

Interleukin-6 Levels in Iraqi Patients with Rheumatoid Arthritis: A Case-Control Study

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ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic, systemic autoimmune inflammatory disease, (IL-6) makes a contribution to both local and systemic inflammation. **Aims:** to examine serum IL-6 concentrations between Iraqi patients with RA and control samples. To study associations with specific clinical variables. **Material And Method:** the study involved 76 participants, 36 diagnosed as RA patients and 40 as a control. CRP, IL-6, demographic and clinical variables were recorded. Statistical analysis was accomplished using independent-sample t-test, chi-square test and Spearman correlation. **Result:** Mean IL-6 was 14.13 ± 12.50 pg/mL in the RA group and 17.30 ± 14.28 pg/mL in controls; the difference was not statistically significant ($P=0.306$). Mean CRP was 7.10 ± 7.37 mg/L in RA patients and 8.94 ± 8.54 mg/L in controls ($P=0.317$). Within RA patients, IL-6 was very strongly correlated with CRP (Spearman $\rho=0.998$, $P<0.001$), whereas its correlation with disease duration was not significant ($\rho=0.117$, $P=0.497$). **Conclusions:** In this dataset, serum IL-6 was not significantly different between the provisionally defined RA and control groups, although IL-6 closely tracked CRP among RA records. The findings should be interpreted in light of the provisional group coding and the absence of DAS28 data.

Keywords: Rheumatoid Arthritis, ELISA, Inflammation, Interleukins-6, CRP.

Article Information

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease characterized by insistent synovial inflammation, progressive joint destruction, and mutable extra-articular association. While the joints are the main location of disease, RA is gradually diagnosed as a systemic inflammatory disorder in which interactions among innate and adaptive immune cells, synovial fibroblasts, macrophages, lymphocytes, inflammatory cytokines and autoantibodies contribute to the initiation and progression of disease. Persistent inflammatory activity may result in joint stiffness, pain, structural damage, functional impairment, and systemic complications, thus causative substantially to long-term disease. [1-3]

The pathogenesis of RA includes intricate linkage of inflammatory intermediaries, among which tumor necrosis factor-alpha (TNF- α) and interleukin-6 (IL-6) have prominent roles. IL-6 is a pleiotropic cytokine involved in both local and systemic inflammatory reactions, including activation of acute-phase protein production, regulation of lymphocyte function, hematopoiesis, and modulation of synovial inflammation. Dysregulated IL-6 signalling occurs through standard and trans-signalling pathways and contributes to the persistent inflammatory environment characteristic of RA. [2,4,5] Current studies has further strengthened the biological and clinical significance of the IL-6 pathway, with IL-6 receptor inhibition

representing an established targeted therapeutic strategy in RA [5,6].

Further than its effects on the musculoskeletal system, persistent systemic inflammation in RA is related with an increased burden of cardiovascular disease (CVD). Cardiovascular risk in RA cannot be attributed solely to conventional risk factors such as hypertension, dyslipidemia, diabetes mellitus, obesity, and smoking. Instead, chronic immune activation and inflammatory signaling act together with these traditional factors to stimulate endothelial dysfunction, oxidative stress, vascular inflammation, and accelerated atherosclerosis. [7,8].

Specifically, inflammatory pathways involving IL-6 and TNF- α have been involved in the mutual biological mechanism linking RA and atherosclerotic cardiovascular disease.[7,9] IL-6 may therefore represent an important biological link between persistent inflammation and systemic manifestations of RA. Elevated IL-6 activity has been associated with inflammatory burden and extra-articular manifestations, while circulating IL-6 also has been interrelated to cardiovascular outcomes in broader populations. [4,7,10] Consequently, characterization of serum IL-6 in patients with RA may provide additional insight into the inflammatory profile of the disease and its potential relationship with established inflammatory markers like CRP marker.

Despite advances in the understanding and treatment of RA, clinically relevant variation in inflammatory activity persists among patients. Epidemiological evidence also indicates a substantial and increasing global burden of RA, emphasizing the importance of identifying accessible biomarkers that may improve characterization of disease activity and systemic inflammation. [3,11]

The present study therefore assessed serum IL-6 levels in Iraqi participants with RA and controls and examined their relationship with CRP and disease duration. The study aimed for further characterization to the inflammatory profile of RA in an Iraqi population and to discover the potential relationship between IL-6 and selected clinical features of the disease, this accomplished by incorporating CRP and IL-6 measurements with medication-related information and demographic variation.

METHODS

Study Strategy And Groups

The case-control study were carried out at Marjan Medical City In Hilla-Babylon, Iraq, in the interim December 2025 to April 2026. The aggregate 76 participant were classified and registered into two main groups according to standard clinical criteria. The first group includes individuals diagnosed with RA and another group participant without RA to serve as a control group. The rheumatoid arthritis group established based on participant clinical and laboratorial result and the applicable classification criteria. Relevant demographic and clinical data, including age, sex, disease duration, comorbidities, smoking status, and medication history, were collected for each participant.

Experiment measurements

The samples (5ml from venous blood) were collected from each participant under aseptic environment. The serum separated by centrifugation at (3000 rpm, 10 minutes) and stored at -8°C for further analysis.

IL-6 Measurement: All samples were measured by a Quantitative Sandwich ELISA kit (Elabscience Biotechnology Co, Ltd, Wuhan, P.C.R.) to measure IL-6. The parameter was measured according to the instructions of the manufacturing company.

Measurement of CRP: the principle of CRP detection in serum (Humatex CRP Kit) based on immunoreactivity between the human CRP present in the serum and the equivalent antibodies to human C-reactive protein bounded to latex particles. The positive reaction point to a clear aggregation of latex particles in the tested cell on slide. The Humatex CRP test has a detection limit of 6mg/L of C-reactive protein in patient serum. The result considered positive if the serum CRP concentration is more than 6mg/L and considered positive when its be less than 6mg/L.

Statistical analysis

IBM Co., Chicago, ILs SPSS Software, 26.0 version was used to execute statistical study. Differences between the two provisional groups were assessed using independent-samples t

tests. Categorical variables were assessed using chi-square tests. Spearman correlation was used to evaluate relationships between IL-6 and CRP and between IL-6 and disease duration within the RA group. A P value <0.05 was considered statistically significant.

Ethical approval

The study was conducted in accordance with the ethical guidelines found in the Helsinki Declaration. The participants verbal and analytical consent was obtained prior to sample collection. In addition the consent and information from an ethics committee at the Al-Furat Al-Awsat Technical University, Al-

Musaib Polytechnic collage, Iraq, assessed and approved the study permission.

RESULTS

Participant characteristics

The dataset contained 36 provisionally classified RA patients and 40 controls. The RA group included 23 females (63.9%) and 13 males (36.1%), while controls included 15 females (37.5%) and 25 males (62.5%). The mean age was 56.03 ± 10.79 years in RA patients and 50.10 ± 17.10 years in controls ($P=0.072$). Sex distribution differed significantly between groups ($P=0.039$).

Table 1. Demographic and inflammatory characteristics of the two provisional study groups.

Parameters	RA (n=36)	Controls (n=40)	P value
Age, years	56.03 ± 10.79	50.10 ± 17.10	0.072
Female, n (%)	23 (63.9%)	15 (37.5%)	0.039
Male, n (%)	13 (36.1%)	25 (62.5%)	
IL-6, pg/mL	14.13 ± 12.50	17.30 ± 14.28	0.306
CRP, mg/L	7.10 ± 7.37	8.94 ± 8.54	0.317

Serum IL-6 concentrations

Serum IL-6 ranged from 2.1 to 47.9 pg/mL in RA patients and from 2.0 to 49.5 pg/mL in controls. The mean concentration was 14.13 ± 12.50 pg/mL in RA patients compared with 17.30 ± 14.28 pg/mL in controls. The between-group difference was not statistically significant ($P=0.306$).

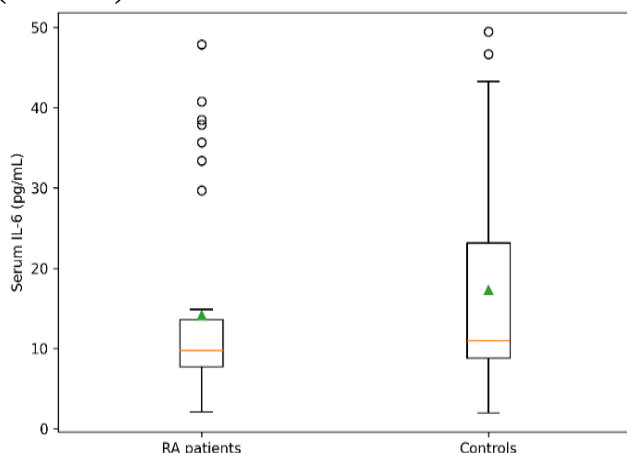


Figure 1. Distribution of serum IL-6 concentrations in RA patients and controls.

Relationship between IL-6 and CRP

Within the RA group, serum IL-6 showed a very strong positive correlation with CRP (Spearman $\rho=0.998$, $P<0.001$). IL-6 was not significantly correlated with disease duration ($\rho=0.117$, $P=0.497$).

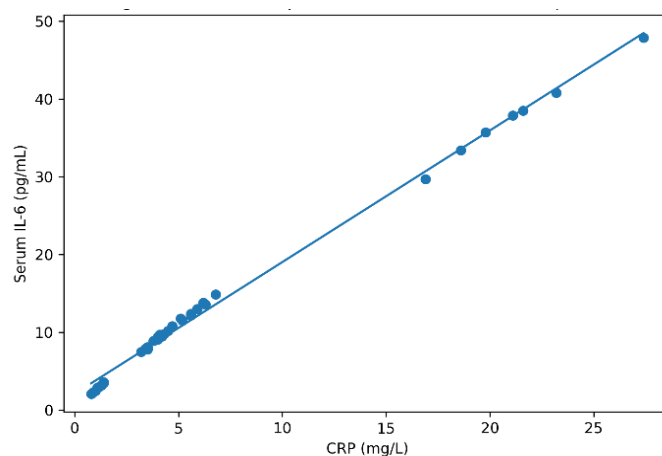


Figure 2. Correlation between serum IL-6 and CRP among RA patients.

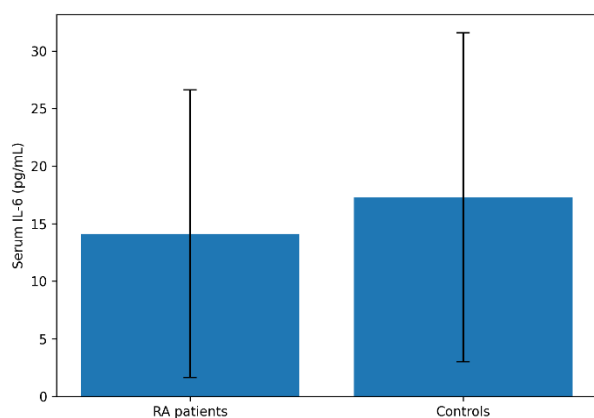


Figure 3. Mean $\pm$ SD serum IL-6 Concentration in the two provisional groups.

CRP qualitative status

CRP was positive in 10/36 (27.8%) RA patients and 13/40 (32.5%) controls. The difference was not statistically significant (χ^2 $P=0.844$).

RA medication profile

Among the 36 provisionally classified RA patients, methotrexate was the most commonly used medication (91.7%), followed by glucocorticoids (58.3%), hydroxychloroquine (41.7%), biologic DMARDs (22.2%), and sulfasalazine (19.4%). Percentages were not mutually exclusive because some patients used multiple medications.

Table 2. Recorded RA medication use among the 36 provisionally classified RA patients.

Medication	N	%
Methotrexate	33	91.7
Hydroxychloroquine	15	41.7
Sulfasalazine	7	19.4
Biologic DMARDs	8	22.2
Glucocorticoids	21	58.3

DISCUSSION

The present dataset did not reveal a statistically significant difference in serum IL-6 levels between the provisionally classified rheumatoid arthritis (RA) and control groups ($P=0.306$). This result is inconsistent with a body of research describing interleukin-6 (IL-6) as a key inflammatory mediator in rheumatoid arthritis. IL-6 is a pleiotropic cytokine involved

in regulating innate and adaptive immune reactions, hepatic acute-phase protein production, lymphocyte differentiation, and inflammatory processes within the synovial membrane; furthermore, persistent dysregulation of IL-6 signaling pathways has been linked to both localized joint inflammation and the systemic manifestations of rheumatoid arthritis. [12,15,16]

The deficiency of a statistically significant difference in serum IL-6 in the current study should not essentially be interpreted as evidence against the association of IL-6 in RA pathogenesis. Relatively, circulating cytokine concentrations may vary noticeably according to disease activity, progression stage, duration of disease, treatment status, comorbidities, timing of blood collection, and characteristics of the study population. Additionally, the biological activity of IL-6 is not determined exclusively by its circulating concentration, because IL-6 can act through typical signaling and trans-signaling pathways at both local and systemic levels, [12,16,19]. Hence, a single serum measurement may not fully represent the inflammatory activity occurring within the rheumatoid synovium.

A number of methodological and clinical reasons may clarify why a significant between-group difference was not detected in this dataset. First, participant classification required reconstruction because the source table obviously documented RA status in only part of the records, whereas disease duration was available for another subset. Consequently, the RA/control classification used for the current analysis should be considered provisional. Misclassification of participants may reduce the ability to detect true biological differences between groups and could contribute to the absence of statistical significance.

Secondly, exposure to treatment undoubtedly affects blood concentrations of interleukin-6. Medication data showed that the majority of patients with established rheumatoid arthritis had been exposed to methotrexate, while smaller proportions received hydroxychloroquine, sulfasalazine, biologic disease-modifying drugs, or glucocorticoids. Disease-modifying drugs and glucocorticoids aim to suppress inflammatory activity and modify the underlying disease course;

consequently, the reduction in inflammatory signaling resulting from treatment may have diminished the differences in interleukin-6 levels between treated rheumatoid arthritis patients and the control group [13, 14, 19]. The relative diversity of treatment regimens leads to additional heterogeneity in cytokine concentrations within the rheumatoid arthritis patient group.

The absence of a standardized assessment of disease activity is another factor contributing to the variation in results. Due in part to the short sample size, the DAS28 score was not accessible in the dataset supplied, making it difficult to categorize participants according to clinically defined disease activity. Because interleukin-6 concentrations may indicate the degree of systemic inflammatory activity rather than just the existence of a rheumatoid arthritis diagnosis, this limitation is especially important. Even when both groups satisfy the clinical criteria and definition for rheumatoid arthritis, patients with clinically managed or low-activity illness may have significantly different inflammatory features from those with active disease. [12, 14, 19]

The current investigation showed a very strong positive connection between serum IL-6 and CRP among the provisionally categorized RA subjects ($\rho=0.998$, $P<0.001$), even though there was no significant between-group difference. Because IL-6 is a major regulator of the hepatic acute-phase response and stimulates the production of acute-phase proteins, including CRP [12,17], this finding is biologically plausible. Therefore, the observed association suggests that variation in circulating IL-6 may parallel systemic inflammatory activity within the RA records examined in this study.

The connection between CRP and IL-6 is also in line with IL-6's wider biological function in RA. Systemic acute-phase responses, immune-cell modulation, and inflammatory amplification are all influenced by IL-6 signaling. Therapeutic inhibition of the IL-6 pathway can produce reductions in inflammatory biomarkers, providing clinical evidence that this pathway is functionally connected with systemic inflammatory activity in RA. [16,19] These observations provide a biological context for the strong IL-6–CRP

relationship observed in the current dataset, although they do not establish IL-6 as an independent marker of disease activity in the absence of DAS28 or other validated clinical measures.

Medication data provide further insight into the observed results. Methotrexate was the most common treatment among the patients with rheumatoid arthritis, while hydroxychloroquine, sulfasalazine, biologic disease-modifying drugs, and glucocorticoids were used less frequently. Current treatment guidelines emphasize the importance of using conventional synthetic disease-modifying drugs, with biologic or targeted therapies employed in specific cases to control inflammatory disease activity [13, 14]. Given the ability of these treatments to modulate inflammatory pathways, variations in the duration of exposure to therapy influence blood cytokine concentrations and reduce the magnitude of differences between groups.

The biological effects of IL-6 are also relevant beyond joint inflammation. IL-6 participates in systemic inflammatory responses and has been implicated in several extra-articular manifestations of RA. [12,15,16] The systemic nature of IL-6 signaling may therefore explain why circulating IL-6 can be associated with inflammatory biomarkers even when its concentration does not significantly distinguish RA patients from controls in a relatively small or heterogeneous dataset.

The current findings should also be considered in the context of genetic and molecular variability in IL-6 signaling. Genetic differences affecting IL-6 production or regulation may contribute to inter-individual variation in cytokine concentrations and potentially influence susceptibility to RA or inflammatory phenotypes. A meta-analysis has reported an association between IL-6 promoter polymorphism and RA, supporting the possibility that host genetic factors may contribute to variability in IL-6-related inflammatory responses. [18] Such variability could partly explain differences in circulating IL-6 concentrations among individuals with clinically similar disease.

It is important to exercise caution when interpreting the extremely strong correlation between IL-6 and CRP observed in the current dataset. A correlation coefficient of $\rho=0.998$ is

remarkably high for clinical biomarker data, even though the direction of this association is biologically plausible. In order to rule out possible data entry mistakes, duplicate observations, group misclassification, or analytical interdependency between the variables, the original patient measurements and statistical processes should be independently validated. It would be far more reliable to interpret this association if it were confirmed in a separate cohort. [19]

One important observation is the apparent contrast between the very strong link between IL-6 and CRP within the rheumatoid arthritis (RA) group and the lack of a statistically significant variation in IL-6 levels between groups. These two analyses pose different questions: the correlation analysis determines whether IL-6 levels fluctuate in tandem with CRP levels in the RA patient data, while the inter-group comparison determines whether IL-6 concentrations differ based on illness classification. Consequently, the absence of a significant difference between groups does not necessarily contradict the observed correlation between IL-6 and CRP; rather, the results suggest that the variation in IL-6 levels within the RA group (as initially classified) is more closely linked to the systemic inflammatory state than to the categorical distinction between RA patients and the control group (healthy individuals).[19, 20]

The findings should nevertheless be regarded as preliminary because of the limitations of the available dataset. The provisional RA/control classification, absence of DAS28 measurements, relatively limited sample size, heterogeneous medication exposure, and lack of treatment-adjusted analyses restrict the strength of causal or clinical inferences. In addition, the cross-sectional nature of the available measurements prevents determination of whether changes in IL-6 precede, accompany, or follow changes in inflammatory disease activity. [20,21] Therefore, future studies should employ clinically confirmed diagnoses of rheumatoid arthritis based on established classification criteria, standardized measures of disease activity such as DAS28, and longitudinal assessments of interleukin-6 (IL-6) and C-reactive protein (CRP) levels. Analyses should

also account for factors such as age, sex, disease duration, medication type and duration, glucocorticoid exposure, and relevant comorbidities. Such an approach would help determine whether IL-6 provides information beyond that of traditional inflammatory markers and whether its measurement holds potential value in characterizing systemic inflammatory activity in rheumatoid arthritis. [20-22]

Overall, the present findings provide preliminary evidence that serum IL-6 was not significantly different between the provisionally classified RA and control groups, while demonstrating a strong positive relationship between IL-6 and CRP among the RA records. The findings thus indicate a possible link between IL-6 and systemic inflammation, although do not confirm IL-6 as a diagnostic or disease-activity biomarker in this group. Validation through clinically substantiated disease categorization, consistent evaluations of disease activity, and rigorously controlled longitudinal research is essential.[21-22]

Limitations

The primary restriction is the lack of a clear group variable in the provided dataset. The current RA/control classification is thus temporary. Additional limits is the absence of DAS28, RF, and anti-CCP metrics in the provided table, the cross-sectional methodology, potential treatment influences on IL-6, and the comparatively limited sample size.

CONCLUSION

The group of patient with RA and the control group did not have substantially different serum interleukin-6 levels. Interleukin-6 may, still represent systemic inflammatory activity linked to rheumatoid arthritis, as evidenced by the high association found between interleukin-6 and C-reactive protein in these patients. Identified initial categorization of the patient groups and the lack of disease activity evaluation using the DAS28 score, these results should therefore be interpreted cautiously. To confirm and clarify the function of interleukin-6 as a potential inflammatory biomarker in rheumatoid arthritis, more research is necessary using clinically

verified diagnoses of the condition and standardized measurements of disease activity.

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