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Article

Serological Evaluation of Anti-Cyclic Citrullinated Peptide Antibodies and Rheumatoid Factor Titer in a Clinical Population

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Abstract: Anti-cyclic citrullinated peptide (Anti-CCP) antibodies and rheumatoid factor (RF) are the main serological markers in the diagnosis and follow-up of rheumatoid arthritis (RA). Here we evaluate their prevalence, positivity rates and inter-marker correlation over a 16 month period. A retrospective study was performed on 266 serum samples collected from January 2024 to April 2025, 175 for Anti-CCP and 91 for RF titers. RF positivity was defined as ≥14 IU/mL and anti-CCP positivity as >20 U/mL. Statistical studies included Shapiro-Wilk test of normality, Mann-Whitney U test, chi-square test and Spearman rank correlation.Anti-CCP positive was found in 16% (n=28) of the samples and 44% (n=40) had RF positivity ($\chi 2=23.14$, $p<0.0001$). Both indicators were significantly different in the sero-positive and -negative groups ($p<0.000001$). The independence of the two markers is supported by the lack of statistically significant association between the two markers ($r=0.019$, $p=0.885$). Anti-CCP and RF titers provide complementary diagnostic information in the evaluation of rheumatoid arthritis. The different positive rates and the lack of a relation between the two indicators show the importance of integrated testing in clinical practice.

Keywords: Anti-CCP, Autoimmune Diagnosis, Rheumatoid Factor, Rheumatoid Arthritis, Serological Markers

Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by persistent synovial inflammation, destruction of bone and cartilage, progressive destruction of joints, morning stiffness, and extra-articular manifestations including fatigue, fever, and formation of rheumatoid nodules [1]. Accurate and timely diagnosis is important to reduce long-term morbidity and prevent permanent joint damage. Two serological markers that are important in the diagnostic workup of RA are rheumatoid factor (RF) and anti-cyclic citrullinated peptide (Anti-CCP) antibodies [2].

Anti-CCP antibodies, also known as anti-citrullinated protein antibodies (ACPA), are identified by enzyme-linked immunosorbent assay (ELISA) and are part of the 2010 ACR/EULAR classification criteria for RA. Anti-CCP has a high specificity (>95%) for RA and can be detected years before the disease manifests clinically. To improve diagnostic performance, Anti-CCP tests have been developed in successive generations. The second-generation assay (Anti-CCP2) had improved sensitivity but good

specificity compared with the first generation. A third-generation assay (Anti-CCP3) was then developed to further increase sensitivity [3].

RF is an autoantibody against the Fc region of IgG and has been used as a diagnostic marker for RA for more than 60 years. However, it has a low specificity and can be seen in other autoimmune diseases and in healthy old people [4].

The degree of agreement between quantitative RF titer and Anti-CCP levels in clinical laboratory practice is still being investigated, despite the fact that both markers are useful on their own. Results that are discordant, meaning that one marker is positive while the other is negative, are common and have different clinical implications [5]. An RF-positive, Anti-CCP-negative profile is more suggestive of inflammatory arthritis other than RA, whereas an Anti-CCP-positive, RF-negative profile may indicate early seroconversion. Understanding these discordance patterns is therefore directly relevant to clinical decision-making [6].

The global burden of RA is considerable with an estimated frequency of 0.5–1 % in adult populations worldwide and higher rates reported in women and older age groups [7]. The epidemiology of RA and associated serological profiles in the Middle East and Arab countries including Iraq is not well understood due to the lack of population-based research. The available data underscores the importance of region-specific research as it suggests that the clinical and serological presentation of RA in Arab populations may be different from the Western cohorts [8].

The pathophysiology of RA involves complex immunologic processes including activation of autoreactive T cells, autoantibody production by B cells and sustained release of cytokines, resulting in synovial hyperplasia and joint deterioration [9]. Citrullination is a post-translational modification of proteins catalysed by peptidyl arginine deiminases (PADs), and plays a key role in the formation of citrullinated antigens that induce ACPA production in genetically susceptible individuals that express HLA-DRB1 shared epitope alleles [10].

From a prognostic point of view, both RF and anti-CCP have been associated with long-term outcomes and disease severity. Anti-CCP seropositivity has been linked to a more aggressive disease course, more rapid joint erosion and structural damage in radiographic imaging [11]. RF, especially at high titres, is associated with extra-articular manifestations of RA including vasculitis, secondary Sjögren's syndrome and increased cardiovascular risk [12]. Furthermore, recent research indicates that pre-clinical seroconversion identifiable years before to symptom onset may present a chance for early intervention measures [13].

The objectives of this retrospective cross-sectional study were: (1) to determine the positivity rates of Anti-CCP and RF titers in a clinical population; (2) to assess the distribution of values between seronegative and seropositive patients; and (3) to investigate the correlation between the two biomarkers.

Materials and Methods

Study Design and Population

This laboratory-based cross-sectional study was conducted in a private clinical laboratory in Iraq. Data were retrospectively collected from the laboratory information system between January 2024 and April 2025.The study comprised 175 Anti-CCP measurements and 91 RF titer measurements. All specimens were processed in a certified clinical laboratory using standard procedures.

Laboratory Methods

Anti-CCP antibodies were measured using second-generation ELISA (Anti-CCP2). Positivity was defined based on established clinical cutoffs of >20 U/mL. The RF titer was assessed using

immunoturbidimetric or latex agglutination methods, and a value ≥14 IU/mL was considered positive, based on the manufacturer's reference ranges.

Statistical Analysis

The normality of data was analyzed by Shapiro-Wilk test. Both datasets were non-normally distributed ($p<0.0001$); therefore, nonparametric tests were applied throughout. Group comparisons (seropositive vs. seronegative) were performed using the Mann-Whitney U test. Differences in positivity rates between Anti-CCP and RF were evaluated by chi-square test. The correlation between the two markers in date-matched samples was assessed using Spearman's rank correlation coefficient. Python 3.12 (SciPy v1.11) was used for all studies. Statistical tests were performed using a significance level of $p < 0.05$.

emicals etc. All the ethical permission associated in the research work must be specified. Indicate the statistical methods used and identify statistical significance using superscripts (* and **) following the data (*P<0.05, **P<0.01).

Results

Sample Characteristics

In total, 266 serum measurements were included: 175 Anti-CCP assays and 91 RF titer assays during a 16-month period (January 2024–April 2025). The descriptive statistics of both markers are shown in Table 1.

Table 1. Descriptive Statistics of Anti-CCP and RF Titer Values

Parameter	Anti-CCP (U/mL)	RF Titer (IU/mL)
Sample size (n)	175	91
Mean ± SD	33.80 ± 85.90	35.67 ± 57.51
Median (IQR)	3.20 (3.00–3.50)	8.02 (6.55–38.35)
Minimum	0.36	0.00
Maximum	>300	203.00
Positivity cutoff	>20 U/mL	≥14 IU/mL
Shapiro-Wilk W	0.390	0.587
Normality p-value	<0.0001*	<0.0001*

* Non-normal distribution; nonparametric tests applied. SD = standard deviation; IQR = interquartile range.

Seroprevalence of Anti-CCP and RF

Anti-CCP positivity (>20 U/mL) was found in 28 of 175 samples (16%) and RF positivity (≥14 IU/mL) in 40 of 91 samples (44%). The positivity rates of the two markers differed significantly by chi-square analysis ($\chi^2=23.14$, df=1, $p<0.0001$), indicating that RF seropositivity was substantially more prevalent in this cohort (Table 2).

Table 2. Seroprevalence of Anti-CCP and RF Titer

Marker	Total (n)	Positive n (%)	Negative n (%)	Cutoff
Anti-CCP	175	28 (16%)	14 7(84.0%)	>20 U/mL
RF Titer	91	40 (44%)	51 (56.0%)	≥14 IU/mL
Chi-square test	$\chi^2=23.14$	df=1	p<0.0001*	--

* Statistically significant difference in positivity rates between Anti-CCP and RF.

Comparison of Seropositive vs. Seronegative Groups

Both markers showed highly significant differences between seropositive and seronegative groups as determined by the Mann-Whitney U test (Table 3). The seropositive group had a significantly higher median value (301.00 U/mL) than the seronegative group (3.10 U/mL; U=3750.0, p<0.000001) for Anti-CCP. Similarly, median titer was significantly higher in RF-seropositive patients (44.20 IU/mL) compared to seronegative patients (7.00 IU/mL; U=1960.0, p<0.000001).

Table 3. Comparison of Seropositive vs. Seronegative Groups (Mann-Whitney U Test)

Marker	Group	n	Mean	Median	U statistic	p-value
Anti-CCP	Positive	28	216.65	301.00	3750.0	<0.000001*
Anti-CCP	Negative	147	3.35	3.10	--	--
RF Titer	Positive	40	82.23	44.20	1960.0	<0.000001*
RF Titer	Negative	51	6.27	7.00	--	--

* Highly significant. Mann-Whitney U test (two-tailed); nonparametric due to non-normal distribution.

Correlation Between Anti-CCP and RF Titer

Spearman rank correlation was performed on 61 date-matched samples for which both Anti-CCP and RF values were available. No statistically significant correlation was found between Anti-CCP and RF titer values (r=0.019, p=0.885) (Table 4, Table 5). The results obtained indicate that the two biomarkers are independent in this population and provide complementary, rather than redundant, diagnostic information.

Table 4. Spearman Rank Correlation Between Anti-CCP and RF Titer

Spearman r	p-value	Interpretation	n (matched)
0.019	0.885 (NS)	No significant correlation	61

NS = Not statistically significant (p>0.05). Matched by collection date.

Table 5. Serological Profile Classification of Date-Matched Patients (Anti-CCP and RF Titer)

Serological Pattern	n	%
Anti-CCP+ / RF+ (dual seropositive)	23	37.7%
Anti-CCP− / RF+ (RF-only positive)	17	27.9%
Anti-CCP+ / RF− (Anti-CCP-only positive)	5	8.2%
Anti-CCP− / RF− (dual seronegative)	16	26.2%
Total matched pairs	**61**	**100%**

*Percentages are based on 61 same-day matched pairs (patients for whom both Anti-CCP and RF measurements were available on the same collection date). Anti-CCP positivity cutoff: >20 U/mL; RF positivity cutoff: ≥14 IU/mL. Spearman r = 0.019, p = 0.885 (NS).

Discussion

This study examined the seroprevalence and distribution of Anti-CCP and RF titer values in a 16-month retrospective clinical cohort. The principal findings were: (1) RF demonstrated a significantly higher positivity rate (44%) than Anti-CCP (16%); (2) both markers showed highly significant differences between seropositive and seronegative groups; and (3) no significant correlation was found between the two markers.

The lower positivity rate of Anti-CCP (16%) compared to RF (44%) is consistent with the established principle that Anti-CCP has higher specificity but lower sensitivity than RF in RA diagnosis. In a nationwide study in Turkey, RF positivity was found to be 14.72% in unselected populations and Anti-CCP positivity was found to be 35.04% between 2018 and 2021. More than 13.9 million RF tests and 1.18 million Anti-CCP tests were performed [14]. The much higher RF positivity in our cohort (44%) reflects the broader etiologic associations of RF, which may be increased in Sjögren's syndrome, mixed connective tissue disease, viral infections, and in the elderly without autoimmune disease [15].

The Mann-Whitney U test showed highly significant results for both markers ($p<0.000001$) and confirms the existence of a clear bimodal distribution separating seropositive from seronegative patients. The difference in magnitude between groups was especially striking for Anti-CCP, with the median in the seropositive group (301.00 U/mL) almost 97 times greater than the median in the seronegative group (3.10 U/mL), in keeping with the high-titer pattern seen in established RA. High Anti-CCP titers have been consistently associated with greater radiographic joint damage and functional impairment. A multicenter Egyptian study (2024) of 5,268 RA patients found that dual-seropositive patients (RF+/anti-CCP+) had higher disease activity scores (DAS28), functional impairment, and a higher incidence of metabolic syndrome than seronegative or single-seropositive patients [16].

Another clinically important finding was that there was no statistically significant correlation between the levels of Anti-CCP and RF ($r = 0.019$, $p = 0.885$). These findings are in agreement with the hypothesis that the two biomarkers provide different and complementary information in the assessment of rheumatoid arthritis. This finding supports the idea that the two biomarkers provide different and complementary information in the assessment of RA. There have been reports of positive correlations between RF and Anti-CCP levels and significant heterogeneity among serological subgroups. These differences may be due to differences in disease duration, selection criteria of patients, ethnic background and methodology of the assay. A recent population based cohort study revealed different clinical outcomes in dual-seropositive, RF-only positive, Anti-CCP-only positive and seronegative patients suggesting that these biomarkers define biologically distinct disease phenotypes [17].

Previous studies have suggested that isolated Anti-CCP positivity may have distinct clinical implications, independent of RF status . Anti-CCP positivity has been associated with increased risk of extra-articular manifestations, especially interstitial lung disease (ILD). A retrospective analysis reported a significantly increased risk of ILD development in Anti-CCP positive, RF negative patients (adjusted OR 3.50, 95% CI 1.52–8.04), indicating the prognostic value of Anti-CCP beyond its diagnostic role [18].

In Iraq and other resource-limited settings, the decision to use RF or Anti-CCP testing is usually dictated by availability and cost. RF testing with immunoturbidimetry or latex agglutination is often readily available and is economical, but Anti-CCP2 ELISA remains less available in many public health laboratories despite better specificity [19]. Clinical laboratories may order Anti-CCP more preferentially for patients with intermediate-probability RA presentations, which could contribute to the disproportionate volume of RF testing (91 samples) compared to Anti-CCP (175 samples) seen in our dataset. There is still a need for standardization of access to both assays in laboratory medicine guidelines for underdeveloped countries [20].

"In our study the seronegative fraction is of special interest. The 84% Anti-CCP-negative and 56% RF-negative figures suggest that a large proportion of the tested population was not seropositive for either marker. In the clinical setting, seronegative RA, defined as the absence of both RF and Anti-CCP, accounts for approximately 20–30% of all RA diagnoses and poses specific diagnostic challenges

[21]. In these patients, imaging findings (ultrasound or MRI showing synovitis), elevated acute phase reactants (ESR, CRP) and clinical criteria remain important diagnostic adjuncts [22]. The development of novel serological markers, such as anti-carbamylated protein (anti-CarP) antibodies and anti-PAD4 antibodies, may contribute to improving diagnostic coverage in seronegative patients [23].

From a temporal perspective, both anti-CCP and RF can be detected in the pre-clinical phase of RA, often years before the development of clinical arthritis. In a landmark longitudinal study, ACPA seroconversion occurred a median of 4.5 years prior to RA diagnosis, and RF seroconversion occurred approximately 3 years before diagnosis [24]. Consistent with this pre-clinical biology, we observed markedly skewed titer distributions, with most Anti-CCP values concentrated around zero, and a small number with extreme values (>300 U/mL). This tested patient cohort may have included patients in early or pre-clinical phases leading to the preponderance of low titer or negative results.

The absence of correlation between Anti-CCP and RF ($r=0.019$, $p=0.885$) in this study is biologically plausible as the two markers represent different immunological pathways. RF, mainly of the IgM isotype, is produced by B cells in response to the Fc portion of IgG via non-antigen-specific mechanisms and is increased in the setting of chronic inflammation of various origin [25]. In contrast, ACPA are induced by antigen-specific immunisation against citrullinated self-proteins, a process that requires specific genetic and environmental co-factors including smoking, periodontal infection and gut dysbiosis [26]. These different pathogenetic mechanisms justify the independent informative value of each marker and the reason for their simultaneous measurement in routine clinical evaluation [27].

The study has demonstrated that Anti-CCP and RF are complementary, and this supports the use of combined testing in clinical practice. The combined use of the two markers increases the diagnostic sensitivity over the use of either marker alone. A systematic review confirmed that the combination of Anti-CCP2 and RF provides a stronger predictor of RA than either biomarker individually, and both are incorporated into the 2010 ACR/EULAR classification criteria for this reason [28,29]. The 2022 EULAR update continues to recommend simultaneous measurement of RF and ACPA in the diagnostic workup of suspected RA [30].

Conclusion

This retrospective analysis confirmed the significantly higher seropositivity rate of RF than Anti-CCP in the study population (44% vs. 16%, $p<0.0001$). Both markers differentiated between seropositive and seronegative patients ($p<0.000001$). They were not correlated with each other ($r=0.019$, $p=0.885$) supporting their complementary role in clinical diagnosis. These findings support the recommendation to measure Anti-CCP and RF simultaneously for maximum diagnostic accuracy in the rheumatologic workup.

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