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ORIGINAL ARTICLE

Anti-CCP antibodies have more diagnostic impact than rheumatoid factor (RF) in a population tested for RF

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Abstract To compare the diagnostic powers of rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) in a population selected for its high statistical relevance, over a 6-month period, an informed consent to test for anti-CCP was obtained from 1,025 consecutive patients for whom RF was ordered at a University laboratory. Within 1 year, a diagnosis was obtained without informing the physician about the anti-CCP result. Extensive statistical analyses were performed. A total of 768 patients satisfied the inclusion criteria, and 132 were classified as having RA, yielding a pre-test probability of RA of 17%. The sensitivities for anti-CCP and RF were 62 and 64% (P= 0.83), and the specificities were 97 and 90% (P<0.001), respectively. The positive predictive value (PPV) was 79% for anti-CCP and 56% for RF (P<0.001), whereas the negative predictive value was 92% for both. The likelihood ratio (LR) was 17.9 for anti-CCP and 6.2 for RF (P< 0.005). Forty RA patients were diagnosed with RA of less than 2 years length, and the same significant statistic differences between anti-CCP and RF were observed. Placing the results of both tests together, or using different cutoff points, increased the diagnostic utility of the tests. The anti-CCP test has statistically shown significant higher specificity, PPV, and LR for RA than the RF test in a clinically diverse population. If new criteria are to be devised to help diagnose early RA, anti-CCP should be included because it has a greater diagnostic impact than RF.

Keywords Anti-CCP antibodies · Anti-citrullinated peptide antibodies · Citrullinated proteins · Likelihood ratio · Rheumatoid arthritis · Rheumatoid factor

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Introduction

Rheumatoid arthritis (RA) is one of the most prevalent autoimmune diseases, affecting up to 1% of some populations [1]. Early diagnosis of RA is an important consideration because aggressive therapy can prevent the development of articular erosions and deformities [1, 2].

The 1987 American College of Rheumatology (ACR) revised criteria for classifying RA [3] have limitations, particularly for early RA [2]. ACR criteria have 91–94% sensitivity and 89% specificity for established RA [3], while the sensitivity is less for people with early RA because some of the criteria, such as rheumatoid factor (RF) and joint erosions, are less prevalent. Radiological features do not appear sensitive enough for early diagnosis, while magnetic resonance is still a research tool, and echographic methods lack standardization [4]. Thus, rheumatologists have debated the need for better criteria to help diagnose early RA [2, 4, 5].

RF, the most accepted and widely used serologic test for RA, is neither highly sensitive nor specific for diagnosing early RA [6]. Anti-citrullinated peptide antibodies (ACPAs) are recognized as being RA-specific [7]. ACPAs comprise a large panel of antibodies, including perinuclear factor detected by immunofluorescence in buccal mucosal cells, anti-keratin antibody in epithelial cells of the stratum corneum of rat

esophagus, and anti-filaggrin detected by Western blotting or enzyme immunoassay [8–18]. Recently, a filaggrin-derived synthetic cyclic citrullinated peptide (CCP) became available as an enzyme-linked immunosorbent assay (ELISA) [19]. Various studies have shown between a 41–80% sensitivity and an 89–99% specificity of anti-CCP for RA diagnosis [20–23]. In some studies, anti-CCP predicts a less favorable course and a greater radiological progression in patients with RA [23]. Other studies have shown that anti-CCP is found earlier in the course of RA than RF and is, thus, a better marker of early RA [24, 25].

The majority of studies on ACPAs have been performed on selected groups of individuals, such as patients with defined disorders, people in early arthritis centers, or healthy controls [15–25]. These groups do not represent the population of patients seen in everyday clinical practice where people have a variety of diseases, a range of RA from mild to severe, and no patient is truly healthy. Clinically relevant specificities and sensitivities for a test are difficult to determine in a population that is different than the normal test group [26, 27]. In addition, the patients in those studies were being seen by rheumatologists, while most requests for RF are ordered for patients being seen by general practitioners or other specialists.

There has been increasing discussion that the 1987 ACR criteria for diagnosing RA are not sufficient for diagnosing early RA today [2, 5]. In this study, we set out to evaluate the clinical utility of anti-CCP antibody by testing for anti-CCP in the group of people who had been tested for RF. No selection criteria were made, so the doctor may have ordered RF for any reason. This population is useful statistically because it is the population that the doctor routinely sees. This group is also clinically important because it is the population that would be tested for anti-CCP if anti-CCP were included with RF in the criteria to diagnose early RA. In that case, both tests would routinely be performed together.

Materials and methods

In this prospective study, an informed consent to test for anti-CCP was obtained from 1,025 consecutive patients whose doctors had ordered an RF test for them from April to October 2003. These patients attended primary, secondary, and tertiary academic centers from Pontifical Catholic University of Rio Grande do Sul (Saint Lucas Hospital–PUCRS, Clinical Medical Center–PUCRS, Fatima Village–PUCRS), Porto Alegre, Brazil. The inclusion criteria were an adult greater than 18 years old, an RF test was ordered and performed, serum was obtained so further testing on anti-CCP was possible, and a definitive diagnosis was obtained within 1 year from the original testing.

IgM–RF was determined by nephelometry in a BNII analyzer (Dade Behring, France) [28, 29]. Levels >15 U/ml were considered positive, according to the manufacturer's instructions. Anti-CCP antibodies were detected by a second-generation ELISA (INOVA Diagnostics, San Diego, USA). The cutoff for the IgG anti-CCP antibody assay was 20 IU/ml, according to the manufacturer's instructions.

Sixty-two patients younger than 18 years old were excluded. In 23 patients, samples were collected twice. Then, the second sample of each patient was excluded. The study was approved by the local ethics committee.

The anti-CCP results were not available to the diagnosing physician throughout the study. Thus, all diagnoses were made by doctors independent of the anti-CCP results. Diagnoses were reviewed a year later. The ACR classification criteria were used for RA diagnosis [3]. The diagnoses remained undefined in 172 patients out of the remaining 940, and therefore, they were excluded from the study. The final number of patients fully studied was 768. Mann–Whitney and Kruskal–Wallis analyses were used for non-parametric or independent variables. Logistic regression analyses were employed. A receiver-operating characteristic curve (ROC curve) of anti-CCP and RF as a graph of the pairs of sensitivity and 100% minus specificity that correspond to each possible cutoff for the diagnostic test result was drawn [27]. Sensitivities, specificities, positive predictive value (PPV), negative predictive value (NPV), likelihood ratios (LRs), and posttest probabilities (PTP), together with their 95% confidence intervals (95%CI) were computed considering Bayes theorem [30, 31].

LR is defined as the ratio of the probabilities of a particular test result among patients with and without disease. The LRs are composite expressions of test power, which incorporate sensitivity (Se) and specificity (Sp) and their respective complements [(1-Se) and (1-Sp)]. The LRs are calculated as follows: positive LR=Se/(1-Sp) and negative LR=Sp/(1-Se).

Odds are an alternative way to express the likelihood that an event can occur. The likelihood of a patient to have a specific disease before testing is called pretest odds or pretest probability. A probability of 50% corresponds to an odds of 1 to 2. The pretest odds are usually related to the prevalence of the disease; however, it is possible to adjust it depending on the characteristics of an overall patient pool or of the individual patient. The odds can be computed by taking the probability of an event and dividing it by one minus the probability. It can be converted back to a probability by taking the odds and dividing it by one plus the odds. The pretest odds of disease multiplied by the LR gives the posttest odds of disease. The posttest odds represent the chance that the patient has a disease and are converted to PTP. Both of these factors incorporate not only information about the disease prevalence, but also the

patient pool, specific patient risk factors (pretest odds or pretest probability), and information about the diagnostic test itself (LR) [31, 32].

LRs were calculated for multiple levels of RF and anti-CCP, and combined tests. A positive result suggests that LRs of 1–2 should alter disease probability by a small and clinically insignificant degree, LRs of 2–10 may be clinically important, and LRs higher than 10 should have a substantial impact on clinical decision-making [27, 31]. Data analyses were performed using MedCalc for Windows (MedCalc Software, Mariakerke, Belgium) and Statistical Package for the Social Sciences (SPSS) for Windows, release 10.0.7 (SPSS, Chicago, USA).

Results

The demographic characteristics of the 768 patients studied are summarized in Table 1. The overall prevalence of RA in this survey was 17%. The ratio of female to male was 4:1 for both the RA and non-RA groups. Non-RA patients were younger than RA patients. In the RA group, 30% had the disease for less than 2 years, while 23% had the disease for longer than 10 years. RFs were requested by rheumatologists in 47% of cases and by other doctors in 53%. The RA and non-RA groups did not differ based on the request for RF coming from their being either an inpatient or outpatient.

Patients were classified as RA or non-RA. More than one rheumatologist confirmed all 132 RA diagnoses according to the ACR criteria [3]. Non-RA patients were subdivided in six groups: other connective tissue disorders (CTD), spondyloarthropathies (SA), soft-tissue rheumatism including fibromyalgia and osteoarthritis (STR), non-rheumatologic autoimmune disorders (NRA), cancers (CA), and other non-classified diseases (other). The distribution of all diagnoses is seen in Table 2.

Test properties of anti-CCP antibodies and RF are shown in Table 3, using the cutoffs between positive and negative recommended by the manufacturers. Statistically significant higher specificity and PPV were obtained for anti-CCP antibodies than for RF. Levels above the 20 U/ml cutoff yielded a LR of 17.9 for anti-CCP antibodies; levels above the 15 IU/ml cutoff showed a LR of 6.2 for RF. This means that RA patients are 17.9 or 6.2 times more likely to have a positive anti-CCP or RF test than non-RA patients.

Table 2 Distribution of diagnoses among the 768 patients studied

Clinical diagnosis	Number of patients N=768	(%)
Rheumatoid arthritis	132	17
Others connective tissue disorders	102	13
Spondiloarthropathies	38	5
Soft tissue rheumatism	264	34
Non-rheumatologic autoimmune disorders	42	5
Cancer	30	4
Others non-classified diseases	160	21

Early RA (duration, <2 years) and non-RA cases with less than 2 years of rheumatic symptoms were also statistically compared (Table 4). Just as with the whole group, the difference in sensitivity between the two tests did not reach statistical significance, while the specificity was significantly higher for anti-CCP antibodies (P<0.001) in patients with early disease.

Anti-CCP antibody levels were significantly higher in RA patients compared to non-RA (P<0.001). This difference remains significant after applying adjustments for sex, age, duration of joint symptoms, and RF. RF levels were also significantly higher in RA than non-RA. However, unlike anti-CCP, this difference is not significant after applying adjustments for sex, age, duration of joint symptoms, and anti-CCP (P=0.15).

The areas under the ROC curve (AUC) for anti-CCP and RF were similar (Fig. 1)—0.83 for anti-CCP and 0.79 for RF, showing a slight advantage for anti-CCP. The sensitivity of anti-CCP for RA was 62%, while it was 64% for RF (Table 3). Including patients who were positive for either test increased the sensitivity of the serologic tests to 71%. The specificity of anti-CCP was 97% compared to 90% for RF (Table 3), while it was 99% when both were positive (not shown).

Calculating the LRs and posttest probabilities for different levels of RF and anti-CCP antibodies showed an increased

Table 1 Demographic characteristics of the 768 patients

Characteristic	Total (%), N=768	Rheumatoid arthritis (%), N=132	Non-rheumatoid arthritis (%), N=636	P values
Sex				
Female	605 (79%)	104 (79%)	501 (79%)	0.606
Male	163 (21%)	28 (21%)	135 (21%)	
Age (years)	52±15	56±15	52±15	0.006[a]
Duration (months)	12 (0–720)	60 (2–720)	6 (0–360)	0.001[a]
Source				
Outpatients	621 (81%)	111 (84%)	510 (80%)	0.544
Inpatients	147 (19%)	21 (16%)	126 (20%)	

[a] Data are presented as counted (percentages), mean±SD for age, or median (interquartile range, P25 to p75) for duration.

Table 3 Tests properties of anti-CCP antibodies and RF in 768 patients with RA and non-RA

n=768	Anti-CCP		RF		P values	95% CI
	n=132, RA	n=636, non-RA	n=132, RA	n=636, non-RA		
Sensitivity	62%		64%		0.83	(−10.4 to 14.4)
Specificity	97%		90%		<0.001	(4.2 to 9.8)
Positive predictive value	79%		56%		<0.001	(11.0 to 35.0)
Negative predictive value	92%		92%		0.99	(−3.1 to 3.1)
Positive likelihood ratio	17.9		6.2		–	–
Negative likelihood ratio	0.4		0.4		–	–
Pretest probability	17%		17%		–	–

probability of disease at higher antibody levels. These data are seen in Table 5. Significantly higher LRs and PTP were obtained from 200 IU of RF and from 50 U of anti-CCP antibodies than from using the manufacturer's cutoffs.

LRs and disease probability after combining RF and anti-CCP antibodies, plus their relationship to each other, are shown in Tables 6 and 7, using the cutoffs recommended by the manufacturers. When both tests are negative, there is nearly a threefold decrease in the likelihood of having RA, down to 6%. The anti-CCP-negative/RF-positive combination showed no significant change from the pretest to posttest probability of having RA. This is related to the finding mentioned above that RF levels are not different in CCP-negative RA patients and non-RA patients. A positive anti-CCP test combined with a negative RF yielded a mild increase in the probability of RA. When both tests are positive, there is a very high LR (43.4) and PTP of RA (90%). More than half of the RA patients (54%, Table 7) were double positive for these serologic markers. The combined information of negative and positive results for RF and anti-CCP showed a significant linear trend in the increase of positive tests and the diagnosis of RA (P<0.001).

Discussion

Several different types of statistical analysis showed that anti-CCP had more power for diagnosing RA than RF in the population we tested. Studies on laboratory testing usually include individuals selected by their final diagnosis. Our survey differed in that patients were recruited solely because RF was ordered for them. Our design avoided selection bias based on original diagnosis. In addition, if new criteria are made to classify early RA, it is possible that anti-CCP could be included. In that case, RF and anti-CCP would likely be ordered together by physicians, and this study was designed to evaluate the clinical utility of anti-CCP in this group.

Our selection criterion yielded very similar distributions of gender and source of referral in both RA and non-RA groups. A small but significant difference was found in age between the groups, but this probably lacks clinical relevance. The duration of rheumatic symptoms differed in the groups as expected because many RF solicitations originated from patients with autoimmune disease but no articular symptoms. Overall, the two groups were quite homogeneous, allowing straightforward statistical comparisons between them.

The rate of RA in this group, 17%, was virtually identical to that found in related studies [33, 34] and is likely similar to that found in many laboratories. During the collection of diagnoses, it was clear that RF was requested for patients who did not have many of the classical rheumatologic symptoms of RA. A battery of statistical tests was used to evaluate the clinical utility of RF and anti-CCP in this population and yielded several novel findings.

Table 4 Tests properties of anti-CCP antibodies and RF in 40 early-RA patients (ERA) and controls (nERA)

Early RA, n=40	Anti-CCP		RF		P values	95% CI
	n=40, ERA[a]	n=404, nERA[a]	n=40, ERA[a]	n=404, nERA[a]		
Sensitivity	62%		57%		0.69	−9.4 to 19.4
Specificity	96%		90%		<0.001	2.8 to 9.6
Positive predictive value	62%		36%		<0.001	13.6 to 38.4
Negative predictive value	96%		95%		0.92	−4.8 to 6.8
Positive likelihood ratio	16.8		5.8		–	–
Negative likelihood ratio	0.4		0.5		–	–
Pretest probability	9%		9%		–	–

[a] ERA and nERA groups had less than 2 years of rheumatic symptoms.

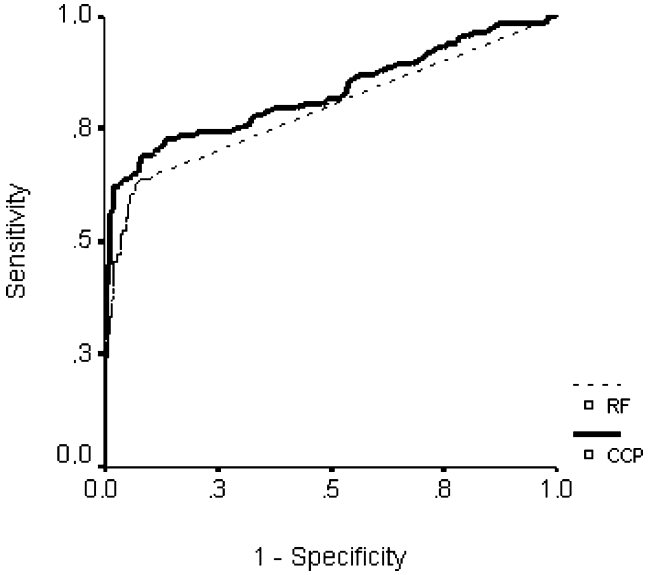


Fig. 1 ROC curve for anti-CCP antibodies and RF

In agreement with other studies [33, 34], but unlike popular perception, RF had a good sensitivity and specificity, giving clinically useful positive and negative predictive values. However, anti-CCP had equal sensitivity and much better specificity and was, thus, even more clinically useful. Combining anti-CCP and RF results using the cutoffs recommended by the manufacturers yielded higher diagnostic power than either by itself, both for the double-positive and double-negative groups.

The utility of LRs for different populations considering individual probability (clinical information) can be demonstrated by assuming, for example, a pretest probability of 50%. Considering a positive LR of 17.9, the PTP of disease would modify to 95% (remember that, in a pretest probability of 17%, the PTP was 79%). On the other hand, applying a pretest probability of 1% (worldwide RA prevalence) for the same LR, the PTP of disease would be reduced to a very low PTP of 15%. This last example explains a false positive test result and the usefulness of LR for test interpretation. Hence, it is not necessary to order RF and anti-CCP in low pretest probability of disease or when the PTP would not change clinical decision-making.

Table 6 Disease probability after combination of RF and anti-CCP antibodies and LRs

Test combination	Likelihood ratio	95% CI	% Posttest probability[a]	95% CI
Anti-CCP negative/ RF negative	0.3	0.2 to 0.4	6.4	4.9 to 8.1
Anti-CCP negative/ RF positive	1.0	0.6 to 1.8	17.2	10.3 to 27.4
Anti-CCP positive/ RF negative	3.4	1.6 to 7.6	41.3	24.2 to 60.8
Anti-CCP positive/ RF positive	43.4	21.4 to 87.8	90.0	81.4 to 94.2

Cutoffs, >15 IU/ml for RF and >20 U/l for anti-CCP were considered.
[a] Posttest probabilities were calculated from the prevalence of RA in the group=17%.

Statistical analyses using higher and lower cutoffs between positive and negative revealed interesting correlations. Low values of anti-CCP, less than 10 UI that is half the value of the cutoff between positive and negative, gave a lower posttest probability of having RA than simply using a negative result. This suggests an additional clinical utility for anti-CCP. Namely, a result less than 10 UI should suggest a diagnosis other than RA.

Another finding was also related to the absolute value of the anti-CCP and RF results. High clinical utility for both RF and anti-CCP, as judged by LRs greater than 10 and posttest probabilities of RA greater than 70%, was found using a cutoff of 200 UI for RF and 50 UI for anti-CCP. An even higher LR, 43, and posttest probability of disease of 90% were found in the RF/anti-CCP double-positive group. The strongest statistical correlation of all was anti-CCP greater than 100 UI, with a LR of 82 and a posttest probability of RA 94%. Of course, the number of people included in the positive group decreases as the cutoff between negative and positive increases.

A surprising statistical result occurs because anti-CCP and RF are often found together in RA patients, but RF is not as specific as anti-CCP (Table 7). Thus, although the presence of RF is correlated with RA, when one includes

Table 5 Likelihood ratios and posttest probabilities for RF and anti-CCP antibodies

Test	Cutoffs	Likelihood ratios	95% CI	% Posttest probability	95% CI
RF	<16	0.4	0.3–0.5	7.6	6.2–9.5
	16–50	1.5	0.8–3.0	23.5	14.2–38.1
	51–200	6.3	3.8–10.5	56.3	43.6–68.2
IU/ml	201–500	12	5.4–26.6	71.1	52.5–84.5
	>500	50.6	12.0–213.2	91.2	71.1–97.8
Anti-CCP	<10	0.3	0.2–0.4	6.2	3.9–7.6
	10–19	1.0	0.6–1.7	17	10.9–25.8
	20–50	3.2	1.3–7.7	39.6	21.0–61.2
U/ml	51–100	15.8	6.9–36.1	76.4	58.6–88.1
	>100	81.9	26.0–258.5	94.4	84.2–98.1

Table 7 Results of RF and anti-CCP in both RA and non-RA groups

n=768	RA, *N*=132		Non-RA, *N*=636	
	Anti-CCP positive	Anti-CCP negative	Anti-CCP positive	Anti-CCP negative
Rheumatoid factor positive	72	12	8	57
Rheumatoid factor negative	10	38	14	557

anti-CCP in the calculation, RF looses its correlation with RA. In the population studied, RF was more closely associated with anti-CCP than it was with RA in general.

Of the 40 early RA patients in this study, 25 were anti-CCP positive and 23 were RF positive. This is consistent with the literature that shows that anti-CCP often arises earlier in RA than RF [24, 25].

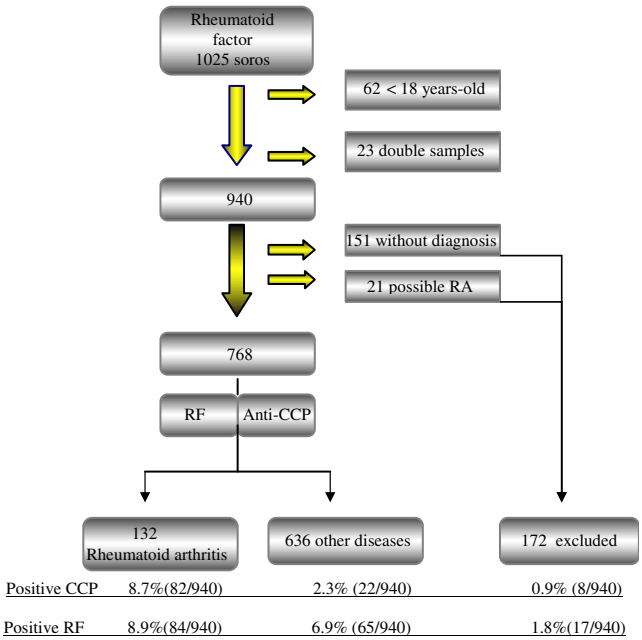
Some findings are hard to quantify statistically. For example, ten of the RA patients were anti-CCP positive but RF negative (Table 7). RF negative patients are sometimes more difficult to diagnose as having RA than RF-positive patients, so the anti-CCP result could give doctors more confidence in their diagnosis. Only 22 of the 768 patients in this study were anti-CCP positive without a diagnosis of RA, and eight of them were also positive for RF. Given the high diagnostic utility of anti-CCP, if the doctors had known the anti-CCP results, it is possible that they would have considered a diagnosis of RA more strongly.

Two groups of patients will be particularly interesting to follow in the future. One group is the 22 patients who are not diagnosed with RA but are positive for anti-CCP, with or without concomitant RF (Table 7), to see if any of them develop RA. At least one study [35] has shown that anti-CCP can appear up to several years in advance of a diagnosis of RA. The other is the group of ten RA patients that is double negative for the serologic markers to see if this group has a higher rate of mild disease than the patients who are positive for the serologic markers.

In the population tested for RF, anti-CCP is a more useful test than RF to help in the diagnosis of RA. Anti-CCP is equally sensitive but more specific than RF, leading to significantly higher statistical correlation with disease for anti-CCP than for RF. This is true for patients with any duration of RA at a pretest probability of disease of 17% and for early RA patients with a pretest probability of disease of 9%. Measuring both RF and anti-CCP is clinically useful because there is an increase in sensitivity when either is positive and an increase in specificity when both are positive, compared to either marker alone. If a new set of criteria is made to classify early RA, anti-CCP should be included because it would increase the diagnostic power of serologic tests compared to RF alone.

Appendix

Appendix 1



Appendix 2

Table 8 Demographic, clinical and laboratorial characteristics of 940 patients, divided in three groups: studied group (768 patients), excluded patients with no diagnosis (151 patients) and excluded patients with undefined diagnosis of rheumatoid arthritis (21 patients)

Characteristics of 940 patients	Studied *N*=768	No diagnosis *N*=151	Doubtful *N*=21
Sex			
Female	605 (79%)	117 (77%)	17 (81%)
Male	163 (21%)	34 (23%)	4 (19%)
Age			
Years	52±15	52±15	59±15
Duration of symptoms			
<2 years	444 (58%)	–	7 (33%)
Source			
Outpatients	621 (81%)	151 (100%)	21 (100%)
Inpatients	147 (19%)	0	0
Anti-CCP			
Positive	104 (13%)	4 (3%)	4 (19%)
Result (U/ml)	113±62	23±15	34±14
FR			
Positive	149 (19%)	11 (7%)	6 (28%)
Result (IU/ml)	102±548	45±139	45±576

Data are presented as counted (percentages) or mean±SD for age and test results.

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