@uzleuven.be

ABSTRACT

Background In the American College of Rheumatology/European Alliance of Rheumatology Associations 2010 classification criteria for rheumatoid arthritis (RA), rheumatoid factor (RF) and anti-citrullinated protein/peptide antibodies (ACPA) are assigned the same weight, although ACPA have proven more specific than RF. We aimed to refine the serological weight factors for RA classification.

Materials and methods Diagnostic samples from 398 patients with RA and 448 diseased controls (DC) were evaluated with RF and ACPA assays from five different manufacturers. A grid search was conducted across all possible integer score pairs for RF and ACPA to identify the weighting combination that optimised the specificity of RA classification. This combination was applied in a refined scoring system (RSS) for three confirmatory cohorts comprising, respectively, 67, 157 and 132 patients with RA and 441, 153 and 193 DC.

Findings In the investigative cohort, the optimal combination of weighting scores was characterised by higher scores for ACPA, higher antibody levels and double RF/ACPA positivity.
Applying the optimal combination of weighting scores decreased misclassification compared with the 2010 RA classification criteria, minimally affecting sensitivity. For seropositive patients, RSS significantly lowered misclassification from 38.3–55.8% to 15.0–26.9%. The improved specificity of RSS (compared with the 2010 criteria) was validated in the confirmatory cohorts. Considering only seropositive patients, the RSS significantly decreased RA misclassification (8.6–36.8% vs 20.0–78.9%), minimally affecting the sensitivity (86.7–97.3% vs 86.7–96.0%).

Interpretation Serological weight factors for RA classification can be improved by taking into account the antibody type, the antibody levels and single or combined positivity. The application of an RSS reduced the number of RA misclassifications.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Rheumatoid factor (RF) and anti-citrullinated protein/peptide antibodies (ACPA) are currently given the same weight in the American College of Rheumatology/European Alliance of Rheumatology Associations 2010 classification criteria.

⇒ The likelihood ratios for rheumatoid arthritis (RA) differ considerably between RF and ACPA.

WHAT THIS STUDY ADDS

⇒ Serological weight factors for RA classification can be improved by taking into account the antibody type (RF vs ACPA), the antibody level and single or combined positivity.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Refinement of serological weight factors can improve the specificity of RA classification, thereby reducing the number of RA misclassifications, without affecting sensitivity.

INTRODUCTION

In patients with rheumatoid arthritis (RA), clinical outcomes such as joint damage and disability can be improved by early diagnosis and an adequate therapy with disease-modifying anti-rheumatic drugs (DMARD).[1] The American College of Rheumatology (ACR) and European Alliance of Rheumatology Associations (EULAR) 2010 classification criteria for RA were developed with the aim to identify and classify patients with early RA.[2] Application of the 2010 classification criteria provides a score of 0–10, with a score of ≥6 being needed for classification of

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a patient as having definite RA. Four domains are integrated in the ACR/EULAR RA classification criteria: (1) number and type of joints involved (providing 0–5 points), (2) acute-phase reactants (providing 0–1 point), (3) duration of symptoms (providing 0–1 point) and (4) serology: rheumatoid factor (RF) and anti-citrullinated protein/peptide antibody (ACPA) test results (providing 0–3 points).[2] Even though classification criteria are not intended for diagnostic purposes, they may facilitate early identification of patients with RA and enable early initiation of DMARD therapy.

Several studies evaluated the accuracy of the ACR/EULAR 2010 criteria for the diagnosis of RA. In an international very early arthritis cohort, Biliavska *et al*[3] compared the ACR/EULAR 2010 criteria to the ACR 1987 RA criteria[4] and demonstrated substantially increased diagnostic sensitivity (85% vs 65%), but lesser diagnostic specificity (64% vs 80%) of the 2010 criteria compared with the former criteria set from 1987. Similar results were reported in other studies,[5–8] with sensitivity figures of the 2010 criteria set ranging from 73.5% to 84% and specificities ranging between 60% and 71%. A potential drawback of this decreased specificity of the ACR/EULAR 2010 classification criteria is the risk of misclassification and over-diagnosis at baseline (ie, patients who do not require DMARD therapy being classified as RA) although the criteria are not intended to be used for diagnostics. Biliavska *et al*[3] documented that part of the lower specificity relates to the fact that RF and ACPA are given high weight in the 2010 classification criteria[2]; 20.5% of 'false positive' (non-RA with a score ≥6) patients were autoantibody positive.

In the ACR/EULAR 2010 classification criteria for RA, a low-positive RF or low-positive ACPA (> the upper limit of normal (ULN) but ≤3 times the ULN) contributes two points, whereas a high-positive RF or ACPA (>3 times the ULN) contributes three points.[2] This implies that the ability of RF and ACPA to discriminate between RA and non-RA would be similar; however, this is not the case. Numerous studies have shown that ACPA has a higher specificity and likelihood ratio (LR) for RA as compared with RF.[9–13] Moreover, the 2010 classification criteria do not consider a difference in contribution for combined positivity of RF and ACPA compared with single positivity.[14–17] In the present multicentre study, we aimed to refine the contribution of the serological scores in the ACR/EULAR 2010 classification criteria such that the specificity would be enhanced without affecting the sensitivity.

PATIENTS AND METHODS

Patient populations

The investigative cohort was based on a European, multicentre study[18] comprising 398 diagnostic samples from patients with RA and 1073 samples from diseased controls (DC). We included in the final analysis only the control patients (n=448) for whom all clinical data necessary for RA classification were available.

In addition, three independent confirmatory cohorts of previous RA serology studies were included: (1) a monocentric, retrospective, consecutive cohort of patients consulting the tertiary rheumatology centre of the University Hospitals of Leuven (Belgium) for the first time (RA=67, DC=441)[19]; (2) a monocentric, retrospective, consecutive cohort of patients in which RF and ACPA levels were determined as part of a diagnostic work-out at the Immunology Service of the Marqués de Valdecilla University hospital (Santander, Spain) (RA=157, DC=153)[20]; (3) a multicentre prospective trial called Stop Arthritis Very Early (SAVE), performed at 26 sites in Europe, two in Mexico and one in Japan, and involving early arthritis patients most of whom did not have a clear diagnosis at study entry (RA=132, non-RA=193).[21]

In all study cohorts, the RA cohort consisted of patients with consecutive newly diagnosed RA. A patient with synovitis was considered to have RA when no alternative diagnosis could better explain the symptoms, and when the treating rheumatologist initiated methotrexate treatment or other disease-modifying antirheumatic drugs (DMARD). RA diagnosis was reviewed after 2 years of follow-up. Demographic data (age, sex) and the clinical data included in the ACR/EULAR RA classification criteria (C reactive protein (CRP) and erythrocyte sedimentation rate (ESR), duration of symptoms, number and type of joints affected) of patients and controls are given in online supplemental data table 1.

Autoantibody assays

In the investigative cohort, all study samples were tested centralised by using five different RF and ACPA assays in parallel. Two IgM isotype-specific RF assays (EliA RF IgM on Phadia 250 (Thermo Fisher Scientific, Sweden) and Alegria RF IgM on Alegria (Orgentec, Germany; currently Sebia, France)) and three isotype-non-specific RF assays (RF-II (Roche Diagnostics, Germany) on a Cobas c501 (Roche Diagnostics), RF on Alinity c (Abbott, Germany) and RF on Atellica CH 930 (Siemens Healthineers, UK)) were included. The ACPA assays were: CCP EliA IgG on Phadia 250 (Thermo Fisher Scientific), anti-CCP hs on Alegria (Orgentec; currently Sebia), anti-CCP IgG on Cobas e601 (Roche Diagnostics), anti-CCP IgG on Alinity I (Abbott) and anti-CCP IgG on Atellica IM1300 (Siemens Healthineers, UK). The antigens used in all assays are cyclic citrullinated synthetic peptides (second generation; CCP2) except for the Orgentec assay which uses cyclic citrullinated vimentin peptides.[18]

For each of the confirmatory cohorts, RA serology data were based on one RF and ACPA assay, used in routine practice for each centre. For the study cohort of Vandebeek *et al* isotype-non-specific RF was determined on IMMAGE800 (Beckman Coulter, California, USA) and ACPA by EliA CCP IgG, Phadia 250.[19] Irure-Ventura *et al* obtained serology results using the isotype-non-specific RF assay on Optilite (Binding Site, Birmingham,

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UK) and ACPA IgG on BIO-FLASH, a third generation (CCP3) assay (Werfen, San Diego, California, USA).[20] In the SAVE trial, isotype-non-specific RF was measured by nephelometry using a Behring nephelometer (Behring Marburg, Germany) and ACPA by CCP EliA IgG on Phadia 250.[21] Detailed assay characteristics are given in online supplemental data table 2.

For both RF and ACPA, three test result intervals were distinguished (negative, low-positive, high-positive), as described in the ACR/EULAR RA classification criteria, based on thresholds defined by the manufacturer: results below the cut-off were considered negative, values between the cut-off and less than three times the cut-off were considered low-positive and results equal to or exceeding three times the cut-off were considered high-positive.[2]

Statistical analysis

Diagnostic performance characteristics (sensitivity, specificity, (partial) area under the receiver operating characteristic curve ((p)AUC) and test result interval-specific LRs) were calculated using MEDCALC (MedCalc Statistical Software V.23.4.2; MedCalc Software bv, Ostend, Belgium) and Python. The LR is the fraction of patients with RA with a specific test result divided by the fraction of controls with the same test result.[22 23]

To investigate the impact of serological weights on RA classification, we performed a grid search over integer assignments (0–5) to the nine cells of the RF×ACPA scoring matrix, attributed based on positivity (no/yes) and antibody level (low/high). In order to limit the number of possible combinations (6^9=10077696) the following constraints were applied: monotonicity (higher score for the antibody levels) and score ACPA≥RF (leaving 23 000 combinations). To ensure alignment with the intended clinical application, we opted for an integer-based scoring system rather than regression-derived coefficients. The serological weight score combination that optimised the specificity of the RA classification criteria (at the ACR/EULAR threshold of ≥6) in the investigative cohort while preserving sensitivity non-inferior to the 2010 criteria was selected. When multiple configurations satisfied this criterion, the one with the highest mean specificity across the five manufacturers was retained and applied on the three confirmatory cohorts. For the classification model analyses, the scikit-learn library in Python was used.

RESULTS

Test result interval-specific LRs

In order to assess the outcome-specific performance of RF and ACPA tests to discriminate RA from controls we determined outcome-specific (result interval-specific) LRs (table 1). The LR of low-positive and high-positive RF results ranged from 2.4 to 8.7 and from 9.8 to 17.8, respectively, depending on the assays used (table 1). The LR for low-positive and high-positive ACPA results ranged from 1.1 to 16.3 and from 24.9 to 37.1, respectively. These data demonstrate that the LRs obtained for

Table 1 Likelihood ratios (and 95% CIs) for RA of different commercial RF and ACPA assays and combinations thereof

	Thermo Fisher	Orgentec	Roche	Abbott	Siemens
RF neg	0.42 (0.37 to 0.48)	0.52 (0.47 to 0.58)	0.40 (0.35 to 0.46)	0.51 (0.46 to 0.56)	0.37 (0.32 to 0.44)
RF low	2.4 (1.5 to 3.6)	2.5 (1.7 to 3.8)	2.5 (1.7 to 3.7)	8.7 (4.7 to 16.1)	2.4 (1.7 to 3.5)
RF high	9.8 (6.4 to 14.9)	17.8 (9.2 to 34.4)	14.2 (8.4 to 24.1)	13.6 (7.3 to 25.6)	11.2 (6.9 to 18.6)
ACPA neg	0.37 (0.33 to 0.43)	0.43 (0.38 to 0.48)	0.39 (0.34 to 0.44)	0.38 (0.34 to 0.44)	0.38 (0.33 to 0.44)
ACPA low	4.5 (1.7 to 11.9)	16.3 (3.9 to 68.0)	1.1 (0.45 to 2.8)	14.6 (3.5 to 61.3)	2.2 (0.91 to 5.5)
ACPA high	37.1 (17.7 to 77.8)	32.5 (15.5 to 68.2)	33.8 (16.9 to 67.4)	24.9 (13.4 to 46.2)	30.0 (15.2 to 60.8)
ACPA neg RF neg	0.33 (0.28 to 0.39)	0.39 (0.34 to 0.45)	0.33 (0.29 to 0.39)	0.33 (0.29 to 0.39)	0.31 (0.26 to 0.37)
ACPA neg RF low	0.63 (0.33 to 1.20)	0.48 (0.24 to 0.95)	0.67 (0.38 to 1.19)	3.2 (1.4 to 7.5)	0.77 (0.47 to 1.3)
ACPA neg RF high	1.3 (0.65 to 2.5)	2.4 (0.99 to 5.9)	1.4 (0.68 to 2.84)	0.84 (0.30 to 2.4)	1.4 (0.67 to 3.0)
ACPA low RF neg	2.8 (0.55 to 14.4)	9.0 (1.1 to 71.7)	0.38 (0.10 to 1.38)	5.6 (1.2 to 25.5)	1.4 (0.38 to 5.2)
ACPA low RF low	3.4 (0.35 to 32.3)	6.8 (0.82 to 55.9)	Infinite* (n.a.)	Infinite* (n.a.)	0.56 (0.05 to 6.2)
ACPA low RF high	6.8 (1.5 to 30.0)	Infinite* (n.a.)	Infinite* (n.a.)	Infinite* (n.a.)	8.9 (1.1 to 71.7)
ACPA high RF neg	32.6 (4.5 to 238.5)	15.8 (4.9 to 50.4)	13.5 (3.2 to 56.8)	16.0 (5.9 to 43.8)	17.8 (2.4 to 135.2)
ACPA high RF low	45.0 (6.2 to 326.0)	27.0 (6.6 to 110.4)	13.7 (5.6 to 33.8)	16.0 (5.9 to 43.8)	17.2 (6.4 to 47.5)
ACPA high RF high	36.5 (15.1 to 87.9)	63.0 (15.7 to 253.5)	174.5 (24.5 to 1240.7)	60.2 (15.0 to 242.3)	51.1 (16.3 to 161.2)

The cut-offs proposed by the manufacturer were applied. Negative: <cut off; low-positive: >cut off to <3 times cut-off; high-positive: >3 times the cut-off.

*This serological combination was not revealed in any of the control patients.
ACPA, anti-citrullinated protein/peptide antibodies; RA, rheumatoid arthritis; RF, rheumatoid factor.

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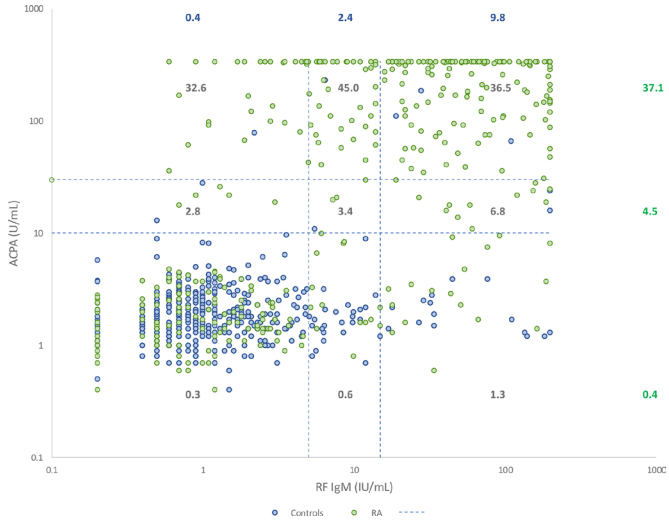


Figure 1 Rheumatoid factor (RF) IgM and anti-citrullinated protein/peptide antibodies (ACPA) test results in patients with rheumatoid arthritis (RA) (green circles) and controls (blue circles). The dashed blue lines represent the manufacturer's cut-off and three times the manufacturer's cut-off. As such these thresholds delimit negative, low-positive and high-positive RF and ACPA results and divide the results in nine sections. The likelihood ratio (LR) for a diagnosis of RA for patients with RF and ACPA test results falling within the sections is provided in blue. The LRs of negative, low-positive and high-positive RF or ACPA are shown in green. Results shown are obtained with assays from Thermo Fisher.

ACPA reached higher values than the LRs obtained for RF, both for low-positive as well as for high-positive test results, confirming previous investigations.[17]

Next, we calculated the LRs for combinations of RF and ACPA. The results are summarised in table 1 and figure 1 and show that the combined interpretation of RF and ACPA has a profound effect on the LR as compared with considering RF and ACPA independently. Importantly, the highest LRs for RA were obtained for double high-positivity for RF and ACPA (ie, 36.5–174.5, depending on the assays used) (table 1).

RA classification according to 2010 ACR/EULAR criteria

We classified control and patients with RA according to the 2010 ACR/EULAR criteria[2] using RF and ACPA results obtained with the cut-offs suggested by the different manufacturers (table 2). For 5.1% of the control patients and 23.9% of the patients with RA, a 2010 ACR/EULAR criteria score ≥6 was obtained solely based on clinical data (ie, duration of symptoms and joint involvement). After inclusion of the acute-phase reactants CRP and ESR, this proportion increased to 5.4% for controls and 26.9% for patients with RA. When RF was considered in addition to clinical and acute-phase response markers, 7.4–10.5% and 57.5–67.4% of the control and patients with RA, respectively, fulfilled the RA classification criteria. When only ACPA was considered in addition to clinical and acute-phase response markers, then 6.2–6.5% and 62.6–66.9% of the control and patients with RA, respectively, fulfilled the criteria. When both RF and ACPA were considered (by combining assays from the same manufacturer), then 7.8–10.5% and 67.8–74.0% of control and patients with RA, respectively, fulfilled the RA classification criteria.

Refining serological score of classification criteria: highest diagnostic specificity

As we observed differences in sensitivity and specificity in RA classification (1) between RF and ACPA, (2) between low and high antibody levels and (3) between single and double positivity we propose that different weights should be given based on the antibody type (RF vs ACPA), the antibody level and the combined antibody result. Therefore, a grid analysis was performed that tested >23 000 possible weighing score combinations of RF and ACPA. The combination of weighing scores for RF and ACPA that resulted in the highest specificity without affecting sensitivity for RA classification was (table 2):

- '0': double negativity or ACPA negative in combination with RF low
- '1' for ACPA negative in combination with RF high-positive or for low-positive ACPA in combination with negative RF
- '3' for low-positive ACPA in combination with low-positive RF or for high-positive ACPA in combination with negative RF
- '4' for low-positive ACPA in combination with high-positive RF or for high-positive ACPA in combination with low-positive RF
- '5' for high-positive ACPA in combination with high-positive RF

Next, we evaluated whether implementing the refined scoring system (RSS) into the 2010 ACR/EULAR classification criteria would improve the differentiation between patients with RA and controls in the investigative cohort. The percentage of controls with an RA classification score≥6 was 7.8–10.5% (depending on the RF and ACPA assay) when applying the current 2010 ACR/EULAR criteria and 6.3–6.9% when applying the RSS (table 2). The percentage of patients with RA with an RA classification score≥6 was 67.8–74.0% when applying the 2010 ACR/EULAR criteria and 67.1–74.0% applying the RSS (table 2). Thus, the RSS decreased RA misclassification of patients with non-RA, without affecting the classification of patients with RA.

These findings were confirmed by AUC analysis: the AUC to distinguish RA from the controls for the investigative cohort was 0.894–0.907 for the current ACR/EULAR scoring and 0.905–0.920 for the RSS ($p<0.05$ for all manufacturers, excluding Abbott). RSS consistently outperformed the ACR/EULAR scoring in the high-specificity region with pAUC ranging from 0.734 to 0.768 and 0.688 to 0.711, respectively (online supplemental data table 3 and figure4).

The positive effect of the RSS on the specificity was even more pronounced when we focused on the RF/ACPA seropositive controls and patients. Misclassification decreased from 38.3–55.8% (applying the current 2010 ACR/EULAR criteria) to 15.0–26.9% (applying the RSS)

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Table 2 RA classification in rheumatoid arthritis and control patients according to different (refined) scoring systems: (a) according to the ACR/EULAR classification criteria: a biomarker score of '2' (low-positive) for test results higher than the manufacturer's cut-off and a score of '3' (high-positive) for test results higher than three times the cut-off. (b) according to the following scores (refined scoring system (RSS)) using the manufacturer's cut-off:

	RF negative	RF low-positive	RF high-positive
ACPA negative	0	0	1
ACPA low-positive	1	3	4
ACPA high-positive	3	4	5

	Patients with rheumatoid arthritis		Control patients	
	ACR/EULAR 2010	RSS	ACR/EULAR 2010	RSS
	% ≥6	% ≥6	% ≥6	% ≥6
Clinical score	23.9	23.9	5.1	5.1
Including inflammation	26.9	26.9	5.4	5.4
Including RF assays				
Thermo Fisher RF IgM	64.6		10.5	
Roche RF	65.1		8.9	
Orgentec RF IgM	58.3		7.8	
Abbott RF	57.5		7.4	
Siemens RF	67.4		10.2	
Range	57.5–67.4		7.4–10.5	
Including ACPA assays				
Thermo Fisher ACPA	66.1		6.3	
Roche ACPA	66.3		6.5	
Orgentec ACPA	62.6		6.3	
Abbott ACPA	65.6		6.3	
Siemens ACPA	66.9		6.2	
Range	62.6–66.9		6.2–6.5	
Including RF/ACPA assays				
Thermo Fisher RF IgM/ACPA	72.1	73.1	10.5	6.9
Roche RF/ACPA	71.9	72.9	9.8	6.7
Orgentec RF IgM/ACPA	67.8	67.1	8.5	6.5
Abbott RF/ACPA	70.1	68.8	7.8	6.3
Siemens RF/ACPA	74.0	74.0	10.2	6.7
Range	67.8–74.0	67.1–74.0	7.8–10.5	6.3–6.9

For every assay, the percentage of patients with RA and disease control patients with an RA classification score≥6 is given (n=448 patients with RA, except for Siemens RF/ACPA n=402).

ACPA, anti-citrullinated protein/peptide antibodies; ACR, American College of Rheumatology; EULAR, European Alliance of Rheumatology Associations; RA, rheumatoid arthritis; RF, rheumatoid factor.

(table 3 and figure 2). The sensitivity was 88.8–90.4% applying the current 2010 ACR/EULAR criteria and 87.2–90.8% applying the RSS (table 3).

Additional illustration of the superior performance of the RSS is provided in online supplemental data tables 5 and 6. In these tables, RSS is not only compared with the 2010 classification criteria but also to two alternative serological scoring systems, one with a maximal score of 3 and one with a maximal score of 4. For both alternative scoring systems, the weight for ACPA was higher than the weight for RF and the weight for double positivity higher than the weight for single positivity. The 3-point scoring system had the highest specificity compared with the 2010 classification criteria, but a lower sensitivity. The 4-point scoring system had a similar specificity as RSS but a slightly lower sensitivity. Compared with the 2010 classification criteria, only RSS improved specificity without affecting sensitivity.

Of note, applying the RSS reduced the inter-manufacturer variation in specificity, that is, 89.5–92.2% (Δ=2.7%) for the current 2010 ACR/EULAR RA classification vs 93.1–93.7% (Δ=0.6%) for classification according to the RSS (table 2).

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Table 3 Diagnostic performance of RA classification of different serological scoring systems applied on the seropositive RA and control patients of the investigative cohort[18] and three different confirmation RA study cohorts: University Hospitals Leuven, Belgium,[19] University Hospital Santander, Spain,[20] and SAVE-RA trial[21]

	Seropositive patient samples (n)		RA		Non-RA	
	RA (n, %)	Non-RA (n, %)	ACR/EULAR 2010 (%)	RSS (%)	ACR/EULAR 2010 (%)	RSS (%)
Investigative cohort[18]	257–283 (64.6–74.0%)	27–60 (6.0–14.9%)	88.8–90.4	87.2–90.8	38.3–55.8	15.0–26.9
Vandebeek *et al*[19]	45 (67.2%)	35 (7.9%)	86.7	86.7	20.0	8.6
Irure-Ventura *et al*[20]	147 (93.6%)	77 (50.3%)	90.1	87.3	24.6	23.1
Machold *et al*[21]	75 (56.8%)	19 (9.8%)	96.0	97.3	78.9	36.8

For every study cohort and for every serological scoring system, the percentage of RA classification is given.
ACR, American College of Rheumatology; EULAR, European Alliance of Rheumatology Associations; RA, rheumatoid arthritis; RSS, refined scoring system; SAVE-RA, Stop Arthritis Very Early—Rheumatoid Arthritis.

Confirmation of the refined serological score of RA classification criteria

Subsequently, the effect of the RSS on RA classification was assessed across three different, independent study cohorts, using the original (serological) data.[19–21] The results are shown in table 4. Sensitivity of RA classification varied among studies from 82.1% to 87.1% applying the current 2010 ACR/EULAR classification criteria and from 79.6% to 87.9% when applying the RSS. Misclassification was observed in 8.6–34.2% of patients with non-RA applying the current 2010 ACR/EULAR classification criteria and in 7.7–30.1% applying the RSS. Thus, in all confirmatory study cohorts, the specificity in RA classification tended to be higher for the RSS than for the current 2010 ACR/EULAR serological scoring. The RSS did not affect the sensitivity, except in one study cohort where it was marginally decreased (table 4). AUC-analysis revealed similar results as for the investigative cohort: RA classification using RSS revealed consistently higher AUC and pAUC at 95% specificity cut-off than ACR/EULAR scoring, significant ($p<0.05$) for two of the three study cohorts (online supplemental data table 7 and figure 8).

When we focused on RF/ACPA seropositive controls, misclassification of patients with non-RA decreased from 20.0–78.9% (2010 ACR/EULAR classification criteria) to 8.6–36.8% (RSS). This increase in specificity, in line with the results we obtained with the international investigative study cohort, was observed for each of the individual confirmatory study groups (table 3 and figure 2). For seropositive patients with RA, sensitivity in RA classification

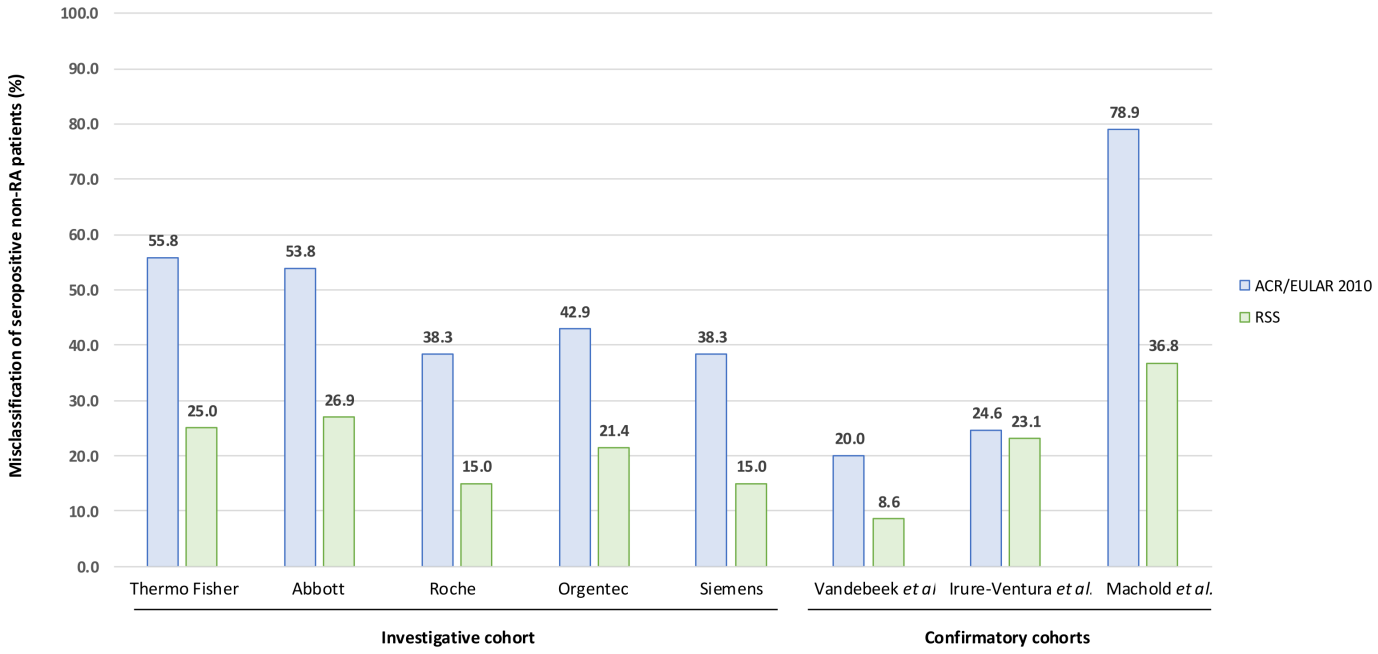


Figure 2 Misclassification of seropositive patients with non-rheumatoid arthritis with the American College of Rheumatology (ACR)/European Alliance of Rheumatology Associations (EULAR) 2010 rheumatoid arthritis (RA) classification criteria and the refined scoring system (RSS) on (1) the investigative cohort[18] including RF/ACPA assays of five different manufacturers and (2) three different confirmation RA study cohorts: University Hospitals Leuven, Belgium,[19] University Hospital Santander, Spain,[20] and Stop Arthritis Very Early—Rheumatoid Arthritis trial.[21]

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Table 4 Diagnostic performance of RA classification of different serological scoring systems applied on the investigative cohort[18] and three different confirmation RA study cohorts: University Hospitals Leuven, Belgium,[19] University Hospital Santander, Spain,[20] and SAVE-RA trial[21]

	Patient numbers		RA		Non-RA	
	RA (n)	Non-RA (n)	ACR/EULAR 2010 (%)	RSS (%)	ACR/EULAR 2010 (%)	RSS (%)
Investigative cohort[18]	362–398	402–448	67.8–74.0	67.1–74.0	7.8–10.5	6.2–6.9
Vandebeek *et al*[19]	67	441	82.1	82.1	8.6	7.7
Irure-Ventura *et al*[20]	157	153	82.2	79.6	10.5	9.8
Machold *et al*[21]	132	193	87.1	87.9	34.2	30.1

For every study cohort and for every serological scoring system, the percentage of RA classification is given. Demographic characteristics of patients and controls are given in online supplemental data table 1.
ACR, American College of Rheumatology; EULAR, European Alliance of Rheumatology Associations; RA, rheumatoid arthritis; RSS, refined scoring system; SAVE-RA, Stop Arthritis Very Early—Rheumatoid Arthritis.

among the confirmatory study cohorts ranged from 86.7% to 96.0% using the current 2010 ACR/EULAR classification criteria and from 86.7% to 97.3% using the RSS. The performance of the alternative scoring systems (see above) is given in online supplemental data table 6.

DISCUSSION

Both RF and ACPA are included as serological markers in the ACR/EULAR 2010 classification criteria for RA and herein given the same weight scores.[2] Consistent with the literature, we found that (1) ACPA had a higher LR for RA than RF,[9–12] (2) high autoantibody levels had a higher LR for RA than low autoantibody levels[12 24] and (3) double positivity had a higher LR for RA than single positivity.[14–17] Based on these findings we developed and validated an RSS for RA classification with higher weights given to test results associated with a higher LR for RA.

The RSS demonstrated higher specificity for RA classification compared with the current 2010 ACR/EULAR serological scoring approach.[25] This was reflected in the lower numbers of controls being misclassified as RA.

The high specificity and positive LR of ACPA for RA is well known[9 11] as is the frequent co-occurrence with RF. In our study, ACPA and RF co-occurred, depending on the manufacturer, in 46.5–55.1% of patients with RA, which is in line with previous reports.[9 26] Co-occurrence of RF and ACPA is known to be a powerful predictor of future RA.[14 15 17 27 28] Furthermore, the combined presence of autoantibodies has been associated with a worse disease phenotype[16] and an increased risk of disease flare when tapering DMARD therapy.[29 30] Our study clearly demonstrates that giving more weight to combined positivity than to single positivity improves RA classification. The broader impact on early diagnosis, prognosis or disease management is to be expected, but needs to be objectified by follow-up studies.

In the current ACR/EULAR 2010 classification criteria for RA, RF/ACPA serology accounts for maximal three of the six points needed enabling RA classification.[2] The proposed RSS implies a substantial increase in the importance of serology for RA classification and was confirmed by a cross-cohort validation evaluating alternative total scoring systems for RA classification (online supplemental data table 12). This change in serological scoring mainly impacts the classification of patients with RA with a lower clinical RA score (joint involvement, duration of symptoms, acute-phase reactants) as well as misclassification of patients with non-RA for whom double positivity is less frequent than in RA and particularly high positivity is rarely observed. In these individuals, RA misclassification based on single positivity is considerably reduced which is mainly due to RF positivity which in the ACR/EULAR criteria is given the same weight as ACPA positivity. However, our data and those of others clearly demonstrate that RF is not very specific for RA when ACPA are not detectable. This is especially true for low RF levels which turned out to have no specificity for RA in the absence of ACPA, whereas low ACPA showed moderate specificity per se. Moreover, these are the individuals for whom RF/ACPA test results can make a significant difference in pre- and post-test probability in a diagnostic context.[31] When applying RSS, patients with RA with double high positivity for ACPA and RF would only need one point from a non-serological criterion. As classification criteria are usually applied (for inclusion in studies) to patients diagnosed with RA, joint involvement is expected to be present. Of note, in our investigative cohort, the joint involvement score in patients with RA with high double-positivity varied between 0 (max. 1 large joint; 5.1%), 1 (2–10 large joints; 7.8%), 2 (1–3 small joints; 20.3%), 3 (4–10 small joints; 39.2%) and 5 (>10 joints; 27.2%). Revised criteria employing RSS could include joint involvement as a prerequisite for classification of RA. This

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would classify all patients with a serological score of 5 and a minimum joint score of 1 as RA, irrespective of disease duration or inflammation. This need not necessarily be the case when using the criteria as part of the diagnostic process (which is far more complex than classification), because it is the clinician's aim to diagnose patients as early as possible even when joint involvement (synovitis, swollen joints) is not yet manifest.

Additionally, our findings are corroborated by the recent publication of the EULAR/ACR risk stratification criteria for development of RA in the risk state of arthralgia.[32] With these criteria, rheumatologists aim to identify a homogeneous risk group of individuals, originating from secondary care, in whom imminent RA is considered more likely than other causes of arthralgia. Within these RA risk stratification criteria, RF and ACPA serology results are included, with a score for low-positive results of, respectively, 2 and 4 and for high-positive results of, respectively, 4 and 8. Therefore, the scoring weights are higher for (1) higher antibody levels, (2) ACPA than for RF and (3) double RF/ACPA positivity which is entirely in line with our results.

The grid search optimisation identified a single scoring combination with optimal specificity (while retaining sensitivity); however, sensitivity analysis revealed that scoring combinations with minor variations (±1 point differences in individual cells) yielded comparable classification performance (specificity differences <0.5%). This robustness suggests that the RSS captures genuine biological relationships between antibody profiles and RA risk, rather than fitting to idiosyncrasies of the investigative cohort. The grid search was performed exclusively on the investigative cohort. The three confirmatory cohorts[19–21] were not used at any stage of model selection or tuning. The consistency of specificity gains across these three independent cohorts (drawn from different countries, populations and assay platforms) and across five RF/ACPA manufacturers within the investigative cohort, is the strongest available empirical evidence against meaningful overfitting. Additionally, the biological plausibility of the final scoring pattern (higher weights for ACPA vs RF, high vs low titres and combined vs single positivity) aligns with established LRs (table 1) and independently developed clinical criteria,[32] providing convergent validity for our data-driven approach.

The impact of the RSS significantly differed among the different study cohorts included and was related to (1) the specific nature of the SAVE cohort[21] versus the two other consecutive routine control cohorts and (2) the 'undifferentiated arthritis' patients in the Irure-Ventura *et al*[20] control cohort of which an important portion was RF/ACPA positive (online supplemental data tables 9–11). In the last decade, the concept of RA as a continuum has been generally accepted, in which antibodies can be present years before clinical onset of the disease.[33] Although the clinical diagnoses of all control patients were reviewed by the investigators up to 2 years after study inclusion, it cannot be excluded that the seropositive patients could still evolve to RA afterwards. In addition, to define low and high RF or ACPA positivity, the cut-offs defined by the manufacturer were used,[2 32] resulting in the range of patients being classified as having RA or not depending on the assays used.[24] In line with previous reports,[34] the use of the CCP3 ACPA IgG assay (Werfen) in the study cohort of Irure-Ventura *et al*[20] could have contributed to the low specificity of serology and lower impact of the RSS on the specificity found in this cohort. Although applying the RSS slightly decreased assay-dependent variations in classification results, heterogeneity among study cohorts remained due to the fundamental differences among RF and ACPA tests used to define seropositivity.[35–37] A first step in the harmonisation of test result interpretation and RA classification would be to replace manufacturers' cut-offs with uniformised specificity-based thresholds.[18 36]

In conclusion, the specificity of the RA classification criteria can be improved without loss of sensitivity by a refined serological RF/ACPA scoring system that takes the antibody type, the antibody level and combined positivity into account.

Author affiliations
[1]Department of Microbiology, Immunology and Transplantation, KU Leuven, Leuven, Belgium
[2]Department of Laboratory Medicine, AZORG Hospital, Aalst, Belgium
[3]Department of Electrical Engineering (ESAT), STADIUS Center for Dynamical Systems, Signal Processing and Data Analytics, KU Leuven, Leuven, Belgium
[4]Immunopathology Group, Department of Immunology, Marqués de Valdecilla University Hospital-IDIVAL, Santander, Spain
[5]Department of Laboratory Medicine, University Hospitals Leuven, Leuven, Belgium
[6]Department of Rheumatology, University Hospitals Leuven, Leuven, Belgium
[7]Department of Rheumatology, AZORG, Aalst, Belgium
[8]Division of Rheumatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria
[9]Department of Internal Medicine, Ghent University, Gent, Belgium
[10]Department of Diagnostic Sciences, Ghent University, Gent, Belgium
[11]Department of Laboratory Medicine, Semmelweis University, Budapest, Hungary
[12]Department of Clinical Immunology and Transfusion Medicine, Sahlgrenska University Hospital Gothenburg, Gothenburg, Sweden
[13]Department of Rheumatology, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden
[14]Department of Rheumatology, University Medical Centre Ljubljana, Ljubljana, Slovenia
[15]Faculty of Pharmacy, University of Ljubljana, Ljubljana, Slovenia
[16]Division of Inflammation and Infection, Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden
[17]Department of Laboratory Medicine, University Hospital Basel, Basel, Switzerland
[18]Department of Laboratory Medicine, Kantonsspital Aarau, Aarau, Switzerland
[19]Department of Laboratory Medicine, Centre Hospitalier de Luxembourg, Luxembourg City, Luxembourg
[20]Department of Laboratory Medicine, AZ Sint-Elisabeth, Zottegem, Belgium
[21]Department of Laboratory Medicine, AZ Rivierenland, Bornem, Belgium
[22]Department of Laboratory Medicine, AZ Sint-Lucas, Bruges, Belgium
[23]Department of Rheumatology, Centre Hospitalier de Luxembourg, Luxembourg City, Luxembourg
[24]Rheumazentrum Ostschweiz GmbH, Waisenhausstr, St.Gallen, Switzerland
[25]Department of Rheumatology, University Hospital Basel, Basel, Switzerland
[26]Department of Rheumatology and Immunology, Semmelweis University, Budapest, Hungary

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[27]Department of Rheumatology, University Hospital Ghent and VIB Inflammation Research Center, Ghent, Belgium
[28]Department of Development and Regeneration KU Leuven, University Hospital Leuven, Leuven, Belgium
[29]Department of Molecular Biology, University of Cantabria, Cantabria, Spain
[30]Ludwig Boltzmann Institute for Arthritis and Rehabilitation, Vienna, Austria

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ORCID iDs
Lieve Van Hoovels https://orcid.org/0000-0002-3462-7288
Christopher Sjöwall https://orcid.org/0000-0003-0900-2048
Alf Kastbom https://orcid.org/0000-0001-7187-1477
Peggy Jacques https://orcid.org/0000-0001-9227-257X
Günter Steiner https://orcid.org/0000-0002-5089-7405
Patrick Verschueren https://orcid.org/0000-0002-0340-3580
Xavier Bossuyt https://orcid.org/0000-0001-6856-8485

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