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Microbiology Section

Comparative Evaluation of Rheumatoid Factor and Anti-CCP Antibody Tests as Diagnostic Markers for Rheumatoid Arthritis: A Cross-sectional Study from a Tertiary Care Centre in Dehradun, Uttarakhand, India

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ABSTRACT

Introduction: Rheumatoid Arthritis (RA) is a chronic autoimmune disease with a global prevalence of approximately 1%. It is characterised by persistent joint inflammation and the production of multiple autoantibodies, leading to joint destruction, deformities, physical disability, and a reduced quality of life. Rheumatoid Factor (RF) is an antibody that targets the Fc portion of human IgG, whereas Anti-Cyclic Citrullinated Peptide (Anti-CCP) is an autoantibody generated following citrullination, often appearing in the early stages of RA. Both RF and anti-CCP are considered valuable serological markers for diagnosing RA.

Aim: To evaluate RF and anti-CCP antibody tests as diagnostic markers for RA.

Materials and Methods: This cross-sectional study was conducted in the Department of Microbiology, Government Doon Medical College and Hospital, Dehradun, Uttarakhand, India over a 12-month period (May 2023 to April 2024). All clinically suspected RA patients above 10 years of age were included in the study. A total of 718 serum samples from clinically suspected RA patients were collected for Anti-CCP and RF testing over one year. Blood samples were collected aseptically and serum was separated for testing. RF was detected using the latex agglutination method on an automated analyser (Bio Systems Diagnostics Pvt. Ltd., Tamil Nadu, India), with values >14 IU/mL considered positive. Anti-CCP antibodies were analysed using a Chemiluminescent Immunoassay (CLIA)-based Abbott Architect iSystem (Abbott Diagnostics, Illinois, USA), with values >5 IU/mL considered positive. All tests were performed according to the manufacturer's instructions. Demographic details such as age and gender were recorded for all participants. Statistical analysis was conducted using Statistical Package for the Social Sciences (SPSS) version 23.0, with a p-value <0.05 considered statistically significant.

Results: Of the 718 serum samples tested, 281 (39.1%) were positive for either Anti-CCP or RF. A total of 118 (16.4%) were Anti-CCP positive, and 109 (15.2%) were RF positive correspondingly among these samples. A total of 437 samples (60.9%) were negative for both Anti-CCP and RF. Among the 718 samples analysed, 163 (22.7%) were RF positive and Anti-CCP negative, while 109 (15.2%) were positive for both Anti-CCP and RF. Nine samples (1.25%) were exclusively Anti-CCP positive.

Conclusion: Anti-CCP shows higher specificity and is useful in predicting disease progression, as it appears early in the course of RA. Patients who are RF seropositive but Anti-CCP seronegative indicate that RF can be elevated in other autoimmune diseases, decreasing its diagnostic reliability for RA. Anti-CCP testing can aid in the early detection of RA, enabling targeted interventions that may modify disease progression and improve patient outcomes and quality of life.

Keywords: Anti-cyclic citrullinated peptide antibody, Autoimmune disease, Serological markers

INTRODUCTION

RA is a systemic autoimmune disease of unknown aetiology, with a global prevalence of approximately 1%. It occurs more commonly in females than males, with a ratio of 2-3:1 [1,2]. RA is the most common form of chronic inflammatory arthritis, characterised by symmetric polyarthritis and the production of several autoantibodies, including RF, Anti-Perinuclear Factor (APF), Anti-Neutrophil Cytoplasmic Antibodies (ANCA), Anti-Keratin Antibodies (AKA), and Anti-CCP, which leads to joint destruction, deformities, and physical disability, thereby affecting quality of life [3]. Extra-articular manifestations of RA include fatigue, subcutaneous nodules, pulmonary involvement, pericarditis, peripheral neuropathy, vasculitis, and haematological abnormalities. The incidence of RA increases between 25-55 years of age, plateaus until 75 years, and subsequently decreases [1,3]. Persistently active RA results in articular cartilage and bone destruction, leading to functional disability. Therefore, early and aggressive diagnosis and treatment are essential before irreversible damage occurs. Among the various autoantibodies, RF and Anti-CCP are considered valuable diagnostic and prognostic biomarkers in patients suspected of having RA.

RF is an antibody specific to the Fc portion of human IgG and was one of the diagnostic criteria for RA established by the American College of Rheumatology (ACR) [4-6]. IgM RF can be detected in approximately 75% of RA patients, but may also be present in 1-5% of healthy individuals. It can be elevated in other connective tissue disorders such as Sjögren's syndrome, Systemic Lupus Erythematosus (SLE), mixed essential cryoglobulinemia, and chronic infections including subacute bacterial endocarditis, hepatitis B, and hepatitis C [1]. In 2010, the ACR and the European League Against Rheumatism (EULAR) revised the 1987 ACR classification criteria for RA, adding Anti-CCP due to its greater specificity for RA diagnosis. Anti-CCP is an autoantibody formed after citrullination and appears during the early phase of RA, often predating clinical symptoms [4]. Its high specificity and prognostic value for erosive disease make anti-CCP an important marker for both diagnosis and prognosis.

This study was undertaken to assess the diagnostic utility of RF and anti-CCP antibodies in patients from the Dehradun region of Uttarakhand, where limited region-specific data are currently available. It provides a comprehensive evaluation of both RF and anti-CCP in a tertiary care centre in Northern India, highlighting regional seroprevalence patterns. The combined assessment of both markers is expected to offer valuable insights for improving early diagnosis and guiding timely treatment decisions in routine clinical practice. This study hypothesises that anti-CCP, whether used independently or alongside RF, provides greater diagnostic specificity and clinical value for early RA detection compared with RF alone. Given the higher specificity and potential prognostic value of anti-CCP antibodies compared to RF, this study was designed to evaluate their utility as diagnostic biomarkers in patients with suspected RA. The primary objective was to assess the association between RF and anti-CCP antibody positivity and to determine their combined usefulness as diagnostic markers in clinically suspected cases of RA. Additionally, the study examined the prevalence and distribution of these markers across demographic groups, identified seronegative cases that may be detected by anti-CCP alone, and explored its potential role in the early identification and management of RA to prevent long-term joint damage.

MATERIALS AND METHODS

This analytical, cross-sectional study was conducted in the Department of Microbiology, Government Doon Medical College and Hospital, Dehradun, Uttarakhand, India over a period of 12 months (May 2023 to April 2024). Blood samples were collected under aseptic precautions from patients clinically suspected of RA attending the Orthopaedics and Medicine Outpatient Departments (OPDs) of the hospital. This was a time-bound cross-sectional study conducted over one year, during which all eligible patients presenting to the tertiary care centre and meeting the inclusion criteria were enrolled. No formal sample size calculation was performed; instead, all eligible subjects available during the study period were included.

Inclusion criteria: All clinically suspected patients of RA above 10 years of age were included in the study.

Exclusion criteria: Pregnant women and established cases of other forms of arthritis were excluded from the study.

Study Procedure

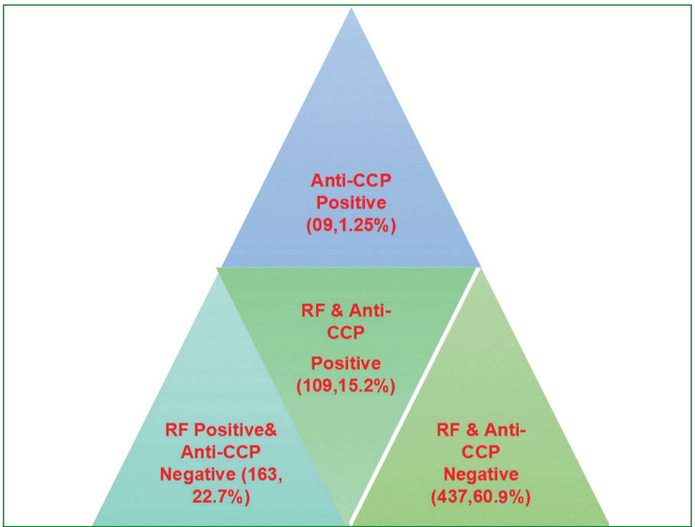
Serum samples were collected from each patient, and tests were performed as per the manufacturer's instructions. RF was determined using the latex agglutination method on an automated analyser (BioSystems Diagnostics Pvt. Ltd., Tamil Nadu, India) [7]. In this method, latex particles coated with human IgG are mixed with the patient's serum. If RF is present, it binds to the Fc portion of IgG on the latex particles, causing visible agglutination. The degree of agglutination is directly proportional to the concentration of RF in the serum and is quantified by the analyser (turbidimetry). A value >14 IU/mL for RF was considered positive based on the manufacturer's instructions (RF Latex Kit, REF: COD22922, COD23922, BioSystems Diagnostics Pvt. Ltd.) [7]. Anti-CCP antibodies were tested using CLIA-based analyser, Abbott Architect iSystem (Abbott Diagnostics, Illinois, USA) [8]. This assay involves the binding of anti-CCP antibodies present in the patient's serum to CCP antigens coated on paramagnetic microparticles. Following binding, a chemiluminescent signal is generated upon reaction with a labelled anti-human IgG conjugate. The intensity of the emitted light is measured and is directly proportional to the concentration of anti-CCP antibodies in the sample. All tests were performed following standard operating procedures and according to the manufacturer's instructions. Values >5 IU/mL for anti-CCP were considered positive (Architect Anti-CCP, Abbott Diagnostics, REF:1P65-25) [8].

STATISTICAL ANALYSIS

Statistical analysis was conducted using SPSS version 23. The Chi-square test was used, and a p-value <0.05 was considered statistically significant.

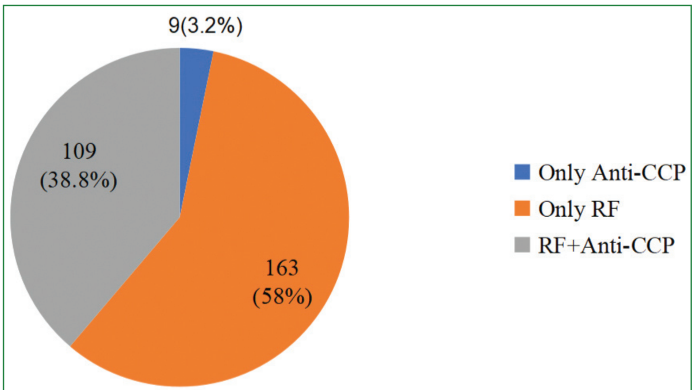
RESULTS

A total of 718 serum samples were evaluated in the Microbiology Laboratory for Anti-CCP and RF over a one-year period (May 2023 to April 2024). Of these, 281 samples (39.1%) tested positive for either Anti-CCP or RF, while 437 samples (60.9%) were negative for both markers. Among the 718 serum samples examined, 163 (22.7%) were RF-positive and Anti-CCP negative, whereas 109 samples (15.2%) were positive for both Anti-CCP and RF. Nine samples (1.25%) were exclusively positive for Anti-CCP [Table/Fig-1].



[Table/Fig-1]: Percentage wise distribution of anti-CCP and RF test results in suspected RA cases (n=718).

Among the 281 seropositive samples, 118 (41.9%) were positive for Anti-CCP (109 + 9/281). Of these, 109 (38.8%) were positive for both Anti-CCP and RF, and 9 (3.2%) were exclusively positive for Anti-CCP and negative for RF [Table/Fig-2]. Likewise, out of the 281 seropositive samples, 272 (96.79%) were RF-positive (109 + 163/281). Of these 281 positive samples, 163 (58%) were only RF-positive and Anti-CCP negative, while 109 (38.8%) were positive for both Anti-CCP and RF [Table/Fig-2].



[Table/Fig-2]: Distribution of Rheumatoid Factor (RF) and Anti-Cyclic Citrullinated Peptide (Anti-CCP) antibodies in seropositive patients (n=281).

An odds ratio was calculated to assess the association between RF and anti-CCP positivity. Based on the above data, an odds ratio of 32.47 (95% Confidence Interval: 16.07–65.59) was determined. This odds ratio suggests that patients who are RF-positive are approximately 32 times more likely to be anti-CCP positive compared to those who are RF-negative [Table/Fig-3].

Among the 718 seropositive samples, the male-to-female ratio was 1:3, with 168 males (23.4%) and 550 females (76.6%). The highest number of patients belonged to the 41-50 years age group (234; 32.6%), followed by 31-40 years (152; 21.2%), 21-30 years (121; 16.9%), 51-60 years (105; 14.6%), 61-70 years (77; 10.7%), 11-20 years (19; 2.6%), and above 70 years (10; 1.4%) [Table/Fig-4].

	Anti-CCP positive	Anti-CCP negative	Total
RF positive	109	163	272
RF negative	9	437	446
Total	118	600	718

[Table/Fig-3]: A 2×2 Contingency table showing Anti-CCP and RF test results in suspected RA cases.
Odds ratio: 32.47 (95% Confidence Interval: 16.07 to 65.59), Chi-square value: 178.17, p-value: <0.0001 (highly significant)

Age (y)	Male	Male (%)	Female	Female (%)	Total (n=718)	Total (%)
11-20	8	1.1	11	1.5	19	2.6
21-30	29	4	92	12.9	121	16.9
31-40	38	5.3	114	15.9	152	21.2
41-50	49	6.8	185	25.8	234	32.6
51-60	22	3.1	83	11.5	105	14.6
61-70	20	2.8	57	7.9	77	10.7
>70	2	0.3	8	1.1	10	1.4

[Table/Fig-4]: Gender-wise distribution of RA cases in different age groups (n=718).

DISCUSSION

The RA is a systemic autoimmune disease that can present with a range of extra-articular manifestations, including fatigue, subcutaneous nodules, lung involvement, pericarditis, peripheral neuropathy, vasculitis, and haematological abnormalities [1]. Studies have shown that accelerated atherosclerosis is a well-recognised feature of RA, with cardiovascular disease being a leading cause of mortality in these patients. The risk of acute myocardial infarction has been reported to be up to four times higher in individuals with RA. Additionally, anti-CCP antibodies have been linked to the development of subclinical atherosclerosis in RA patients, further highlighting their potential role beyond joint pathology [9,10].

In the present study, a total of 718 patients were included, with a male-to-female ratio of approximately 1:3. This female predominance aligns with findings from studies conducted by Dedwal AK et al., and Thoti H et al., both of which reported a higher prevalence of RA in females compared to males [2,3]. Dedwal AK et al., observed a male-to-female ratio of 1:2.9, while Thoti H et al., reported a ratio of 1:3.2, reinforcing the well-documented higher susceptibility of females to RA. The most common age group among clinically suspected RA cases in the present study was 41-50 years, followed by 31-40 years. This finding was consistent with studies by Malaviya AN et al., and Das SK et al., which also reported the highest prevalence of RA in the 40-50 years age group [11,12]. However, a study by Chopra A et al., found a slightly earlier peak incidence in the 30-40 years age group, highlighting possible variations due to genetic, environmental, and demographic factors [13].

Among the tested patients, RF was positive in 272 (37.8%) cases, while anti-CCP was positive in 118 (16.4%) cases. A total of 109 (15.2%) patients tested positive for both serological markers, whereas 163 (22.7%) samples were positive for RF but negative for anti-CCP. In the present study, RF-positive individuals were over 32 times more likely to also be anti-CCP positive compared to RF-negative individuals (OR=32.47), suggesting a strong association between the two serological markers. Although the present study did not categorise patients based on a confirmed RA diagnosis, this significant correlation supports the combined diagnostic value of RF and anti-CCP in suspected RA cases. A meta-analysis of 24 studies by Yang X et al., reported a high odds ratio of 53.43 (95% CI: 34.46-82.40) for the combined use of anti-CCP and RF, highlighting the superior diagnostic accuracy achieved when both serological markers are used together [14]. These findings support the enhanced diagnostic utility of using both anti-CCP and RF, especially when both markers are positive, consistent with the results of the present study.

A study by Bizzaro N et al., demonstrated that anti-citrullinated peptide antibodies have high diagnostic value for RA with strong disease specificity [6]. Similarly, Chou CT et al., found that anti-CCP offered better diagnostic accuracy than RF alone [15]. These studies emphasise that anti-CCP has a higher predictive value for RA, which was consistent with the high OR observed in the present analysis. Using both tests together improves the likelihood of diagnosing RA early and accurately by combining their strengths, allowing for more sensitive detection and greater specificity.

Several studies have suggested that in other autoimmune diseases like SLE and infection-associated arthritis (e.g., hepatitis), the prevalence of anti-CCP titres is low. Das SK et al., reported that anti-CCP antibodies were detected in only 7.5% of patients with Sjögren's syndrome in their study [12]. This supports the observation that anti-CCP is more specifically associated with RA. Therefore, anti-CCP can be useful in distinguishing patients with RA from those with other autoimmune and infection-associated arthropathies.

Serum RF has been found in approximately 75% of patients with RA; therefore, a negative result does not exclude the presence of the disease [1]. In the present study, nine samples were Anti-CCP positive but RF negative. Among these, five patients belonged to the age group of less than 45 years. Similar results were observed in a study conducted by Esmat MM et al., which suggested that while RF is present in around 75% of RA patients, anti-CCP antibodies may be a more specific marker, particularly in RF-negative cases. Their study showed that a subset of patients who tested negative for RF still had detectable levels of anti-CCP antibodies (1.6%), reinforcing the idea that anti-CCP testing is valuable for diagnosing seronegative RA [16].

Patients with early arthritis who are anti-CCP positive are at an increased risk of developing RA and erosive joint disease, resulting in articular cartilage and bone destruction [2]. Hence, it becomes imperative to treat such patients early and aggressively with Disease-Modifying Antirheumatic Drugs (DMARD) therapy to prevent joint damage and functional disability. In the early stages of RA, joint damage may not be visible on radiological investigations, whereas anti-CCP antibodies appear early, making them a crucial biomarker for the timely diagnosis of RA. Long-term studies have shown a strong association between anti-CCP and erosive arthritis as well as disease severity. Anti-CCP antibodies also have prognostic significance because anti-CCP–positive patients have been shown to develop significantly more severe radiological damage than anti-CCP-negative patients [5,6,17]. Therefore, anti-CCP is a specific indicator for early prediction, identification, and diagnosis of RA, as well as a prognostic marker for bone destruction, the overall clinical course of the disease, and treatment monitoring.

In the present study, most RF-positive patients received symptomatic treatment, mainly short-term pain-relieving medications. A six-month follow-up conducted via telephone revealed that only five out of 163 patients occasionally required painkillers, while the rest experienced clinical improvement and no longer required medication. Since these patients were RF positive but anti-CCP negative, they were not diagnosed with RA. Instead, their RF seropositivity may have been associated with other diseases or autoimmune conditions, consistent with the findings of Dedwal AK et al., [2]. RF lacks diagnostic specificity and may be detected in various chronic inflammatory diseases that present with arthritis as a clinical feature. Multiple studies have shown that RF is not exclusive to RA and may also be present in conditions such as SLE, Sjögren's syndrome, and chronic infections. Therefore, RF alone cannot be considered a reliable marker for the diagnosis of RA [1,15,18].

According to the 2010 ACR/EULAR classification criteria for RA, the combined assessment of RF and anti-CCP antibodies enhances early and accurate diagnosis, enabling timely initiation of disease-modifying therapy to reduce the risk of adverse outcomes [19]. Present study supports the clinical utility of incorporating anti-CCP testing alongside RF, particularly in early-stage or seronegative RA cases where RF alone may not be sufficient for diagnosis and may yield false-negative results. Early detection using anti-CCP allows for timely therapeutic intervention, potentially preventing joint damage and improving long-term outcomes. Consistent with existing literature, present study findings show that the combination of RF and anti-CCP improves diagnostic performance, offering increased sensitivity when either marker is positive and enhanced specificity when both are positive compared to the use of either marker alone [14].

Limitation(s)

This study had a few limitations. The lack of clinical and radiological correlation, along with the absence of long-term follow-up, limits a thorough evaluation of disease progression and severity. Additionally, selection bias may have influenced the results, as patients were primarily recruited from specific OPDs, potentially limiting the representativeness of the study population. Despite these limitations, the study strongly reinforces the diagnostic importance of anti-CCP antibodies, particularly for early detection and seronegative presentations of RA.

CONCLUSION(S)

Anti-CCP is a highly specific marker for RA and plays a crucial role in early detection, allowing for timely intervention to alter disease progression and improve patients' quality of life. In contrast, RF lacks specificity, as it can be elevated in other autoimmune conditions, making it a less reliable standalone marker for RA. While clinical diagnosis remains the cornerstone of RA classification, serological markers such as RF and anti-CCP play a valuable role in supporting early detection, guiding prognosis, and enhancing diagnostic confidence. The comparative evaluation of these markers offers important insights, especially in suspected cases where a definitive clinical diagnosis has not yet been established. Moreover, the combination of anti-CCP and RF testing enhances diagnostic accuracy by increasing sensitivity when either marker is positive and improving specificity when both are present. This combined approach strengthens early diagnosis and optimises disease management, ultimately benefiting patient outcomes.

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