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RESEARCH ARTICLE
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DIAGNOSTIC UTILITY OF ANTI-CCP, RHEUMATOID FACTOR, AND CRP IN RHEUMATOID ARTHRITIS: A PROSPECTIVE STUDY AT GEMS SRIKAKULAM, ANDHRA PRADESH.

Arundhati N.[1*], Sravanthi M.[2], Sangeeta P[3] Samatha P[4]

[1*]Assistant Professor, Department of Microbiology, Mobile no 9923497701, Great Eastern Medical School Ragolu, Srikakulam Andhra Pradesh, India, email id: arundhatinimale@gmail.com
[2]Sravanthi Mude Assistant Professor, Department of Microbiology, Mobile no :7075559888, Great Eastern Medical School Ragolu, Srikakulam Andhra Pradesh, India,
email id: dr.sravanthimude@gmail.com
[3]Samatha P Professor and Head of Department of Microbiology, Mobile no: 9440913543, Great Eastern Medical School Ragolu, Srikakulam Andhra Pradesh, India,
email id :samathamicrobiology@gmail.com
[4]Sangeeta Panighary Assistant Professor Department of Microbiology, Mobile no: 9440129457, Great Eastern Medical School Ragolu, Srikakulam Andhra Pradesh, India,
email id: sangeeta1987july@gmail.com

[*]**Corresponding Author:** Arundhati N
[*]Assistant Professor Microbiology email id: arundhatinimale@gmail.com Mobile no 9923497701, Great Eastern Medical School, Aditya Education society, Ragolu (Village) Srikakulam District, Andhra Pradesh, Pin code -532484

Abstract
Rheumatoid arthritis, a chronic autoimmune disease-causing joint inflammation and disability, lacks reliable standalone diagnostics. This study assesses anti-CCP antibody's performance against RF and CRP in suspected RA patients at a tertiary care hospital in Andhra Pradesh.
Aim & Objective: To determine the utility of Anti CCP antibody in comparison with RF and CRP for diagnosis of clinically suspected patients with Rheumatoid arthritis
Methods:
A prospective analysis was conducted on 200 blood samples from patients attending Medicine and Orthopaedics OPDs over one year (Dec 2022–Nov 2023). RF was tested using latex agglutination, anti-CCP via ELISA, and CRP through standard protocols.
Results:
Majority of patients were aged 40–60 years (59%) and female (62%). Positivity rates: RF 42%, Anti-CCP Ab- 67%, CRP 57%. Notably, anti-CCP positivity was observed in 74 seronegative RA cases. Triple marker positivity (RF, anti-CCP, CRP) was seen in 26.5% of cases. Diagnostic metrics showed:
- RF vs anti-CCP: Sensitivity 59.70%, Specificity 81.70%, PPV 85.60%, NPV 52.70%
- Anti-CCP vs CRP: Sensitivity 83.80%, Specificity 54.40%, PPV 64.30%, NPV 77.50%
- CRP vs RF: Sensitivity 74.4%, Specificity 70.9%, PPV 67.70%, NPV 77.20%

Conclusion: Anti-CCP testing is highly sensitive and correlates with inflammation, aiding early RA diagnosis. When combined with RF and CRP, it improves diagnostic accuracy and timely care.

Keywords: Rheumatoid arthritis, Rheumatoid Factor, Anti CCP Antibody, C-Reactive protein

Take home message: Anti-CCP testing improves early RA detection, especially in seronegative cases. Combined biomarker analysis strengthens diagnostic confidence.

Conflict of Interest: None declared

Introduction

RA is the most common inflammatory joint disease, affecting 1-2% of world population, with female to male ratio of 2.5:1. The exact aetiology of RA remains a mystery, in spite of many years of intensive research. Besides environmental influences, like infectious agents, smoking and oral contraceptives, genetic factors are believed to play a pivotal role in pathogenesis of RA in approximately 60% of the patient population [1].

Appropriate intervention with effective treatment modalities alters the course of the disease, reduce functional impairment and can improve the quality of life. Thus, efficient biomarkers are needed for early diagnosis and to monitor the prognosis of the disease to determine better outcome [2] The criteria to define RA used internationally was defined by American College of Rheumatology (ACR) in 1987 [3]. New criteria for RA classification (or diagnosis) were introduced in 2010 [4]. Anti CCP was included in the ACR/EULAR (European League against Rheumatism) RA classification criteria in 2010. Rheumatoid factor (RF) is another serological test along with acute phase reactant tests like Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) which are included in RA classification criteria [4]. Rheumatoid factor (RF) is an antibody specific for the FC portion of human immunoglobulin (IgG) which is considered as a marker for RA. It is one of the diagnostic criteria for RA established by the American College of Rheumatology (ACR) [5]. It is present in 75% of RA patients, but this antibody can also be detected in other autoimmune diseases, infectious diseases, in 3-5% of healthy population which increases to 10-30% in elderly illustrating that these antibodies are not very specific for RA [6]. Anti CCP antibodies represent a novel group of auto antibodies, currently under study, which has the highest specificity for diagnosis of RA [7]. The anti CCP antibodies are produced locally in inflamed synovium of RA patients [8, 9] and can be Detected very early in the course of RA and can therefore be helpful in early diagnosis and in limiting irreversible joint damage. But its sensitivity is low and thus a negative test result does not exclude the disease. These antibodies are not detected in other diseases unlike RF and hence are more specific than RF in RA diagnosis and its confirmation [10,11]. Although C-reactive protein (CRP) and Erythrocyte sedimentation rate (ESR) correlate with degree of joint inflammation and development of erosions, they are indicators of inflammation in general that may be influenced by other stimuli as an acute phase response.

Aim: To assess the diagnostic utility of Anti-CCP, RF, and CRP, individually and in combination, in the diagnosis of rheumatoid arthritis among patients presenting with joint symptoms at the GEMS Hospital, Srikakulam, Andhra Pradesh.

Objective:

- ❖ Evaluate sensitivity, specificity, PPV, and NPV of Anti-CCP, RF, and CRP in RA patients
- ❖ Identify correlations between these biomarkers and clinical characteristics.
- ❖ Develop improved diagnostic protocols for early RA detection

Materials and Methods:

Setting: The study was conducted in the Department of Microbiology, Great Eastern Medical School, Srikakulam, Andhra Pradesh.

Type of study: Prospective study based on 200 patients with clinically suspected rheumatoid arthritis attending Medicine and Orthopaedics OPDs between December 2022 and November 2023.

Inclusion criteria:

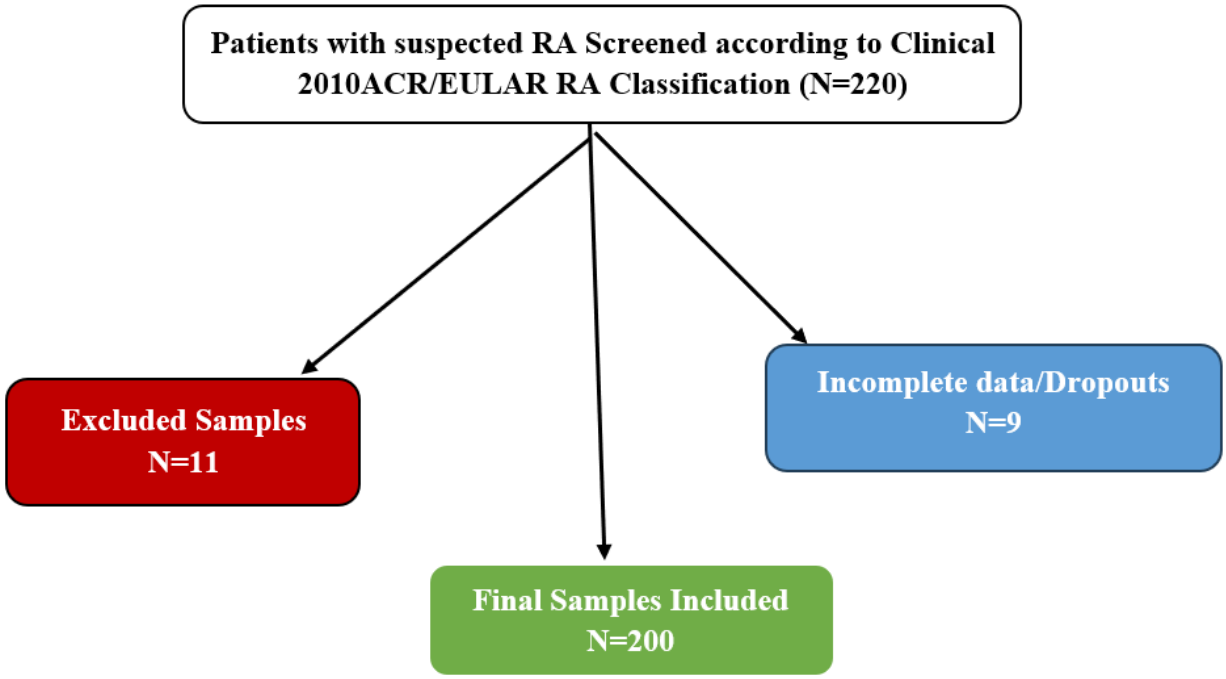
1. Patients aged 20–65 years presenting with joint pain, swelling, or stiffness involving at least one joint for ≥6 weeks.

2. **Rheumatoid arthritis suspected cases defined according to the 2010 ACR/EULAR classification criteria, Independent of biomarker status.**
3. Willingness to provide informed consent.

Exclusion criteria:

1. Patients with confirmed diagnoses of other autoimmune diseases (systemic lupus erythematosus, psoriatic arthritis, ankylosing spondylitis).
2. Patients with infectious arthritis, crystal-induced arthritis (e.g., gout, pseudogout), or osteoarthritis.
3. Patients with malignancy, chronic infections (e.g., tuberculosis, hepatitis), or other conditions known to elevate RF or CRP.
4. Pregnant and lactating women.
5. Patients unwilling or unable to provide informed consent.

Cohort flow: A total of 220 patients with suspected RA were screened. Of these, 11 were excluded (not meeting criteria), and 9 were lost to follow-up or had incomplete data, leaving 200 patients for final analysis.



Ethical clearance: 128/IEC/GEMS&H/2022 dated 9/11/2022.

Sample collection: Blood samples were collected from eligible patients and tested for RF, CRP, and Anti-CCP antibodies in the Department of Microbiology, Great Eastern Medical School & Hospital Srikakulam.

Laboratory methods:

- **Rheumatoid Factor (RF):** Measured by latex agglutination using the RHELAX-RF kit (Tulip Diagnostics). A qualitative assessment was performed, followed by semi-quantitative titration. Positivity was defined as ≥10 IU/mL.
- **Anti-CCP Antibodies**: Measured by ELISA (IMTEC Anti-CCP Antibodies, Germany). Cut-off values: <20 IU/mL (negative), ≥25 IU/mL (positive).
- **C-Reactive Protein (CRP):** Measured using Beacon Diagnostics latex agglutination kit, providing qualitative/semi-quantitative assessment. A threshold of ≥6 mg/L (≥0.6 mg/dL) defined positivity.

Intermediate values: Intermediate ("grey zone") results were defined as RF 10–19 IU/mL, Anti-CCP 20–24 IU/mL, and CRP borderline agglutination near 5–6 mg/L. These intermediate results were excluded from sensitivity, specificity, PPV, and NPV calculations to preserve diagnostic precision.

Blinding: All laboratory testing was performed in a blinded manner, with technicians unaware of the clinical status of the patients as well as Sample order to minimise bias.

Statistical Analysis: Data were entered into Microsoft Excel and analysed using SPSS version 25.0, Descriptive statistics were expressed as frequencies and percentages. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated using clinical diagnosis as the reference standard. Categorical variables were compared using the Chi-square test, and a P-value <0.05 was considered statistically significant.
Results: Out of the 200 clinically suspected RA patients analysed, the majority were aged 40–60 years (n = 119, 59%). Female patients (n = 124, 62%) outnumbered males (n = 76, 38%).

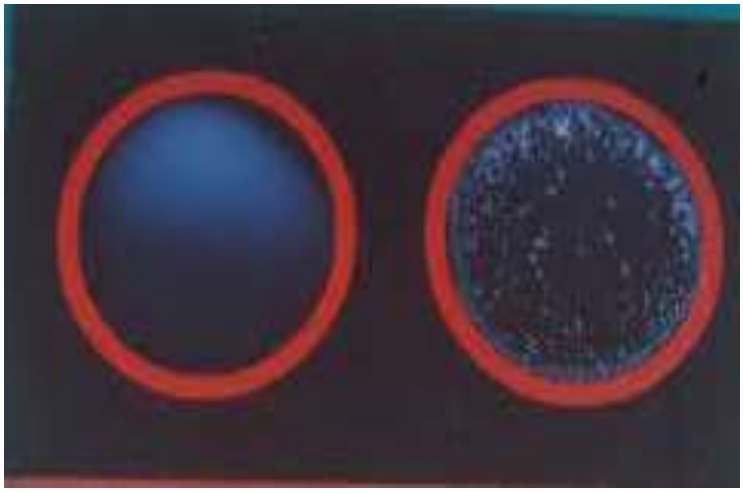
Test positivity:
- RF was positive in 83 patients (42%).
- Anti-CCP was positive in 134 patients (67%).
- CRP was positive in 113 patients (57%).

Serological patterns observed:
- RF-positive & Anti-CCP-positive: n = 60 (30%).
- RA-negative but Anti-CCP-positive: n = 74 (37%).
- RF-positive & Anti-CCP-negative: n = 23 (11.5%).
- Negative for both RF and Anti-CCP: n = 43 (21.5%).
- RF-positive & CRP-positive: n = 58 (29%).
- Anti-CCP-positive & CRP-positive: n = 108 (54%).
- Triple marker positivity (RF + Anti-CCP + CRP): n = 53 (26.5%).

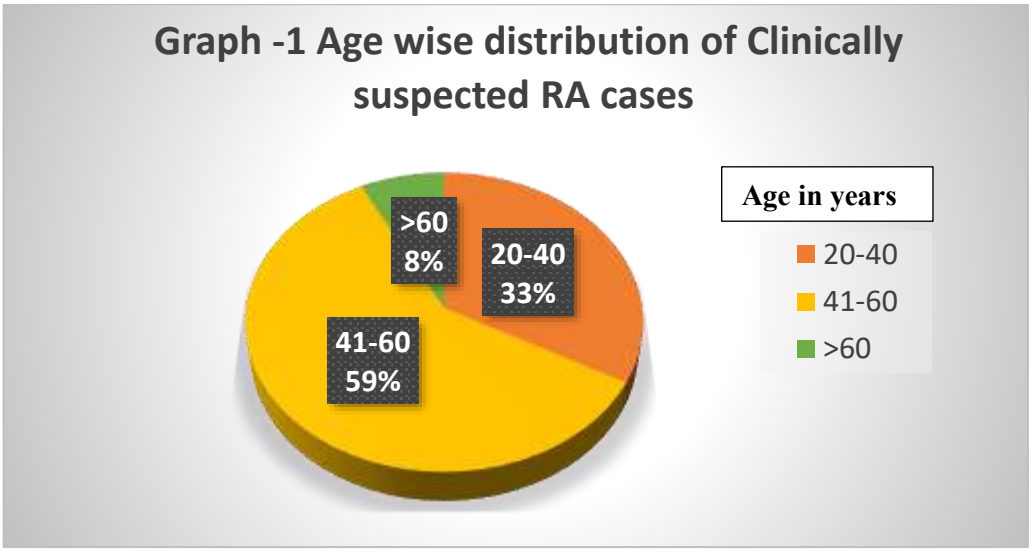
Statistical Analysis: Data were entered into Microsoft Excel and analysed using SPSS version 25.0 (IBM Corp., Armonk, NY). Descriptive statistics were expressed as frequencies and percentages. Diagnostic parameters, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), were calculated using the clinical diagnosis of rheumatoid arthritis (based on 2010 ACR/EULAR classification criteria) as the reference standard. Associations between categorical variables were assessed using the Chi-square test. A p-value of <0.05 was considered statistically significant.

RF Latex Agglutination test

Anti CCP Ab Elisa test



C- Reactive Protein test – Latex Agglutination test



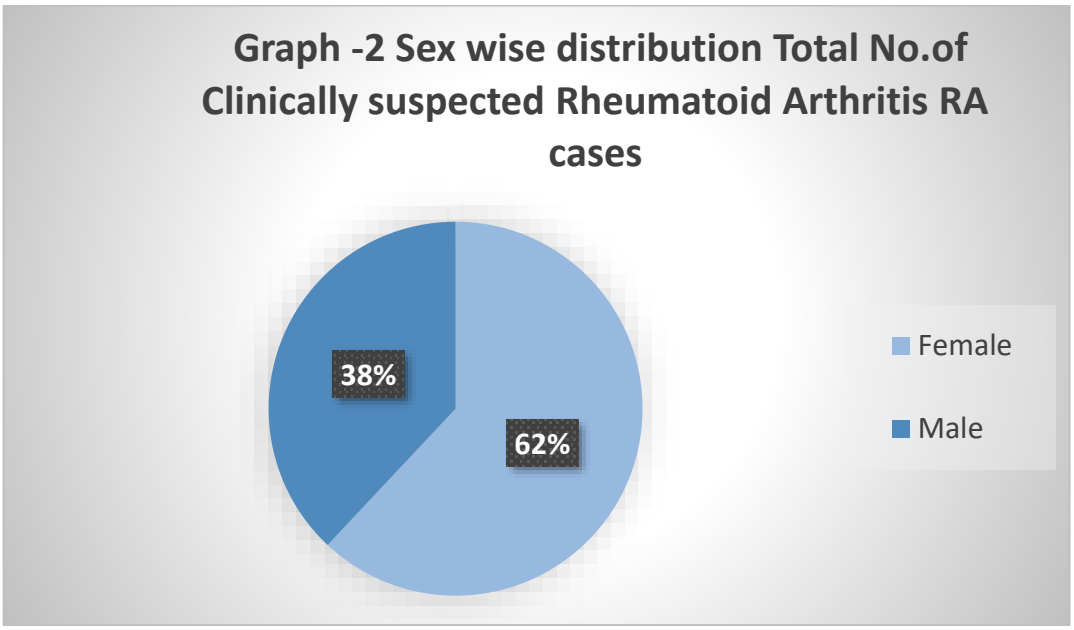


Table no 1. Total positivity of samples with respect to RF, Anti CCP Ab, CRP test

Results	Rheumatoid Factor test (RF)	ANTI CCP Ab test	C- Reactive Protein test
POSITIVE	83 (42%)	134 (67%)	113 (57%)
NEGATIVE	117(58%)	66 (33%)	87 (43%)

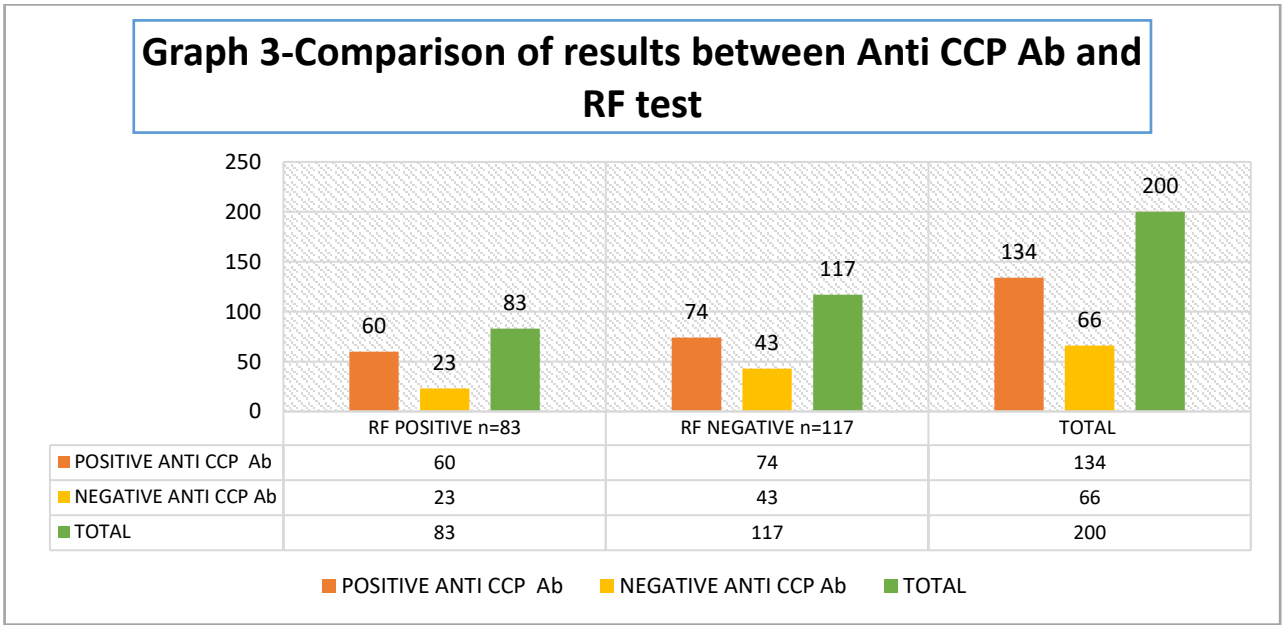


Table 2- Correlation of C-reactive Protein, Rheumatoid factor and Anti CCP Ab test.

C- reactive Protein	RF Positive	RF Negative	Anti CCP Positive	Anti CCP Negative
CRP Positive n=113	58	55	108	5
CRP Negative n= 87	25	62	26	61
Total n= 200	83	117	134	66

Table 3 – Comparative table for sensitivity, specificity, Positive predictive value and negative predictive value for all three tests RF, Anti CCP Ab and CRP test.

Test	Sensitivity	Specificity	Positive predictive value	Negative Predictive value
Rheumatoid factor test Vs Anti CCP Ab	59.68%	81.70	85.55%,	52.72%,
Anti CCP Ab test Vs CRP	83.80%	54.4%,	64.30%	77.50%,
C- Reactive Protein Vs RF test	74.40	70.90%	67.70%,	77.20%,

Discussion:

The present prospective study conducted at Great Eastern Medical School (GEMS), Srikakulam, Andhra Pradesh, evaluated the diagnostic utility of Anti-Cyclic Citrullinated Peptide (Anti-CCP) antibodies, Rheumatoid Factor (RF), and C-Reactive Protein (CRP) in 200 clinically suspected rheumatoid arthritis (RA) patients. The findings explain the individual and combined performance of these biomarkers, offering insights into their role in enhancing diagnostic accuracy in a tertiary care setting. This discussion associates the results within the existing literature, highlighting their clinical implications and limitations.

The study cohort predominantly comprised individuals aged 40–60 years (59%), with a smaller proportion aged 20–40 years (33%) and over 60 years (8%). This age distribution aligns with the established epidemiology of RA, which peaks in incidence during the fourth to sixth decades [12]. The observed female predominance (62% vs. 38% male) corroborates the well-documented female-to-male ratio of approximately 2.5:1, attributed to hormonal influences, genetic predispositions (e.g., HLA-DR4 alleles), and environmental factors such as smoking [13]. These demographic findings reinforce the representativeness of the study population relative to global RA epidemiology. Anti-CCP positivity (67%) was higher than RF (42%) and CRP (57%). Anti-CCP demonstrated the highest sensitivity (83.8% vs. CRP, 74.4% vs. RF), supporting its established role in early RA detection. [14]. consistent with its established role as a sensitive marker for RA, particularly in early disease stages Its inclusion in the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria underscores its diagnostic significance [15]. However, the specificity of Anti-CCP (54.4% vs. CRP) was lower than that of RF (81.70%), indicating a higher likelihood of false positives, particularly in populations with overlapping autoimmune conditions [16,17]. .RF demonstrated a sensitivity of 59.68% and a specificity of 81.70% when compared to Anti-CCP, aligning with prior studies reporting RF positivity in 60–80% of RA patients but also in 3–5% of healthy individuals, increasing to 10–30% in the elderly [18].The positive predictive value (PPV) of RF vs. Anti-CCP (85.55%) suggests that RF positivity, when corroborated by Anti-CCP, strongly supports an RA diagnosis. However, its negative predictive value (NPV) of 52.72% indicates that a negative RF result is unreliable for ruling out RA, particularly in seronegative cases [19]. CRP, an acute-phase reactant, showed a positivity rate of 57%, with a sensitivity of 74.40% and specificity of 70.90% vs. RF. The strong correlation between Anti-CCP and CRP (54% co-positivity) suggests a linkage between autoantibody production and systemic inflammation, a hallmark of active RA [20]. The high NPV of Anti-CCP vs. CRP (77.50%) indicates that negative results for both markers are highly effective in excluding RA, enhancing their utility in differential diagnosis [21]. The combined analysis of biomarkers revealed significant diagnostic synergy. Notably, 72.3% of samples positive for both RF and Anti-CCP were strongly associated with RA, reflecting the complementary nature of these tests [22]. Anti-CCP positivity in seronegative RA (37% of cases) highlights its critical role in identifying patients who test negative for RF, a diagnostically challenging subset [23] Conversely, 11.5% of samples were RF-positive but Anti-CCP-negative, emphasizing the necessity of Anti-CCP testing to avoid misdiagnosis in these cases Samples negative for both RF and Anti-CCP (21.5%) likely represent non-RA cases or early RA not yet detectable by these markers, underscoring the importance of clinical correlation[24,25] and serial testing [26]Triple positivity for RF, Anti-CCP, and CRP, observed in 26.5% of samples, indicates a subgroup with highly active disease and significant inflammatory burden. This finding is clinically significant, as triple-positive patients are associated with more severe disease and poorer prognosis, necessitating aggressive therapeutic

intervention [27]. The correlation between Anti-CCP and CRP further supports their prognostic utility, as CRP reflects ongoing inflammation that may exacerbate joint damage in Anti-CCP-positive patients [28**]** The sensitivity, specificity, PPV, and NPV analyses provide a nuanced understanding of biomarker performance. Anti-CCP's high sensitivity (83.80%) and moderate specificity (54.4%) vs. CRP position it as a robust screening tool, particularly for early RA detection [29] the high PPV of RF vs. Anti-CCP (85.55%) suggests that RF positivity in the presence of Anti-CCP strongly supports an RA diagnosis, while the high NPV of Anti-CCP vs. CRP (77.50%) reinforces its role in excluding RA [30]. Overall, Anti-CCP proved to be the most sensitive biomarker, particularly valuable in seronegative RA, while RF provided higher specificity. CRP contributed by reflecting inflammatory activity. The complementary nature of these tests strengthens diagnostic accuracy when used together

Limitations: Our study did not include healthy or disease controls for independent specificity estimation. Additionally, only point diagnostic parameters (sensitivity, specificity, PPV, NPV) were calculated; extended analyses such as confidence intervals were not included.

Conclusion: Anti-CCP testing is highly sensitive and particularly useful in detecting seronegative RA. When combined with RF and CRP, it enhances diagnostic accuracy and clinical decision-making, facilitating timely intervention in RA management**.**

Contribution from authors: Arundhati Nimale: Data collection, Performing test, literature review, manuscript preparation, final approval. **Sravanthi Mude**: literature review, manuscript preparation, manuscript editing**, Samatha P:** manuscript editing, final approval **Sangeeta Panighary:** Data compiling, Performing test, literature review.

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