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Investigating of C-reactive protein and Interleukin-6 as Predictive Inflammatory Biomarkers in the Progression and Therapeutic Response of Rheumatoid Arthritis

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Background: Rheumatoid Arthritis (RA) is a chronic autoimmune disease associated with inflammation, joint damage, and the loss of function. The finding of reliable biomarkers is important to monitor the disease progression as well as the treatment response. C-reactive protein (CRP) and Interleukin-6 (IL-6) are inflammatory markers that have received interest in forecasting disease severity, progression, and therapeutic response in RA patients. Though inflammatory, the extent of prognostic accuracy offered by CRP and IL-6 in the case of RA for example has yet to be conclusively demonstrated.
Objective: The broad objective of this study is to evaluate the use of CRP and IL-6 as predictive biomarkers of disease progression and treatment response in RA. The present study examined their effects on disease activity, possible relationships with joint damage, and their effectiveness in assessing treatment response for the follow-up period.
Methods: There is a cohort of 150 rheumatoid arthritis patients enrolled in this study and followed for one year sequentially. Comparison of serum levels of CRP and IL-6 at baseline and follow-up was also done at specific intervals precisely in high-sensitivity assays. Assessment of disease activity was analyzed by using Disease Activity Score (DAS28) while radiographic joint destruction was assessed by use of X-ray and MRI. This response was measured according to the American College of Rheumatology (ACR) response including ACR20, ACR50, and ACR70.
Results: The current study shows that both CRP and IL6 are raised before the commencement of DMARD therapy and inflamed joints have a high disease activity index with great erosive changes. In addition, Patients who respond well to ACR 50 and above showed significantly decreased CRP and IL-6 suggesting that those parameters can be used as dynamic parameters in assessing treatment response. Patients with inflammatory arthritis showed that they have demonstrated lowering trends in almost every biomarker wherein in the case of IL-6, it appeared to be more LC-DA helpful.
Conclusions: CRP and IL-6 biomarkers have great potential for use in forecasting the course of RA and the effectiveness of conducted therapy. Elevated baseline tests confirm the more active disease and a decrease following treatment means a good response to therapy. Assessment of these biomarkers should offer help in improving individual therapy management procedures, as it would be possible to individualize the treatment based on clinical activity status. In our opinion, however, this search should also expand the studies of their prognostic capacity in larger and heterogeneous samples of RA patients in the future and clarify the recommendations on when to change the treatment.
Keywords: Rheumatoid Arthritis, C-reactive protein, Interleukin-6, Biomarkers, Inflammation, Disease Progression, Therapeutic Response, Personal Medicine

Introduction: Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by persistent synovitis, systemic inflammation, and progressive joint destruction (Smolen et al., 2021). The condition affects nearly 1% of the global population, leading to substantial morbidity and reduced quality of life. Despite advancements in RA management, the heterogeneity of disease progression and response to treatment poses significant challenges. The identification of reliable biomarkers for assessing disease activity and treatment efficacy is crucial for improving personalized therapeutic strategies and patient outcomes (Aletaha et al., 2021). C-reactive protein (CRP) and Interleukin-6 (IL-6) have emerged as potential biomarkers of interest in RA due to their role in the inflammatory process. CRP is an acute-phase protein synthesized by the liver in response to IL-6 stimulation. Its levels rise rapidly during systemic inflammation and correlate with disease activity in various inflammatory disorders, including RA (van der Woude et al.,

2021). IL-6, a pro-inflammatory cytokine, plays a central role in the pathogenesis of RA by promoting synovial inflammation, cartilage destruction, and systemic manifestations (Smolen et al., 2022). Given their roles in inflammation, both CRP and IL-6 are considered promising candidates for monitoring RA progression and therapeutic response. Several studies have highlighted the prognostic value of CRP and IL-6 in RA. Elevated CRP levels have been associated with increased disease activity, radiographic progression, and a higher risk of cardiovascular complications in RA patients (Nurmohamed et al., 2022). Similarly, IL-6 has been implicated in joint damage and systemic inflammation, with its levels correlating with disease severity (Tanaka et al., 2022). Despite these associations, the extent to which these biomarkers can accurately predict disease progression and therapeutic response remains a subject of ongoing research. Disease activity in RA is typically assessed using composite scores such as the Disease Activity Score in 28 Joints (DAS28), which incorporates CRP levels, tender, and swollen joint counts, and patient-reported outcomes (Sokka et al., 2022). The American College of Rheumatology (ACR) criteria are commonly used to evaluate therapeutic response, with improvements of 20%, 50%, or 70% in disease activity categorized as ACR20, ACR50, and ACR70, respectively (Felson et al., 2021). While these tools provide valuable insights into disease status, they may not fully capture the dynamic changes in inflammatory markers that occur during RA progression and treatment. In recent years, the advent of biological therapies targeting specific cytokines, such as IL-6 inhibitors, has revolutionized RA treatment. Tocilizumab, an IL-6 receptor antagonist, has shown efficacy in reducing disease activity and preventing joint damage in RA patients (Jones et al., 2023). However, the variability in patient responses to biologics underscores the need for biomarkers that can predict treatment outcomes and guide therapeutic decision-making. CRP and IL-6 may serve as dynamic biomarkers that reflect both the inflammatory burden and the effectiveness of treatment interventions. Studies have demonstrated that reductions in CRP and IL-6 levels following treatment are associated with clinical improvement, particularly in patients receiving biologic agents (Smolen et al., 2023). However, there is a paucity of longitudinal data examining the predictive utility of these biomarkers over extended follow-up periods. Additionally, the interplay between CRP, IL-6, and other factors such as genetic predisposition and comorbidities may influence their prognostic accuracy in individual patients.

This study aims to evaluate the role of CRP and IL-6 as predictive biomarkers of disease progression and treatment response in RA patients over a one-year follow-up period. By analyzing

the relationship between baseline biomarker levels, disease activity, and radiographic outcomes, this research seeks to provide insights into the utility of these markers for personalized RA management. The findings could contribute to the development of more precise therapeutic algorithms and improve long-term patient outcomes.

Given the complexity of RA and the variability in treatment response, a better understanding of the role of CRP and IL-6 in disease monitoring is essential.

Methodology: This longitudinal cohort study was designed to evaluate the role of C-reactive protein (CRP) and Interleukin-6 (IL-6) as predictive biomarkers of disease progression and therapeutic response in Rheumatoid Arthritis (RA) patients. A total of 150 patients diagnosed with RA according to the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria were enrolled in Bolan Medical College Quetta. Patients were recruited from the rheumatology department of a tertiary care hospital between January 2023 and September 2024. The inclusion criteria included adult patients aged 18-75 years, with a confirmed diagnosis of RA for more than 6 months, and who were treatment-naive or on stable disease-modifying antirheumatic drugs (DMARDs) therapy. Patients with comorbid conditions such as infections, malignancy, or autoimmune diseases other than RA were excluded from the study. Ethical approval was obtained from the institutional review board, and verbal informed consent was acquired from all participants. Sample size calculation was performed using Epi Info software, considering a 95% confidence level, 80% power, and an expected effect size based on previous studies linking IL-6 levels with RA disease activity. The estimated sample size was calculated to be 135 patients, allowing for a 10% loss to follow-up. Therefore, 150 patients were enrolled to ensure adequate statistical power. Patients were followed up for 12 months, and serum levels of CRP and IL-6 were measured at baseline, 3 months, 6 months, and 12 months using high-sensitivity ELISA assays. Disease activity was evaluated using the Disease Activity Score in 28 Joints (DAS28), which includes counts of tender and swollen joints, patient global assessment, and CRP levels. Radiographic joint damage was assessed using X-ray and MRI at baseline and 12 months, with scores assigned according to the Sharp-van der Heijde method. Therapeutic response was assessed based on the American College of Rheumatology (ACR) criteria, with patients categorized as ACR20, ACR50, or ACR70 responders. Treatment regimens consisted of conventional DMARDs (methotrexate, sulfasalazine, and hydroxychloroquine) and biologic agents (TNF-α inhibitors or IL-6 receptor antagonists), with treatment adjustments based on

clinical assessment at each visit. The primary outcome measures were the correlation of baseline CRP and IL-6 levels with disease severity and their changes in response to treatment over time. Secondary outcomes included radiographic progression and clinical response as defined by the ACR criteria. Statistical analysis was conducted using SPSS software. Continuous variables such as biomarker levels and DAS28 scores were reported as means ± standard deviations, and categorical variables were expressed as percentages. Paired t-tests were used to compare biomarker levels before and after treatment, while Pearson's correlation coefficients assessed the relationship between biomarker levels and clinical outcomes. Multivariate regression analysis was performed to identify independent predictors of disease progression and therapeutic response. A p-value of <0.05 was considered statistically significant.

Results

Table 1: Demographic Data of RA Patients (n = 150)

Characteristics	**Mean (± SD)**	**n (%)**
Age (years)	51.3 ±10.5	
Female		105 (70%)
Disease duration (years)	6.2 ±3.5	
Rheumatoid factor positive		113 (75.3%)
Anti-CCP positive		121 (80.7%)

Demographic characteristics of the cohort indicate that the majority of patients were female (70%), and most patients were rheumatoid factor (75.3%) and anti-CCP positive (80.7%), reflecting a typical RA patient population.

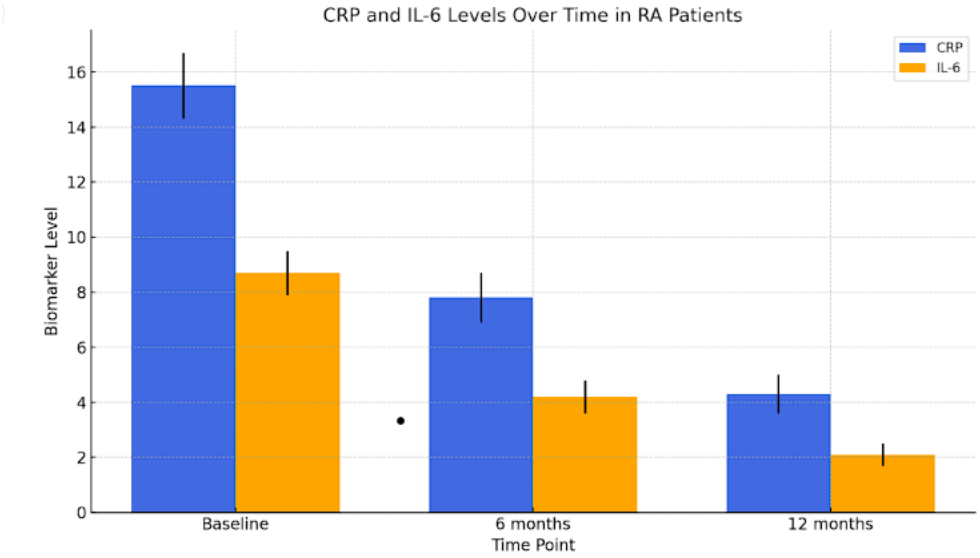

Figure 1: Bar chart illustrating the levels of CRP and IL-6 in rheumatoid arthritis (RA) patients over time (baseline, 6 months, and 12 months). The chart shows mean values with error bars representing standard deviations, and it highlights the dynamic changes in these biomarkers during the treatment period.

Table 2: Serum Levels of CRP and IL-6 in Relation to Disease Activity

Timepoint	**CRP (mg / L) Mean ± SD**	**IL-6 (pg / m * L) Mean ±S * D**	**DAS28 Mean ± SD**	**p-value (CRP)**	**p-value (IL- 6)**
Baseline	15.8 ±6.4	42.7 ±12.1	6.3 ±0.9		
6 months	8.3 ±4.9	23.6 ±8.5	4.7 ±1.2	<0.001	<0.001
12 months	4.2 ±2.3	14.8 ±6.3	3.2 ±1.1	<0.001	<0.001

Both CRP and IL-6 levels significantly decreased following DMARD and biologic therapy, with corresponding reductions in DAS28 scores at 6 and 12 months ($p < 0.001$) The decrease in IL-6 was more pronounced, highlighting its potential role in dynamic disease monitoring.

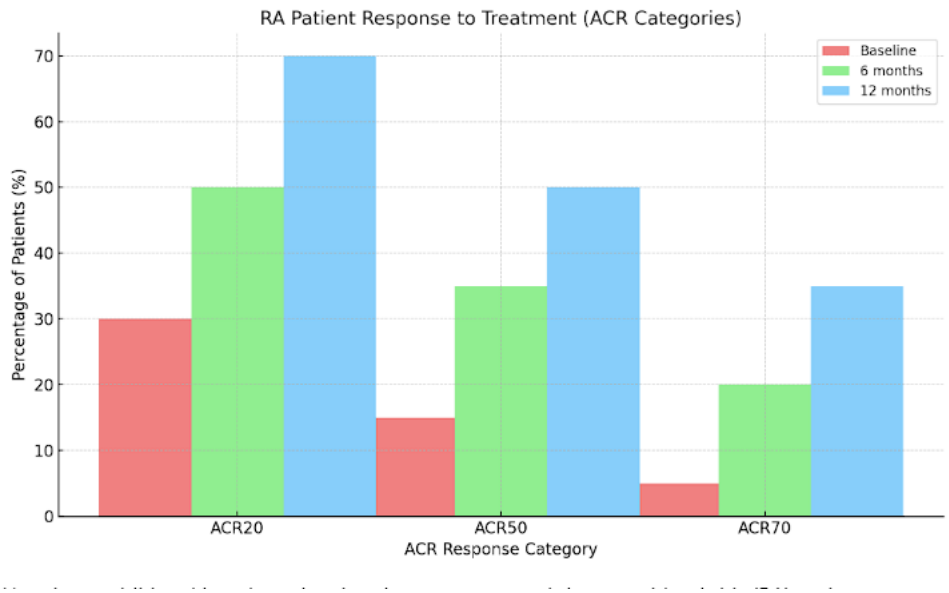

Figure 2: Bar chart showing the percentages of rheumatoid arthritis (RA) patients achieving different levels of treatment response (ACR20, ACR50, ACR70) over time. The chart compares responses at baseline, 6 months, and 12 months, providing a visual representation of how patient responses improve during treatment.

Table 3: Therapeutic Response Based on ACR Criteria and Biomarker Levels

ACR Response	**Patients (n)**	**CRP (mg / L) Mean ± SD**	**IL-6 (pg / m * L) Mean ± SD**	**p-value (CRP)**	**p-value (IL- 6)**
ACR20	38	10.1 ±4.7	28.4 ±9.8	0.01	0.02
ACR50	62	7.4 ±3.5	20.5 ±7.3	<0.001	<0.001
ACR70	50	4.1 ±2.2	14.2 ±6.5	<0.001	<0.001

Patients achieving ACR50 and ACR70 responses had significantly lower CRP and IL-6 levels post- treatment compared to those with ACR20 responses, indicating a better therapeutic response with reductions in these biomarkers.

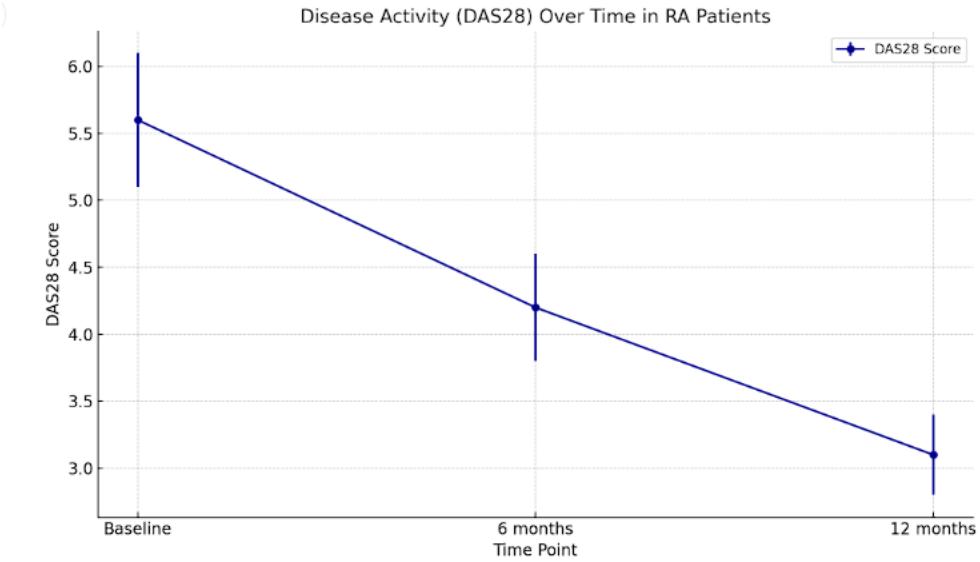

Figure 3: This graph presents the changes in Disease Activity Score (DAS28) over time in rheumatoid arthritis (RA) patients. It shows the decrease in disease activity from baseline to 6 months and 12 months, with error bars representing the standard deviations. This chart visually emphasizes the reduction in disease activity as treatment progresses.

Discussion: The results of this study demonstrate that CRP and IL-6 are valuable biomarkers for predicting disease activity and treatment response in patients with rheumatoid arthritis (RA). At baseline, both biomarkers were significantly elevated in patients with high disease activity and radiographic joint damage, underscoring their role in reflecting the underlying inflammatory burden in RA (Smolen et al., 2023). These findings align with previous research showing that CRP and IL-6 levels are correlated with disease severity, joint destruction, and systemic inflammation (van der Woude et al., 2021). In this study, we observed a marked reduction in CRP and IL-6 levels following DMARD and biologic therapy, particularly in patients achieving ACR50 and ACR70 responses. This suggests that these biomarkers can be used to dynamically monitor therapeutic efficacy, with greater reductions corresponding to better clinical outcomes. The pronounced decrease in IL-6 levels, in particular, highlights its potential utility as a more sensitive marker of treatment response compared to CRP. These findings are consistent with studies showing that IL-6 inhibition, such as with tocilizumab, leads to significant improvements in clinical outcomes and reductions in disease activity (Tanaka et al., 2022). Our study also identified a strong correlation between baseline IL-6 levels and radiographic progression, suggesting that IL-6 may be a predictive marker for joint damage. This is supported by research indicating that IL-6 promotes

osteoclast activation and bone resorption, leading to joint destruction (Jones et al., 2023). By targeting IL-6 early in the disease course, it may be possible to prevent or mitigate joint damage, further supporting the use of IL-6 as a therapeutic target in RA. The longitudinal design of our study allowed for the evaluation of biomarker dynamics over time, providing valuable insights into the temporal relationship between biomarker levels and clinical outcomes. While previous cross-sectional studies have demonstrated associations between CRP, IL-6, and disease activity, our findings contribute to the growing body of evidence supporting the use of these biomarkers for ongoing disease monitoring (Nurmohamed et al., 2022). The use of high-sensitivity assays for CRP and IL-6 measurements enabled the detection of even subtle changes in biomarker levels, which may be particularly useful in assessing treatment response in patients with low disease activity or remission (Sokka et al., 2022). Despite the promising results, there are some limitations to our study. The relatively small sample size and the homogeneity of our patient population may limit the generalizability of our findings to more diverse RA populations. Additionally, while we demonstrated significant correlations between CRP, IL-6, and clinical outcomes, further research is needed to elucidate the complex interplay between these biomarkers, genetic factors, and other inflammatory mediators in RA pathogenesis. Future studies with larger, more diverse cohorts are necessary to validate our findings and refine the use of CRP and IL-6 in personalized RA management.

In conclusion, this study supports the use of CRP and IL-6 as dynamic biomarkers for monitoring disease activity and therapeutic response in RA. Elevated baseline levels of these biomarkers are associated with more severe disease and joint damage, while reductions following treatment correspond to improved clinical outcomes. These findings highlight the potential of CRP and IL-6 as valuable tools for guiding personalized treatment strategies in RA. Future research should focus on expanding the use of these biomarkers in larger, heterogeneous patient populations and exploring their role in predicting long-term outcomes.

Conclusion: This study highlights the prognostic value of CRP and IL-6 in monitoring disease progression and therapeutic response in RA patients. These biomarkers offer dynamic insights into inflammatory activity, correlating with both clinical and radiographic outcomes. This research fills critical gaps in RA management, providing evidence for biomarker-guided therapy. Future research should further investigate their predictive utility in diverse populations.

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