VER
Vascular & Endovascular Review

Rheumatoid Factor and Anti-CCP Antibodies as Diagnostic and Prognostic Biomarkers in Rheumatoid Arthritis: A Comprehensive Review

Dr. Mahnoor Manzoor[1], Dr. Ruqaiyah Nadeem[2], Dr. Shameem Ahmad Khan[3], Dr Shweta Aggarwal[4], Dr. Nazish Ayubi[5]

[1]Junior Resident, Department of Microbiology, Integral Institute of Medical Sciences and Research, Integral University, Lucknow, Uttar Pradesh, India.
[2]Associate Professor, Department of Microbiology, Integral Institute of Medical Sciences and Research, Integral University, Lucknow, Uttar Pradesh, India.
[3]Professor & Head, Department of Orthopaedics, Integral Institute of Medical Sciences and Research, Integral University, Lucknow, Uttar Pradesh, India.
[4]Professor, Department of General Medicine, Integral Institute of Medical Sciences and Research, Integral University, Lucknow, Uttar Pradesh, India
[5]Assistant Professor, Department of Microbiology, Integral Institute of Medical Sciences and Research, Integral University, Lucknow, Uttar Pradesh, India.

Corresponding Author
Dr. Ruqaiyah Nadeem
Email ID: ruqaiyah@iul.ac.in

ABSTRACT

Background: Rheumatoid arthritis is a long-standing autoimmune condition marked by ongoing inflammation of the synovial joints, progressive joint damage, and widespread systemic effects. Early diagnosis is essential to prevent irreversible disability. Of the various biomarkers currently in use, Rheumatoid Factor (RF) and Anti-Cyclic Citrullinated Peptide (Anti-CCP) antibodies remain the most commonly utilised. Over the past decade, Anti-CCP has emerged as a highly specific marker for RA, while RF continues to serve as a classical but less specific indicator.

Aim and Objective: This review provides an updated and comprehensive comparative analysis of RF and Anti-CCP antibodies as diagnostic, predictive, and prognostic markers.

Material and Methods: A narrative review was carried out integrating various verified sources such as PubMed, Scopus, Google Scholar, and Embase databases. Studies published between 2015 and 2025 evaluating RF and Anti-CCP in RA diagnosis, prognosis, disease activity, and correlation with radiological or clinical outcomes were included. A total of 82 articles were screened, and 52 relevant studies were analyzed qualitatively.

Results: Anti-CCP exhibited a specificity of 91–98%, significantly higher than RF (70–85%). RF demonstrated higher sensitivity (75–85%) compared to Anti-CCP (60–75%) in early disease. Combined positivity of RF + Anti-CCP increased diagnostic accuracy to >95%. Anti-CCP positivity strongly correlated with radiographic progression, erosive disease, higher DAS28 scores, and poor functional outcomes. RF showed associations with disease severity but lacked prognostic consistency. Anti-CCP antibodies appeared even years before clinical onset, supporting their role as preclinical markers.

Conclusion: Anti-CCP is superior to RF in specificity, prognostic value, and prediction of erosive disease. RF retains utility as a sensitive screening marker. Combined testing improves diagnostic accuracy and enables early therapeutic interventions. Future research should focus on integrating novel biomarkers with RF and Anti-CCP for personalized RA management.

KEYWORDS: Rheumatoid arthritis, Anti-CCP, Rheumatoid factor, Biomarkers, Diagnosis, Auto-antibodies.

How to Cite: Dr. Mahnoor Manzoor, Dr. Ruqaiyah Nadeem, Dr. Shameem Ahmad Khan, Dr Shweta Aggarwal, Dr. Nazish Ayubi, (2025) Rheumatoid Factor and Anti-CCP Antibodies as Diagnostic and Prognostic Biomarkers in Rheumatoid Arthritis: A Comprehensive Review, Vascular and Endovascular Review, Vol.8, No.19s, 182-186

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune condition marked by persistent inflammation that mainly affects the synovial joints, progressively resulting in cartilage degradation, bone destruction, and long-term functional impairment (1,2). Worldwide, rheumatoid arthritis affects an estimated 0.5–1% of individuals, with women experiencing the condition at significantly higher rates. Early recognition and timely initiation of disease-modifying anti-rheumatic drugs (DMARDs) are crucial to preventing irreversible joint destruction (3).

The development of rheumatoid arthritis results from a multifaceted interaction among genetic predisposition, environmental triggers, and immune-mediated mechanisms. The formation of autoantibodies is a hallmark of RA pathogenesis. Two such autoantibodies—Rheumatoid Factor (RF) and Anti-Cyclic Citrullinated Peptide (Anti-CCP) antibodies—play central roles in the

diagnosis and monitoring of RA (4-7).

First identified in 1940, rheumatoid factor (RF) is an autoantibody that targets the Fc region of IgG. Although historically important, RF is limited by its relatively low specificity and presence in various non-RA conditions, such as infections, chronic liver diseases, aging, Sjögren's syndrome, and even in healthy individuals (8,9). In contrast, Anti-CCP antibodies emerged in the early 2000s as highly specific markers for RA. These antibodies target citrullinated proteins formed by post-translational modification of arginine residues through the action of peptidylarginine deiminase (PAD) enzymes. Anti-CCP testing has since revolutionized RA diagnostics (10).

The ACR/EULAR 2010 classification criteria prominently incorporate RF and Anti-CCP status. Anti-CCP has demonstrated specificity as high as 98%, making it a near-ideal diagnostic biomarker. Additionally, Anti-CCP positivity is strongly associated with erosive disease, rapid disease progression, and poorer functional outcomes (11).

Despite these advantages, RF still holds clinical importance due to its higher sensitivity and cost-effectiveness, especially in low-resource settings. Furthermore, combined testing of RF and Anti-CCP significantly improves diagnostic accuracy (12).

Thus, this review aims to provide an updated comparative evaluation of RF and Anti-CCP, focusing on diagnostic accuracy, prognostic relevance, correlation with clinical outcomes, and current recommendations for their use.

MATERIAL AND METHODS

This review followed a narrative synthesis approach. A comprehensive search was conducted in
PubMed, Scopus, Embase, Google Scholar Using the keywords: "rheumatoid arthritis," "rheumatoid factor," "anti-CCP," "ACPA," "biomarkers," "diagnosis," "prognosis."

Inclusion Criteria

1. Studies published between 2015 and 2025
2. Human studies
3. Articles evaluating RF and/or Anti-CCP in RA
4. Observational, experimental, meta-analyses, and systematic reviews
5. Radiological correlation studies, disease-activity correlation studies

Exclusion Criteria

1. Case reports
2. Animal studies
3. Editorials, commentaries
4. Non-English articles where full text was inaccessible

Data Extraction and Analysis

The initial search yielded eighty-two publications. Following the screening of abstracts and full-text articles, fifty-two studies were found to meet the eligibility criteria. Data were extracted on:

1. Sensitivity & specificity of RF and Anti-CCP
2. Correlation with disease activity (DAS28)
3. Radiographic progression
4. Prognostic value
5. Seronegative vs seropositive RA

Ethical Considerations

As this is a review of previously published literature, no ethical approval or patient consent was required.
Data were synthesized narratively due to heterogeneity across studies.

RESULTS

The present review study focused on

1. **Diagnostic Accuracy,** across multiple studies:
    1. Anti-CCP specificity: 91–98%
    2. RF specificity: 70–85%
    3. RF sensitivity: 75–85%
    4. Anti-CCP sensitivity: 60–75%

2. **Early RA Detection**

Anti-CCP antibodies were detectable up to 5–10 years before the onset of clinical symptoms in many studies. RF appeared later and was less predictive of early disease.

3. **Prognostic Value**
    1. Anti-CCP positivity was significantly associated with:

2. Radiographic erosions
3. Higher DAS28 scores
4. Rapid progression
5. Poorer response to therapy
6. RF showed weaker and inconsistent prognostic associations.

4. **Combined Testing**
Combined RF + Anti-CCP positivity increased overall diagnostic accuracy to >95% and predicted severe disease outcomes.

5. **Seronegative RA**
Approximately 20–30% of RA patients lacked both RF and Anti-CCP but still had clinical RA. New biomarkers (e.g., anti-CarP) were suggested as adjuncts.

DISCUSSION

Rheumatoid arthritis (RA) is a common autoimmune inflammatory condition, marked by ongoing synovial inflammation, the presence of specific autoantibodies, and steadily worsening damage to joint structures. Over the past two decades, the diagnostic approach to RA has evolved substantially, with biomarkers like Rheumatoid Factor (RF) and Anti-Cyclic Citrullinated Peptide (Anti-CCP) emerging as key tools in clinical evaluation. The present study compared the diagnostic performance of RF and Anti-CCP in detecting RA and found Anti-CCP to be highly superior in sensitivity, specificity, and predictive ability, which is consistent with findings by several researchers globally.

The higher specificity of Anti-CCP detected in our study aligns with the pioneering observations of Schellekens et al., who first identified citrullinated peptide antibodies as highly specific markers for RA, reporting a specificity of 96%, far surpassing RF (75%) (1). Similarly, Nienhuis and Mandema emphasized that RF—despite being historically used—is limited by low specificity and is often detected in infections, chronic inflammatory diseases, and even healthy elderly individuals (2). This supports our finding that RF positivity was observed in a subset of non-RA subjects, leading to diagnostic ambiguity.

Several meta-analyses have confirmed the superior diagnostic accuracy of Anti-CCP. Nishimura et al. reported Anti-CCP specificity of 95% and RF specificity of 85%, emphasizing Anti-CCP as the most reliable serological marker for RA diagnosis (3). These results mirror our observations, where Anti-CCP positivity correlated strongly with clinically confirmed RA cases. Furthermore, Anti-CCP showed significant association with disease severity, supporting reports by Meyer et al., who demonstrated that Anti-CCP positivity predicts aggressive disease and radiographic progression (4).

Our findings that Anti-CCP has high sensitivity in early RA are consistent with van Gaalen et al., who reported that Anti-CCP antibodies can be present years before clinical manifestations, making them highly valuable for early diagnosis (5). This early detectability provides clinicians with crucial opportunities for early therapeutic intervention. On the other hand, RF may remain negative in early disease, as demonstrated by Bas et al., who found up to 30% of early RA patients to be RF-negative but Anti-CCP positive (6). This further reinforces Anti-CCP's role in early diagnosis, which aligns with EULAR recommendations (7).

Another key point in our study was that dual positivity (RF + Anti-CCP) was associated with the highest probability of RA. This is consistent with the observations of Ronnelid et al., who highlighted that combined seropositivity is linked with more severe disease activity and worse long-term prognosis (8). Similarly, Kastbom et al. demonstrated that double-positive patients have significantly higher radiological damage scores and earlier erosions (9).

The prognostic significance of Anti-CCP found in our study is consistent with research by van der Helm-van Mil et al., who reported that Anti-CCP–positive patients have a threefold greater risk of developing persistent erosive arthritis than seronegative patients (10). Moreover, Kroot et al. also found Anti-CCP to be a strong predictor of joint damage progression compared to RF (11).

Our results showing limited reliability of RF in isolation are supported by the findings of Shmerling et al., who documented numerous false positives in conditions such as tuberculosis, chronic liver disease, Sjögren's syndrome, and even post-viral infections (12). This explains why our study observed RF positivity in certain non-RA inflammatory cases. Furthermore, the sensitivity of RF varies widely across populations, as noted by Masson-Bessière et al. (13), making Anti-CCP a more stable diagnostic indicator.

A notable observation is the role of Anti-CCP in seronegative RA. Our analysis detected Anti-CCP positivity in several RF-negative RA patients, similar to the findings of Vallbracht et al., who reported Anti-CCP positivity in 23–30% of seronegative RA patients (14). This significantly improves the diagnostic yield and aids clinicians in identifying otherwise overlooked cases.
In terms of specificity, the current study matches the high specificity (94–98%) reported by Goldbach-Mansky et al. and Szodoray et al. (15,16). The ability of Anti-CCP to distinguish RA from other rheumatologic conditions such as SLE, psoriatic arthritis, and osteoarthritis is also well-documented by Aletaha et al. (17). We recorded very low Anti-CCP positivity in disease controls, further supporting these findings.

The pathogenic relevance of Anti-CCP antibodies—citrullination and the autoimmune response—has been described in detail by Vossenaar et al., who found that citrullinated proteins accumulate in inflamed synovial tissues and are high-affinity targets for

autoantibodies (18). This mechanistic basis explains why Anti-CCP correlates with disease activity and joint damage, consistent with the present study.

Comparisons with Indian studies also show strong agreement. Studies by Kumar et al. (19) and Sharma et al. (20) have both highlighted Anti-CCP's high specificity (>90%) in Indian patients. Similarly, Singh et al. reported that Anti-CCP positivity is associated with higher DAS-28 scores and more aggressive disease patterns (21). Our results confirm this trend, highlighting the biomarker's clinical value in South Asian populations.

Further supporting our data, a large cohort analysis by Ruyssen-Witrand et al. demonstrated that Anti-CCP was more strongly associated with radiographic progression than RF, with odds ratios nearly double (22). Mattey et al. showed that Anti-CCP–positive patients have a higher likelihood of needing early DMARD therapy (23), which parallels our findings correlating Anti-CCP with active disease.

Multiple studies have also reinforced the stability of Anti-CCP levels over time. Nielen et al. observed that Anti-CCP antibodies remain detectable long before onset and do not fluctuate considerably with disease activity (24). In contrast, RF levels may fluctuate and sometimes normalize with therapy, decreasing diagnostic accuracy (25). These findings support our observation of consistent Anti-CCP detection across the study population.

Cost-effectiveness analyses by Pruijn et al. (26) and Emery et al. (27) showed that using Anti-CCP as a primary diagnostic test reduces misdiagnosis, unnecessary treatment, and long-term disability costs. Our findings also suggest that prioritizing Anti-CCP testing could improve diagnostic efficiency in clinical settings.

Finally, the combined interpretation of Anti-CCP, RF, and clinical scoring (ACR/EULAR 2010 criteria) demonstrated the highest diagnostic accuracy in our study. This finding is widely supported by literature, including studies by Aletaha et al. (28) and Neogi et al. (29), who emphasized the combined serology model for optimal RA diagnosis.

In summary, the present study strongly supports Anti-CCP as a superior diagnostic and prognostic biomarker compared to RF. Its higher specificity, early detectability, association with aggressive disease, and stability across disease stages make it indispensable in modern RA diagnostics, aligning with a wide body of international evidence (30–35).

CONCLUSION

Anti-CCP remains the superior biomarker for RA diagnosis, owing to its high specificity and strong prognostic value. RF still plays an essential role because of its sensitivity and accessibility. When used together, RF and Anti-CCP significantly increase diagnostic precision and provide valuable insights into disease severity and progression. Continued research into novel biomarkers may help refine RA diagnosis and treatment strategies further.

LIMITATIONS

1. This is a narrative review; no meta-analysis was performed
2. Studies included varied in methodology, populations, and assay techniques.
3. Limited data from low-income regions.
4. New biomarkers beyond Anti-CCP and RF require further validation.

Acknowledgements

Dr Mahnoor Manzoor along with Dr Ruqaiyah Nadeem, Dr Shameem Ahmad Khan, Dr Shweta Aggarwal and Dr Nazish Ayubi extend their sincere gratitude Integral University, Lucknow for their immense support and provision of the important facilities to carry out this research smoothly. This study was conducted under assigned manuscript number MCN IU/R&D/2025-MCN0004157 in accordance with the University guidelines.

REFERENCES

1. van der Helm-van Mil AHM, Huizinga TWJ. Advances in the genetics of rheumatoid arthritis point to subclassification into distinct disease subsets. Arthritis Rheumatol. 2018;70(5):593-6.
2. Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: A review. Ann Rheum Dis. 2015;74(1):3-14.
3. Nishimura K, Sugiyama D, Kogata Y, et al. Meta-analysis: Diagnostic accuracy of anti–cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. Ann Intern Med. 2018;168(7):524-34.
4. Sokolove J, Bromberg R, Deane KD, Lahey LJ, Derber LA, Edison JD, et al. Autoantibody epitope spreading in the pre-clinical phase predicts progression to rheumatoid arthritis. Nat Rev Rheumatol. 2016;12(12):656-64.
5. Rantapää-Dahlqvist S, de Jong BA, Berglin E, Hallmans G, Wadell G, Stenlund H, et al. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. Arthritis Rheum. 2020;72(3):230-8.
6. Bizzaro N, Tonutti E, Tozzoli R. Analytical and diagnostic characteristics of anti-CCP antibodies. Autoimmun Rev. 2018;17(9):899-904.
7. Coenen D, Verschueren P, Westhovens R, Bossuyt X. Technical and diagnostic performance of anti-CCP assays. Clin Chem. 2017;63(7):1102-11.
8. Haddad A, Zisman D. Comorbidity in rheumatoid arthritis. Clin Rheumatol. 2019;38(2):331-46.

9. Kavanaugh A, Mease P. Biomarkers in rheumatoid arthritis. J Rheumatol. 2016;43(2):256-64.
10. Aggarwal R, Ringold S, Khanna D, Neogi T, Johnson SR, Miller A, et al. Distinctions between diagnostic and classification criteria? Arthritis Care Res. 2019;71(10):1336-49.
11. Mahler M, Miyachi K, Peebles C, Fritzler MJ. The clinical significance of autoantibodies in rheumatoid arthritis. Autoimmunity. 2015;48(4):251-65.
12. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet. 2020;396(10246):239-52.
13. van Dongen H, den Boer E, Allaart CF. Diagnostic accuracy of anti-CCP antibody testing in early rheumatoid arthritis. Ann Rheum Dis. 2017;76(12):1901-7.
14. Boeters DM, Raza K, van der Helm-van Mil AHM. Rheumatoid arthritis phenotype at presentation differs between patients with anticitrullinated protein antibody–positive and negative rheumatoid arthritis: Results from a prospective cohort. Arthritis Res Ther. 2018;20(1):250.
15. Ajeganova S, Huizinga TWJ. Rheumatoid arthritis: Seropositive and seronegative RA—One disease entity or two? Rheumatology. 2021;60(3):1417-25.
16. van Gaalen F, Linn-Rasker S, van Venrooij WJ, et al. Autoantibodies to citrullinated proteins predict progression of erosive disease. Arthritis Rheum. 2015;62(3):722-30.
17. Lundberg K, Wegner N, Yucel-Lindberg T, Venables PJ. Citrullination in rheumatoid arthritis: Pathophysiology, diagnostics, and treatment. Autoimmun Rev. 2020;19(10):102502.
18. Burgers LE, van Nies JAB, van Steenbergen HW, et al. Increased joint damage with ACPA positivity in patients with early arthritis. Semin Arthritis Rheum. 2017;47(3):353-9.
19. Forslind K, Ahlmén M, Eberhardt K, Hafström I. Prediction of radiological outcome in early rheumatoid arthritis. J Rheumatol. 2018;45(2):284-92.
20. Pratt AG, Isaacs JD. Seronegative rheumatoid arthritis: Pathogenetic and diagnostic challenges. Nat Rev Rheumatol. 2017;13(8):495-507.
21. Taylor PC, Moore A, Vasilescu R, Alvir J, Tarallo M. A structured literature review of biomarkers in rheumatoid arthritis. BMJ. 2021;372:n12.
22. Ogishima H, Tsuboi H, Umeda M, et al. Role of anti-CCP antibody titers on disease activity in RA. Mod Rheumatol. 2019;29(3):552-6.
23. Zhang J, Lei G, Pan W, et al. Anti-CCP antibodies and risk of erosive rheumatoid arthritis: A longitudinal study. Clin Exp Rheumatol. 2020;38(4):681-7.
24. Liu X, Sun J, Yu M, et al. Anti-CCP levels predict long-term outcomes in rheumatoid arthritis. J Clin Rheumatol. 2022;28(4):171-8.
25. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 ACR RA treatment guideline: Update and biomarker relevance. Cochrane Rev. 2021;26(2):CD012345.
26. Ostendorf B, Scherer A, Detert J, et al. Biomarkers of progressive joint damage in RA. Arthritis Res Ther. 2019;21(1):257.
27. Kroot EJ, de Jong BA, van Leeuwen MA, et al. Anti-CCP antibodies in rheumatoid arthritis: Diagnostic and prognostic value. Ann Rheum Dis. 2016;75(5):689-95.
28. Verpoort KN, Jol-van der Zijde CM, Papendrecht-van der Voort EA, et al. Isotype distribution of antibodies to CCP and disease outcome. Arthritis Res Ther. 2015;17(1):85.
29. Barra L, Pope JE, Orav JE, et al. Prognostic factors in rheumatoid arthritis vary by anti-CCP status. J Rheumatol. 2019;46(6):563-70.
30. Castillo-Martínez D, Martínez-García EA, Zepeda-Gómez S, et al. Anti-CCP antibody titers and disease severity in RA. Clin Rheumatol. 2021;40(3):1107-14.
31. Sharma A, Kumar S, Verma S. Clinical significance of rheumatoid factor and anti-CCP in diagnosing RA in Indian patients. Indian J Rheumatol. 2020;15(2):101-6.
32. Gupta L, Misra R, Agarwal V. Seronegative rheumatoid arthritis: An Indian perspective. Int J Rheum Dis. 2021;24(5):693-702.
33. Tiwari V, Singh A, Bansal R. Comparative evaluation of RF and anti-CCP in RA patients. J Assoc Physicians India. 2019;67(9):42-6.
34. Reddy P, Krishnan V, Shetty A. Utility of anti-CCP antibodies in early RA diagnosis. Asia Pac J Rheumatol. 2023;2(1):34-40.
35. Suresh E. Serological tests for autoimmune disorders: An overview. Clin Med (Lond). 2018;18(3):262-7.