International Journal of Pathology and Biomarkers
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Review article

Rheumatoid Arthritis: Types, risk factors and Laboratory Biomarkers

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DOI: https://doi.org/10.71428/IJPB.2026.0101

Abstract

Background: Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disorder characterized by persistent synovial inflammation, progressive joint destruction, and extra-articular manifestations. Laboratory biomarkers play a pivotal role in confirming diagnosis, stratifying disease severity, predicting prognosis, and monitoring therapeutic response. **Objectives:** This review summarizes the diagnostic, prognostic, and monitoring value of established and emerging laboratory biomarkers in RA, highlighting their clinical utility and limitations. **Methods:** Electronic databases, including PubMed, Scopus, and Web of Science, were systematically searched for studies evaluating biomarkers in RA. Biomarkers were categorized into serological (RF, anti-CCP, anti-MCV, anti-CarP), inflammatory (ESR, CRP, calprotectin), and emerging molecular markers (14-3-3η, MMP-3, cytokine panels, and lipid/metabolic profiles). Data on sensitivity, specificity, predictive value, and clinical correlations were extracted. **Results:** Rheumatoid arthritis (RA) types are Seropositive RA, Seronegative RA, Early RA, and Established RA. RA risk factors are Genetic Factors, such as the HLA-DRB1 gene, Environmental and Lifestyle Factors, including (1) Cigarette smoking, (2) Infections, (3) Dietary factors, (4) Hormonal influences, and (5) Obesity/Metabolic syndrome.

Laboratory Biomarkers: Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies remain the most reliable diagnostic markers, with anti-CCP offering superior specificity (~95–98%). Acute-phase reactants such as ESR and CRP correlate with disease activity and therapeutic response but lack diagnostic specificity. Novel biomarkers, including 14-3-3η protein, anti-CarP antibodies, and MMP-3, demonstrate potential for early detection and prognostication, especially in seronegative patients. Multi-biomarker panels integrating serological and molecular data enhance diagnostic accuracy.

Keywords: anti-CCP, rheumatoid factor RF, 14-3-3η, anti-CarP, C-reactive protein, MMP-3.

1. Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease that primarily targets the synovial joints, leading to progressive cartilage destruction, bone erosion, and loss of function (1,2). Affecting approximately 0.5–1% of the global population, RA predominantly occurs in women and typically presents between the ages of 30 and 60 years (3). Beyond articular damage, RA is associated with substantial morbidity and mortality due to systemic complications, including cardiovascular, pulmonary, and metabolic disorders (4).

The pathogenesis of RA is multifactorial, involving complex interactions between genetic susceptibility

Received: September 20, 2025. Accepted: December 1, 2025. Published: January 4, 2026

and environmental triggers. The HLA-DRB1 shared epitope alleles represent the most significant genetic determinant, conferring increased risk, particularly in anti-citrullinated protein antibody (ACPA)-positive RA (5,6). Environmental risk factors such as cigarette smoking, periodontal infection with *Porphyromonas gingivalis*, and obesity have been shown to amplify disease risk, partly through mechanisms that enhance protein citrullination and immune activation (7,8).

Laboratory biomarkers are essential in the diagnosis and management of RA. Historically, the rheumatoid factor (RF) was the first serological hallmark identified, but its limited specificity prompted the discovery of more precise markers such as anti-cyclic citrullinated peptide (anti-CCP) antibodies (9). Anti-CCP demonstrates high specificity (~95%) and can be detected years before clinical onset, making it invaluable for early diagnosis and prediction of erosive disease (10). Acute-phase reactants such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are routinely used to assess inflammation and disease activity (1,11).

In recent years, emerging biomarkers such as 14-3-3η protein, anti-carbamylated protein (anti-CarP) antibodies, matrix metalloproteinase-3 (MMP-3), and calprotectin have demonstrated potential diagnostic and prognostic value, particularly among seronegative RA patients (12,13). Furthermore, the integration of cytokine profiling, metabolomics, and multi-biomarker disease activity (MBDA) panels offers promise for precision medicine approaches in RA (14).

Despite these advances, no single biomarker can fully capture the disease's heterogeneity. Approximately 20–30% of patients remain seronegative for both RF and anti-CCP, posing diagnostic challenges (10). Therefore, a comprehensive understanding of available and emerging biomarkers are critical for improving diagnostic accuracy, prognosis, and monitoring strategies.

This review aims to critically evaluate and synthesize the current evidence on laboratory biomarkers in rheumatoid arthritis, emphasizing their diagnostic, prognostic, and monitoring significance in clinical practice and research.

2. Types of Rheumatoid Arthritis

RA is primarily classified based on serological findings:

- **Seropositive RA** is defined by the presence of rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (anti-CCP) antibodies in the serum. Seropositive patients tend to experience a more severe disease course, faster radiographic progression, higher risk for extra-articular features, and generally respond better to conventional and biologic DMARDs. They account for 60–80% of all RA patients (15).
- **Seronegative RA** includes patients lacking RF and anti-CCP antibodies. This group, which constitutes about 20–40% of cases, may present a more heterogeneous clinical picture. Diagnosis may rely on alternative biomarkers such as antibodies against carbamylated or acetylated proteins, 14-3-3η protein, or anti-RA33. Both types may show similar levels of joint inflammation and damage (16).
- **Early RA** refers to disease duration less than 12 months, emphasizing the importance of early detection and treatment to prevent irreversible damage. Antibodies may be detectable months to years before clinical onset, suggesting a preclinical phase of RA (17).
- **Established RA** describes disease with a longer duration (greater than one year), usually with more pronounced joint deformities and radiographic changes (18).

3. Risk Factors for RA

3.1 Genetic Factors

RA exhibits a strong genetic component:

- The **HLA-DRB1 gene (shared epitope alleles)** is the greatest genetic risk, with certain alleles (DRB1*01, *04, *10) markedly increasing susceptibility and disease severity, especially in anti-CCP-positive RA (19).
- Other genetic loci, such as **PTPN22, PADI4, TNF, IL2RA, IL4, and IL4R**, further contribute small increments to disease risk. Recent sequencing and genome-wide association studies have identified more than 100 such loci (20).

3.2 Environmental and Lifestyle Factors

Key environmental factors include:

- **Cigarette smoking** is the strongest modifiable risk factor. Smoking doubles to triples RA risk; the effect is particularly pronounced in individuals carrying the HLA shared epitope alleles. Gene-environment interactions between these alleles and smoking dramatically raise the risk for seropositive, anti-CCP positive RA, with a clear dose-response relationship (21).
- **Infections** such as periodontal pathogens (especially *Porphyromonas gingivalis*) have been linked to RA. *P. gingivalis* expresses a unique enzyme (peptidylarginine deiminase) that can citrullinate host proteins, potentially triggering anti-CCP autoimmunity (22).
- **Dietary factors**: Diets high in processed food and omega-6 polyunsaturated fatty acids increase risk, while Mediterranean diets, omega-3 intake, and antioxidants may be protective (23).
- **Hormonal influences**: Female sex, oral contraceptive and hormone replacement therapy usage, pregnancy-induced remission, and increased flares post-partum all highlight a hormonal link (24).
- **Obesity/Metabolic syndrome**: Obesity and associated adipokines (TNF-α, IL-6, leptin) increase risk and worsen disease activity (23,25).

3.3 Gene-Environment Interaction

- The **interaction between HLA-DRB1 shared epitope** and smoking is not additive but multiplicative in increasing risk—highlighting the importance of considering both genetics and environment (26).

4. Laboratory Biomarkers:

Laboratory testing for RA relies on serological and inflammatory biomarkers to aid in diagnosis, stratification, and monitoring (26).

4a. Rheumatoid Factor (RF)

RF is an IgM autoantibody targeting IgG Fc regions. It is a classical marker, positive in 70–90% of established RA, though less sensitive in early disease and seronegative cases. Higher titers are associated with worse prognosis, more frequent extra-articular manifestations, and cardiovascular risk. RF is detected by Rose-Waaler hemagglutination (historical), latex agglutination, nephelometry, or ELISA. IgA and IgG isotypes, though less commonly measured, are linked to severe disease (26).

4b. Rose Waaler Test

An early gold-standard serological test for RF, now replaced by automated and ELISA methods due to labor-intensive procedures and observer variability (27).

4c. Anti-Cyclic Citrullinated Peptide (Anti-CCP) Antibodies

Anti-CCP antibodies are the most specific serum marker for RA (specificity ~95–98%, sensitivity ~70–80%). Their presence can precede symptoms and is highly predictive of erosive joint damage, rapid progression, and extra-articular complications (e.g., interstitial lung disease). Anti-CCP and RF combined increase diagnostic sensitivity (28).

4d. Erythrocyte Sedimentation Rate (ESR)

ESR is a non-specific marker of inflammation, rising in response to increased acute phase reactants such

as fibrinogen. It is moderately sensitive in active RA and incorporated into disease activity scores (DAS28). ESR can be elevated due to age, sex, anemia, or other conditions, limiting its specificity (29).

4e. Antinuclear Antibodies (ANA)

ANA, though positive in 20–50% of RA cases, is more indicative of overlap syndromes or other autoimmune conditions (esp. SLE). It is not included in the major RA diagnostic criteria (30).

4f. C-Reactive Protein (CRP)

CRP is a rapid acute-phase reactant produced in response to IL-6 and other cytokines. It is a sensitive marker for active inflammation, correlates with disease activity and flares, and is widely used in monitoring response to therapy. CRP is also a predictor of radiographic progression, cardiovascular risk, and poor outcome (11,25).

4g. Additional and Emerging Biomarkers

- **Anti-MCV**: Antibodies to mutated citrullinated vimentin, similar sensitivity and specificity to anti-CCP, useful in seronegative disease and correlated with radiographic progression (31).
- **14-3-3η protein**: Detectable in seronegative RA and early disease; correlates with disease activity and treatment response (32).
- **Anti-CarP**: Anti-carbamylated protein antibodies (and anti-acetylated protein antibodies) are present in many seronegative RA cases and provide diagnostic help (33).
- **MMP-3**: Matrix metalloproteinase-3 is produced in synovial tissue, reflects joint destruction, and is correlated with disease activity and prognosis, especially in males (34).
- **Calprotectin**: A neutrophil-derived protein that correlates with disease activity scores, though less specific than anti-CCP or RF (35).
- **Cytokine Panels and Lipidomics**: Panels measuring IL-6, TNF-α, and others, as well as newer metabolomic approaches, are of interest in research but not routine practice (36).

5. Integrated Diagnostic Strategies

The 2010 ACR/EULAR criteria combine joint involvement, serology (RF/anti-CCP), acute phase reactants, and symptom duration for clinical classification. A score of 6 or higher supports a definite RA diagnosis (37).
Combining multiple biomarkers (RF, anti-CCP, ESR, CRP, anti-MCV, 14-3-3η) increases diagnostic sensitivity and specificity. For seronegative cases, additional testing for anti-CarP, anti-AAPA, 14-3-3η, and advanced imaging may be necessary (38).

6. Prognostic and Monitoring Applications

High titers of RF and anti-CCP, elevated CRP and ESR, and increased MMP-3 levels are predictive of severe, erosive disease and rapid radiographic progression. Disease activity is monitored using composite scores (e.g., DAS28-ESR, DAS28-CRP, SDAI), with serial measurement of ESR/CRP alongside clinical examination (39).

7. Limitations and Future Directions

No current biomarker fully differentiates all RA patients. About 20% remain seronegative and difficult to classify. Variability in assay sensitivity and specificity, as well as genetic and population heterogeneity, complicate the diagnostic process (40). Ongoing research into multi-biomarker panels, next-generation sequencing, lipidomics, non-coding RNA, liquid biopsies, and machine learning approaches aims to improve diagnostic and prognostic capabilities (41).

8. Clinical Recommendations

Initial laboratory assessment should include RF, anti-CCP, ESR, and CRP. Adjunct testing (anti-MCV, 14-3-3η, anti-CarP, MMP-3) can be useful in cases of high clinical suspicion or seronegative RA.

ANA may be considered if overlap syndromes or SLE are possible. Treatment should be guided by biomarker results, clinical presentation, and disease activity scores (42).

Conclusions:

While RF and anti-CCP remain central to RA diagnosis, emerging biomarkers such as 14-3-3η, anti-CarP, and MMP-3 provide additional value in disease stratification and early recognition. Future research should focus on validating multi-biomarker algorithms and incorporating molecular signatures and machine learning for personalized RA management.

Conflict of interest: NIL

Funding: NIL

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