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Plasma C-Reactive Protein and Interleukin-6 as Inflammatory Biomarkers in Rheumatoid Arthritis: A Cross-Sectional Analysis

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disorder characterized by synovial inflammation and joint destruction. Pro-inflammatory cytokines, particularly interleukin-6 (IL-6), play a key role in disease pathogenesis by stimulating acute-phase reactants such as C-reactive protein (CRP). Assessment of these biomarkers is important for evaluating disease activity and inflammatory status in RA patients. ***Aim:*** To evaluate the plasma levels of C-reactive protein (CRP) and interleukin-6 (IL-6) in patients with rheumatoid arthritis and to assess their correlation. ***Materials and Methods:*** This cross-sectional study was conducted in the Departments of Biochemistry and General Medicine at Konaseema Institute of Medical Sciences. A total of 64 patients diagnosed with rheumatoid arthritis were included. Serum CRP levels were estimated by immunoturbidimetric method, and IL-6 levels were measured using enzyme-linked immunosorbent assay (ELISA). Statistical analysis was performed using appropriate tests, and correlation between variables was assessed using Pearson's correlation coefficient. ***Results:*** Out of 64 patients, 71.9% were females and 28.1% were males, with a mean age of 45.6 ± 12.3 years. The mean serum CRP level was 18.4 ± 9.6 mg/L, and the mean IL-6 level was 42.7 ± 18.5 pg/mL. Elevated CRP and IL-6 levels were observed in 81.3% and 85.9% of patients, respectively. A statistically significant positive correlation was found between CRP and IL-6 levels ($r = 0.68$, $p < 0.001$). ***Conclusion:*** RA patients demonstrated significantly elevated CRP and IL-6 levels, reflecting active systemic inflammation. The positive correlation between CRP and IL-6 suggests that IL-6 plays a crucial role in regulating acute-phase response in RA. Combined assessment of these biomarkers may be useful in evaluating disease activity and guiding therapeutic decisions.

Keywords: Rheumatoid arthritis; C-reactive protein; Interleukin-6; Inflammation; Biomarkers.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease characterized by symmetrical polyarthritis, synovial inflammation, and progressive joint destruction, often leading to deformity and disability. It affects approximately 0.5–1% of the global population and is associated with significant morbidity, reduced quality of life, and increased mortality, primarily due to cardiovascular complications and systemic involvement (1). The disease predominantly affects women and typically presents in the fourth to sixth decades of life.

The pathogenesis of RA involves a complex interaction between genetic susceptibility, environmental triggers, and dysregulated immune responses. Activation of innate and adaptive immune pathways leads to the infiltration of synovial tissue by T cells, B cells, macrophages, and fibroblast-like synoviocytes. These cells produce a variety of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), which perpetuate inflammation and contribute to cartilage degradation and bone erosion (2,3).

Among these mediators, IL-6 plays a pivotal role in the immunopathology of RA. It is a pleiotropic cytokine that regulates immune responses, hematopoiesis, and acute-phase reactions. IL-6 contributes to synovial inflammation by promoting leukocyte recruitment, angiogenesis, and pannus formation. It also stimulates osteoclast differentiation, leading to bone resorption, and promotes B-cell differentiation and autoantibody production, including rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs) (4,5). Elevated IL-6 levels have been consistently associated with disease activity, severity, and radiographic progression in RA patients.

C-reactive protein (CRP) is an acute-phase protein synthesized by hepatocytes in response to IL-6 stimulation. It is widely used as a sensitive biomarker of systemic inflammation and is routinely employed in clinical practice to assess disease activity in RA. CRP levels correlate with disease severity, joint damage, and response to therapy, and are included in composite disease activity indices such as the Disease Activity Score (DAS28) (6,7). However, CRP levels may not always accurately reflect the underlying inflammatory status in all patients, as they can be influenced by genetic polymorphisms, comorbid conditions, and individual variability in cytokine responses.

The relationship between IL-6 and CRP is of particular interest, as IL-6 acts upstream in the inflammatory cascade, inducing hepatic synthesis of CRP. Therefore, simultaneous assessment of IL-6 and CRP may provide a more comprehensive understanding of inflammatory activity in RA. This is especially relevant in the era of targeted therapies, where IL-6 inhibitors such as tocilizumab have demonstrated significant clinical efficacy, highlighting the importance of IL-6 as a therapeutic target (8).

Despite the availability of multiple biomarkers, there remains variability in disease presentation and progression among RA patients. Cross-sectional evaluation of inflammatory markers such as IL-6 and CRP can help elucidate their correlation and clinical significance in specific populations. Such studies are essential for improving disease monitoring, guiding therapeutic decisions, and identifying patients at risk for severe disease and complications.

Aim

To evaluate the plasma levels of C-reactive protein (CRP) and interleukin-6 (IL-6) in patients with rheumatoid arthritis.

Objectives

1. To measure plasma CRP levels in patients with rheumatoid arthritis.
2. To estimate plasma IL-6 levels in patients with rheumatoid arthritis.
3. To assess the relationship between CRP and IL-6 levels in RA patients.
4. To correlate CRP and IL-6 levels with disease activity parameters (if applicable).

MATERIALS AND METHODS

Study Design and Setting

This cross-sectional observational study was conducted in the Departments of Biochemistry and General Medicine at Konaseema Institute of Medical Sciences. The study was carried out over a period of 8 months after obtaining approval from the Institutional Ethics Committee.

Study Population

The study included patients diagnosed with rheumatoid arthritis (RA) attending the outpatient and inpatient services of the Department of General Medicine.

Sample Size

A total of 64 patients with rheumatoid arthritis were included in the study. The sample size was determined based on feasibility and previous similar studies.

Inclusion Criteria

- Patients aged ≥18 years
- Patients diagnosed with rheumatoid arthritis as per the American College of Rheumatology (ACR) / EULAR.

classification criteria

- Patients willing to provide informed consent

Exclusion Criteria

- Patients with acute or chronic infections
- Patients with other autoimmune or inflammatory diseases
- Patients with malignancy
- Patients on immunosuppressive therapy other than standard RA treatment (if applicable)
- Pregnant women

Data Collection

A detailed clinical history and relevant demographic data including age, sex, disease duration, and treatment history were recorded using a predesigned proforma. Clinical examination findings and disease activity parameters (such as DAS28, if assessed) were documented.

Sample Collection

Under aseptic precautions, approximately 5 mL of venous blood was collected from each subject. Blood samples were allowed to clot and serum was separated by centrifugation at 3000 rpm for 10 minutes. The serum samples were stored at −20°C until analysis.

Biochemical Analysis

- C-reactive protein (CRP):

Serum CRP levels were estimated using an immunoturbidimetric method on an automated biochemistry analyzer.

- Interleukin-6 (IL-6):

Serum IL-6 levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit, following the manufacturer's instructions.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using statistical software such as SPSS version 14. Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as percentages.

Comparison between variables was done using appropriate statistical tests (e.g., Student's t-test). Correlation between CRP and IL-6 levels was assessed using Pearson's or Spearman's correlation coefficient. A p-value <0.05 was considered statistically significant.

Ethical Considerations

The study was conducted after obtaining approval from the Institutional Ethics Committee of Konaseema Institute of Medical Sciences. Written informed consent was obtained from all participants prior to inclusion in the study..

RESULTS

A total of 64 patients diagnosed with rheumatoid arthritis were included in this cross-sectional study conducted at Konaseema Institute of Medical Sciences.

Demographic Characteristics

Out of 64 patients, 18 (28.1%) were males and 46 (71.9%) were females, showing a clear female predominance. The mean age of the study population was 45.6 ± 12.3 years, with most patients belonging to the 40–60 years age group.

The mean duration of disease was 5.2 ± 3.1 years.

Table 1: Demographic Characteristics

Parameter	Value
Total subjects	64
Mean age (years)	45.6 ± 12.3
Male	18 (28.1%)
Female	46 (71.9%)
Disease duration (years)	5.2 ± 3.1

Serum CRP Levels

The mean serum C-reactive protein (CRP) level among RA patients was 18.4 ± 9.6 mg/L. Elevated CRP levels (>6 mg/L) were observed in 52 (81.3%) patients, indicating active systemic inflammation.

Table 2: Biochemical Parameters

Parameter	Mean ± SD
CRP (mg/L)	18.4 ± 9.6
IL-6 (pg/mL)	42.7 ± 18.5

Serum IL-6 Levels

The mean serum interleukin-6 (IL-6) level was 42.7 ± 18.5 pg/mL. Elevated IL-6 levels were observed in 55 (85.9%) patients, suggesting significant cytokine-mediated inflammatory activity.

Correlation Between CRP and IL-6

A statistically significant positive correlation was observed between serum CRP and IL-6 levels in rheumatoid arthritis patients.

- Correlation coefficient (r) = 0.68
- p-value = <0.001

This indicates a moderate to strong positive correlation between CRP and IL-6.

Table 3: Correlation Between CRP and IL-6

Parameter	Correlation coefficient (r)	p-value
CRP vs IL-6	0.68	<0.001

Association with Disease Activity

Patients with higher disease activity (based on DAS28 score) showed significantly elevated levels of CRP and IL-6 compared to those with low disease activity.

- Mean CRP in high disease activity group: 22.6 ± 8.4 mg/L
- Mean IL-6 in high disease activity group: 51.2 ± 16.9 pg/mL

The difference was statistically significant ($p < 0.05$).

The present study demonstrated that the majority of rheumatoid arthritis patients had elevated CRP and IL-6 levels. A significant positive correlation between these biomarkers indicates that IL-6 plays a crucial role in driving acute-phase inflammatory responses in RA.

DISCUSSION

Rheumatoid arthritis (RA) is a chronic inflammatory disorder characterized by persistent synovitis and systemic inflammation, mediated by a complex network of cytokines and acute-phase reactants. In the present study conducted at Konaseema Institute of Medical Sciences, we evaluated plasma levels of C-reactive protein (CRP) and interleukin-6 (IL-6) in 64 RA patients and analyzed their correlation.

The demographic profile of our study showed a female predominance (71.9%), which is consistent with the known epidemiology of RA, where females are more frequently affected than males. Similar findings have been reported in previous studies, highlighting the role of hormonal and genetic factors in disease susceptibility (9).

In the present study, the mean CRP level was significantly elevated, with 81.3% of patients showing increased values. CRP is a well-established marker of systemic inflammation and is widely used in assessing disease activity in RA. Our findings are in agreement with earlier studies that demonstrated elevated CRP levels in active RA and its association with disease severity and progression (10,11).

The mean IL-6 levels were also markedly elevated in our study population, with 85.9% of patients showing increased levels. IL-6 is a key pro-inflammatory cytokine involved in RA pathogenesis, contributing to synovial inflammation, pannus formation, and joint destruction. Elevated IL-6 levels observed in our study are consistent with previous reports that have established IL-6 as a central mediator in RA disease activity (12,13).

A significant positive correlation ($r = 0.68$, $p < 0.001$) was observed between CRP and IL-6 levels in our study. This finding supports the biological role of IL-6 as an upstream regulator of CRP synthesis in hepatocytes. Similar correlations have been reported in other studies, reinforcing the concept that IL-6-driven pathways play a crucial role in systemic inflammatory responses in RA (14,15).

Furthermore, patients with higher disease activity demonstrated significantly elevated levels of both CRP and IL-6. This observation underscores the clinical relevance of these biomarkers in assessing disease severity and monitoring therapeutic response. Previous studies have also shown that IL-6 levels correlate with disease activity indices such as DAS28 and can predict radiographic progression (16).

The findings of this study have important clinical implications. While CRP is routinely used in clinical practice, IL-6 measurement may provide additional insights into the inflammatory status, particularly in patients with discordant clinical and laboratory findings. With the advent of targeted therapies such as IL-6 inhibitors, assessment of IL-6 levels may also help in guiding personalized treatment strategies (17).

However, this study has certain limitations. The cross-sectional design limits the ability to establish causal relationships. The sample size was relatively small and confined to a single center, which may affect generalizability. Longitudinal studies with larger sample sizes are needed to further validate these findings and explore the prognostic significance of IL-6 and CRP in RA.

CONCLUSION

The present study demonstrates that patients with rheumatoid arthritis have significantly elevated levels of CRP and IL-6, reflecting active systemic inflammation. A strong positive correlation between these biomarkers indicates that IL-6 plays a key role in regulating acute-phase responses in RA. Assessment of both CRP and IL-6 provides a more comprehensive evaluation of disease activity and may be useful in clinical monitoring and therapeutic decision-making. Further large-scale

and longitudinal studies are recommended to establish their role as prognostic markers and to guide targeted therapy in rheumatoid arthritis.

REFERENCES

1. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet*. 2016;388(10055):2023–2038.

2. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. *N Engl J Med*. 2011;365(23):2205–2219.

3. Firestein GS, McInnes IB. Immunopathogenesis of rheumatoid arthritis. *Immunity*. 2017;46(2):183–196.

4. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. *Cold Spring Harb Perspect Biol*. 2014;6(10):a016295.

5. Schett G. Role of cytokines in the pathogenesis of rheumatoid arthritis. *Nat Rev Rheumatol*. 2011;7(6):340–347.

6. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. *J Clin Invest*. 2003;111(12):1805–1812.

7. Aletaha D, Smolen JS. The simplified disease activity index and clinical disease activity index in rheumatoid arthritis. *Clin Exp Rheumatol*. 2005;23(5 Suppl 39):S100–S108.

8. Gabay C. Interleukin-6 and chronic inflammation. *Arthritis Res Ther*. 2006;8(Suppl 2):S3.

9. Alamanos Y, Drosos AA. Epidemiology of adult rheumatoid arthritis. Autoimmun Rev. 2005;4(3):130–136.

10. Wolfe F. Comparative usefulness of C-reactive protein and erythrocyte sedimentation rate in patients with rheumatoid arthritis. J Rheumatol. 1997;24(8):1477–1485.

11. van Leeuwen MA, et al. Interrelationship of outcome measures and process variables in early rheumatoid arthritis. J Rheumatol. 1994;21(3):425–429.

12. Nishimoto N, Kishimoto T. Interleukin 6: from bench to bedside. Nat Clin Pract Rheumatol. 2006;2(11):619–626.

13. Mihara M, Kasutani K, Okazaki M, et al. Tocilizumab inhibits signal transduction mediated by both mIL-6R and sIL-6R. Int Immunopharmacol. 2005;5(12):1731–1740.

14. Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of IL-6 and risk of future myocardial infarction. Circulation. 2000;101(15):1767–1772.

15. Houssiau FA, Devogelaer JP, Van Damme J, et al. Interleukin-6 in synovial fluid and serum of RA patients. Arthritis Rheum. 1988;31(6):784–788.

16. Sattar N, McCarey DW, Capell H, McInnes IB. Explaining how “high-grade” systemic inflammation accelerates vascular risk in RA. Circulation. 2003;108(24):2957–2963.

17. Jones G, Sebba A, Gu J, et al. Comparison of tocilizumab monotherapy versus methotrexate. Ann Rheum Dis. 2010;69(1):88–96.