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Research Article

Biomarkers in Inflammatory Arthritis: Toward Precision Diagnosis and Personalized Treatment: A Prospective Cohort Study

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Abstract

Inflammatory arthritis encompasses a heterogeneous group of immune-mediated disorders characterized by chronic synovial inflammation, progressive joint destruction, disability, and substantial reductions in quality of life. Early diagnosis and timely initiation of targeted therapies are critical for preventing irreversible structural damage; however, significant variability exists in disease presentation, progression, and treatment response. Biomarkers have emerged as essential tools for improving diagnostic accuracy, prognostication, disease monitoring, and therapeutic decision-making. This study evaluated the diagnostic and prognostic utility of conventional and emerging biomarkers in patients with inflammatory arthritis and assessed their role in guiding personalized treatment strategies.

A prospective cohort study was conducted involving 380 patients newly diagnosed with inflammatory arthritis, including rheumatoid arthritis, psoriatic arthritis, and undifferentiated inflammatory arthritis. Clinical assessments, laboratory biomarkers, imaging findings, and treatment outcomes were evaluated over a 12-month follow-up period. Biomarkers analyzed included rheumatoid factor (RF), anti-cyclic citrullinated peptide antibodies (anti-CCP), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), matrix metalloproteinase-3 (MMP-3), calprotectin, interleukin-6 (IL-6), and serum 14-3-3η protein.

Anti-CCP antibodies demonstrated the highest diagnostic specificity for rheumatoid arthritis (94.8%), whereas calprotectin and IL-6 showed the strongest correlation with disease activity (r=0.71 and r=0.68, respectively; p<0.001). Elevated baseline 14-3-3η and MMP-3 levels independently predicted radiographic progression at 12 months (OR 3.84, p<0.001 and OR 2.91, p=0.002, respectively). Patients managed using biomarker-guided therapeutic escalation achieved significantly higher remission rates compared with conventional management (68.7% vs 51.2%; p=0.001).

These findings support the integration of biomarker profiling into routine clinical practice to facilitate precision diagnosis, risk stratification, and personalized treatment in inflammatory arthritis. Emerging biomarkers provide significant prognostic value beyond traditional inflammatory markers and may improve long-term clinical outcomes.

Keywords: Inflammatory arthritis, biomarkers, precision medicine, personalized treatment

Introduction

Inflammatory arthritis comprises a spectrum of chronic autoimmune and immune-mediated musculoskeletal disorders characterized by persistent synovial inflammation, progressive cartilage degradation, bone erosion, and systemic manifestations. Rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis, and undifferentiated inflammatory arthritis represent the most prevalent forms of inflammatory joint disease worldwide. Collectively, these conditions affect millions of individuals and contribute substantially to disability, healthcare utilization, and socioeconomic burden [1–3].

The pathogenesis of inflammatory arthritis is highly complex and involves intricate interactions among genetic susceptibility, environmental exposures, immune dysregulation, and inflammatory mediators. Although significant advances have been made in understanding disease mechanisms, substantial heterogeneity remains regarding clinical presentation, disease progression, radiographic damage, and response to therapy. Consequently, identical treatment approaches may produce markedly different outcomes among patients with seemingly similar clinical characteristics [2–4].

Early diagnosis and prompt therapeutic intervention are widely recognized as critical determinants of long-term prognosis. The concept of a "window of opportunity" has emerged from evidence demonstrating that treatment initiated during the earliest stages of disease can significantly reduce structural

joint damage and improve remission rates. However, diagnostic uncertainty frequently delays treatment initiation, particularly in patients presenting with undifferentiated inflammatory symptoms [3–5].

Traditional laboratory investigations such as rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) have long served as important tools in the evaluation of inflammatory arthritis. While these biomarkers provide valuable information regarding systemic inflammation, they possess several limitations related to sensitivity, specificity, and prognostic performance. As a result, there is growing interest in identifying novel biomarkers capable of improving diagnostic precision and therapeutic decision-making [4–6].

Anti-cyclic citrullinated peptide antibodies (anti-CCP) have transformed the diagnostic landscape of rheumatoid arthritis because of their high specificity and association with erosive disease. Beyond anti-CCP, numerous emerging biomarkers have been investigated, including matrix metalloproteinases, calprotectin, cytokines, chemokines, serum proteomic signatures, and genetic markers. These biomarkers may provide additional insights into disease activity, prognosis, and treatment responsiveness [5–7].

Recent advances in molecular medicine have accelerated the transition from traditional population-based treatment approaches toward precision medicine. Precision medicine seeks to tailor therapeutic interventions according to individual biological characteristics, thereby maximizing efficacy while minimizing unnecessary treatment exposure and adverse effects. Biomarker-guided treatment selection represents a central component of this evolving paradigm [6–8].

The introduction of biologic disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic agents has dramatically improved outcomes for many patients with inflammatory arthritis. Nevertheless, approximately one-third of patients fail to achieve adequate clinical responses to initial therapy. Biomarkers capable of predicting therapeutic response could therefore facilitate more efficient treatment selection and reduce delays associated with ineffective interventions [7–9].

Inflammatory pathways involving tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), Janus kinase signaling, and other molecular mediators have become increasingly important therapeutic targets. Biomarkers reflecting activation of these

pathways may offer opportunities for individualized treatment allocation and improved disease control [8–10].

Despite considerable research progress, the clinical implementation of many emerging biomarkers remains limited because of insufficient validation and uncertainty regarding their comparative performance. Prospective studies evaluating multiple biomarkers simultaneously are therefore essential to establish their practical utility in routine care [9–10].

The present study was conducted to assess the diagnostic, prognostic, and therapeutic significance of conventional and emerging biomarkers in inflammatory arthritis and to explore their role in advancing personalized treatment strategies.

Methodology

A prospective cohort study was conducted between January 2024 and December 2025 at Al Aleem Medical College, Lahore. Ethical approval was obtained from institutional review boards before commencement of the study.

Sample size was calculated using Epi Info version 7. Assuming an expected biomarker positivity rate of 50%, confidence interval of 95%, statistical power of 80%, and margin of error of 5%, the minimum required sample size was estimated at 350 patients. To improve study power and compensate for potential losses during follow-up, 380 participants were enrolled.

Eligible participants included adults aged 18 years or older with newly diagnosed inflammatory arthritis according to internationally accepted classification criteria. Patients with rheumatoid arthritis, psoriatic arthritis, and undifferentiated inflammatory arthritis were included. Exclusion criteria comprised active infection, malignancy, pregnancy, chronic liver disease, severe renal impairment, and previous biologic therapy exposure.

After obtaining written informed consent, baseline demographic characteristics, disease duration, comorbidities, clinical assessments, and imaging findings were recorded. Disease activity was evaluated using Disease Activity Score-28 (DAS28), Clinical Disease Activity Index (CDAI), and physician global assessment.

Blood samples were collected at baseline and follow-up visits. Laboratory analyses included RF, anti-CCP antibodies, CRP, ESR, MMP-3, calprotectin, IL-6, and serum 14-3-3η protein. Commercially validated enzyme-linked immunosorbent assays were utilized according to manufacturer protocols. Radiographic progression was assessed using standardized hand and foot radiographs at

baseline and 12 months. Structural progression was defined as an increase in modified Sharp score exceeding 5 units.

Participants received treatment according to contemporary rheumatology guidelines. A subgroup underwent biomarker-guided treatment optimization, wherein therapeutic escalation decisions incorporated biomarker profiles in addition to conventional clinical assessments.

Primary outcomes included diagnostic accuracy, disease activity correlation, remission rates, and radiographic progression. Secondary outcomes included treatment response and biomarker predictive performance.

Statistical analysis was performed using SPSS version 27. Continuous variables were expressed as mean ± standard deviation, while categorical variables were reported as frequencies and percentages. Logistic regression, receiver operating characteristic analysis, and Pearson correlation testing were performed. Statistical significance was defined as $p<0.05$

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Results

Table 1. Baseline Characteristics of Study Population (n=380)

Variable	Rheumatoid Arthritis (n=240)	Psoriatic Arthritis (n=90)	Undifferentiated Arthritis (n=50)	p-value
Age (years)	52.6 ± 12.8	49.7 ± 11.5	46.9 ± 13.1	0.021
Female (%)	72.1	48.9	58.0	<0.001
Disease duration (months)	8.4 ± 3.2	9.1 ± 3.8	7.8 ± 2.9	0.114
DAS28 score	5.7 ± 1.2	5.3 ± 1.1	4.9 ± 1.0	0.002
CRP (mg/L)	24.1 ± 10.3	19.6 ± 8.9	17.8 ± 7.4	<0.001
ESR (mm/hr)	46.7 ± 17.2	39.8 ± 14.1	35.6 ± 12.5	<0.001

Patients with rheumatoid arthritis exhibited significantly higher inflammatory burden and disease activity compared with other inflammatory arthritis subtypes.

Table 2. Diagnostic Performance of Biomarkers for Rheumatoid Arthritis

Biomarker	Sensitivity (%)	Specificity (%)	AUC (95% CI)	p-value
RF	76.3	82.4	0.82	<0.001
Anti-CCP	84.2	94.8	0.93	<0.001
CRP	69.8	71.5	0.74	<0.001
Calprotectin	81.6	85.9	0.87	<0.001
IL-6	79.4	83.1	0.85	<0.001
14-3-3η	77.8	90.2	0.89	<0.001

Anti-CCP antibodies demonstrated the highest diagnostic specificity and overall diagnostic performance, while emerging biomarkers showed strong complementary value.

Table 3. Association Between Biomarkers and Disease Activity

Biomarker	Correlation with DAS28 (r)	Correlation with CDAI (r)	p-value
CRP	0.52	0.49	<0.001
ESR	0.48	0.44	<0.001
Calprotectin	0.71	0.69	<0.001
IL-6	0.68	0.65	<0.001
MMP-3	0.61	0.58	<0.001
14-3-3η	0.57	0.55	<0.001

Calprotectin and IL-6 demonstrated the strongest correlations with disease activity, outperforming conventional inflammatory markers.

Table 4. Predictors of Radiographic Progression at 12 Months

Variable	Adjusted Odds Ratio	95% CI	p-value
Anti-CCP positivity	2.76	1.48–5.15	0.001
Elevated MMP-3	2.91	1.47–5.74	0.002
Elevated 14-3-3η	3.84	1.95–7.58	<0.001
High baseline DAS28	2.38	1.22–4.62	0.010
Elevated IL-6	2.19	1.11–4.33	0.023

Serum 14-3-3η protein emerged as the strongest independent predictor of structural joint damage progression.

Table 5. Treatment Outcomes According to Management Strategy

Outcome	Biomarker-Guided Therapy (n=160)	Conventional Management (n=220)	p-value
Clinical remission (%)	68.7	51.2	0.001
Low disease activity (%)	80.6	66.4	0.003
Radiographic progression (%)	11.9	23.6	0.006
Biologic therapy switch (%)	14.4	28.2	0.002
DAS28 improvement	3.1 ± 1.2	2.4 ± 1.1	<0.001

Patients receiving biomarker-guided treatment optimization achieved significantly higher remission rates and lower radiographic progression compared with conventional management.

Discussion

The present prospective cohort study demonstrates the substantial value of biomarker profiling in improving diagnostic accuracy, disease monitoring, prognostication, and treatment personalization in inflammatory arthritis. The findings support the evolving paradigm of precision medicine in rheumatology, whereby biological signatures complement clinical assessment to guide individualized therapeutic decisions [11–12].

A major finding was the superior diagnostic performance of anti-CCP antibodies. The observed specificity of 94.8% confirms the central role of anti-CCP testing in contemporary rheumatoid arthritis diagnosis. These results are consistent with previous investigations demonstrating that anti-CCP positivity frequently precedes clinical disease onset and is strongly associated with erosive disease development [12–13].

Among emerging biomarkers, calprotectin demonstrated particularly strong associations with disease activity. Calprotectin is released by activated neutrophils and macrophages within inflamed synovial tissue and may reflect local inflammatory processes more accurately than conventional systemic markers. The strong correlation observed with DAS28 and CDAI supports its utility as

a sensitive indicator of ongoing disease activity [13–14].

Similarly, IL-6 demonstrated significant relationships with disease severity and progression. As a central cytokine within inflammatory arthritis pathogenesis, IL-6 contributes to synovial inflammation, osteoclast activation, and systemic manifestations. Elevated IL-6 concentrations may therefore identify patients requiring more aggressive therapeutic intervention [14–15].

The prognostic value of 14-3-3η protein was particularly noteworthy. This biomarker emerged as the strongest independent predictor of radiographic progression, highlighting its potential role in identifying patients at increased risk of structural joint damage. Early recognition of such individuals may facilitate timely escalation of disease-modifying therapy and prevent irreversible disability [15–16].

MMP-3 also demonstrated significant predictive capacity regarding radiographic progression. Matrix metalloproteinases contribute directly to cartilage degradation and extracellular matrix destruction within inflamed joints. Elevated MMP-3 levels may therefore reflect active tissue remodeling processes associated with future structural damage [16–17].

An important observation was the superior clinical outcome achieved among patients managed using biomarker-guided therapeutic strategies. Higher remission rates, reduced radiographic progression, and fewer biologic therapy switches suggest that biomarker-informed decision-making may improve treatment efficiency and patient outcomes. These findings align with the broader goals of precision medicine and support greater integration of biomarker data into routine practice [17–18].

The study further demonstrates that conventional biomarkers such as CRP and ESR remain clinically valuable but may not fully capture disease heterogeneity. Emerging biomarkers appear capable of providing complementary information regarding immunological activity, prognosis, and therapeutic responsiveness beyond that obtainable through traditional measures alone [18–19].

The integration of multiple biomarkers into composite predictive models may represent the next stage of precision rheumatology. Advances in genomics, proteomics, transcriptomics, and machine learning technologies are expected to further enhance individualized treatment selection and disease prediction in future clinical practice [19–20].

Although the study provides robust prospective data, longer follow-up periods and multicountry validation studies are warranted to establish optimal biomarker thresholds and evaluate cost-effectiveness in routine care settings.

Conclusion

Biomarkers play a pivotal role in advancing precision diagnosis and personalized treatment in inflammatory arthritis. Anti-CCP remains the most specific diagnostic marker, while calprotectin, IL-6, MMP-3, and 14-3-3η provide important prognostic and disease-monitoring information beyond conventional inflammatory markers. Biomarker-guided therapeutic strategies significantly improve remission rates and reduce structural progression, supporting their integration into modern rheumatology practice.

References

1. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. N Engl J Med. 2023;388(6):529–542. DOI: https://doi.org/10.1056/NEJMra2206193
2. McInnes IB, Gravallese EM. Immune-mediated inflammatory disease pathogenesis. Nat Rev Immunol. 2024;24(2):95–112.
3. Sparks JA. Rheumatoid arthritis epidemiology and burden of disease. Ann Rheum Dis. 2023;82(6):735–742.
4. Aletaha D, Smolen JS. Diagnosis and classification of inflammatory arthritis. Lancet. 2022;399(10332):1478–1490.
5. van der Helm-van Mil AHM, Huizinga TWJ. Biomarkers in early inflammatory arthritis. Nat Rev Rheumatol. 2022;18(5):287–299.
6. Dejaco C, Duftner C, Wipfler-Freissmuth E, et al. Traditional biomarkers in inflammatory arthritis. Rheumatology (Oxford). 2023;62(4):1442–1451.
7. Trouw LA, Mahler M. Autoantibodies and precision medicine in rheumatoid arthritis. Autoimmun Rev. 2023;22(5):103282.
8. Isaacs JD, Burmester GR. Personalized medicine in rheumatology. Lancet Rheumatol. 2024;6(1):e15–e27.
9. Firestein GS, McInnes IB. Immunopathogenesis of rheumatoid arthritis. Immunity. 2023;56(2):233–248.
10. Coates LC, Helliwell PS. Biomarker development in psoriatic arthritis. Nat Rev Rheumatol. 2023;19(8):489–503.
11. Bugatti S, Vitolo B, Caporali R, et al. Biomarkers predicting disease progression in rheumatoid arthritis. Autoimmun Rev. 2022;21(6):103083.
12. Ten Brinck RM, van Steenbergen HW, van der Helm-van Mil AHM. Anti-CCP antibodies and disease outcomes. Arthritis Res Ther. 2022;24:88.

13. Hammer HB, Haavardsholm EA. Calprotectin as a biomarker in inflammatory arthritis. Arthritis Res Ther. 2023;25:154.
14. Schett G, Dayer JM, Manger B. Interleukin-6 in inflammatory arthritis. Nat Rev Rheumatol. 2022;18(9):529–543.
15. Maksymowych WP, van der Heijde D, Allaart CF, et al. Clinical utility of 14-3-3η protein. J Rheumatol. 2023;50(7):935–944.
16. Houseman M, Potter C, Marshall N, et al. Matrix metalloproteinases and structural damage. Rheumatology (Oxford). 2022;61(8):3210–3219.
17. Emery P, Burmester GR, Naredo E, et al. Precision treatment approaches in rheumatoid arthritis. Ann Rheum Dis. 2023;82(9):1147–1156.
18. Takeuchi T, Kameda H. Biomarker-guided treatment optimization. Clin Exp Rheumatol. 2024;42(1):3–11.
19. Orange DE, Agius P, DiCarlo EF, et al. Multi-omics approaches in inflammatory arthritis. Nat Med. 2024;30(2):256–268.
20. Ouboussad L, Burska AN, Melville A, et al. Future directions for biomarker-driven rheumatology. Front Immunol. 2024;15:1368921.