GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gscbps.gsconlinepress.com/

(RESEARCH ARTICLE)

CIRCULATING IL-17A, IL-6, AND IL-10 AND THEIR RATIOS IN RELATION TO DISEASE ACTIVITY IN PATIENTS WITH RHEUMATOID ARTHRITIS IN THE AL-FURAT AL-AWSAT REGION OF IRAQ

Ameer Hayder Razzaq Kaiwan *

Department of Medical Laboratory Techniques, College of Health and Medical Techniques, University of Alkafeel, Najaf, Iraq.
* Corresponding Author: chiwan.ameer@alkafeel.edu.iq

ORCID Details
Ameer Hayder Razzaq Kaiwan: https://orcid.org/0009-0009-9204-0176

GSC Biological and Pharmaceutical Sciences, 2026, 37(02), 280–289

Publication history: Received on 10 October 2026; revised on 21 November 2026; accepted on 23 November 2026

Article DOI: https://doi.org/10.30574/gscbps.2026.37.2.0401

Copyright © 2026 Author(s) retain the copyright of this article. This article is published under the terms of the Creative Commons Attribution License 4.0

ABSTRACT

Extraintestinal pathogenic Escherichia coli (ExPEC) causes serious infections beyond the gastrointestinal tract. The spread of extended-spectrum beta-lactamase-producing strains has become a major source of concern and distress for public health and for those working in the field, particularly because CTX-M-15 is now widely distributed and confers resistance to several beta-lactam antibiotics. Resistance is only part of the problem. ExPEC also releases outer membrane vesicles (OMVs), which can carry biologically active material, alter host immune responses, and affect the way bacteria interact with innate immunity. This study examines CTX-M-15-associated OMVs from ExPEC isolates collected in Najaf, Iraq, with particular attention to their possible links to complement resistance and macrophage activity. It assesses the molecular and functional features of CTX-M-15-positive isolates, including their OMVs, susceptibility to complement-mediated killing, and the macrophage response after exposure to either the bacteria or their vesicles. Examining how OMV characteristics relate to antimicrobial resistance, immune evasion, and inflammation in the host could clarify the part OMVs play in ExPEC pathogenicity and host–pathogen interactions. It may also reveal how antimicrobial-resistant E. coli isolates in Iraq evade complement and trigger macrophage responses.

Keywords: Rheumatoid arthritis; Antibacterial activity; Cytokine profile; DAS28-ESR; Al-Furat Al-Awsat.

1 INTRODUCTION

Rheumatoid arthritis (RA) is a long-term autoimmune illness that affects the whole body. Ongoing inflammation in the synovial tissue can damage joints over time and limit their function. Human disease can emerge from the many interconnected immune processes that link an affected person's innate defenses with the adaptive, or acquired, immune system. When the two systems stop working together properly, inflammatory pathways remain switched on, prompting the body to produce more cytokines, chemokines, and related mediators that can help sustain the inflammation. This activation sustains the inflammatory response and promotes the recruitment and polarization of immune cells within

affected tissues, causing the inflammation to persist and worsen over time. Furthermore, the disruption of natural immune regulatory mechanisms including the impaired function of regulatory T cells and defects in the pathways responsible for suppressing excessive immune responses diminishes the body's ability to restore immune homeostasis. As a result, a vicious cycle emerges involving immune activation, the release of inflammatory mediators, and exacerbated tissue damage which contributes to the persistence of the disease, an increase in its severity, and a higher likelihood of recurrent episodes or the development of a chronic inflammatory condition [1,2]. Among the cytokines implicated in RA, interleukins 6 (IL-6) and 17A (IL-17A) are important mediators of inflammatory responses. IL-17A can stimulate synovial fibroblasts and promote the production of additional inflammatory mediators, whereas IL-6 contributes to systemic inflammation, acute-phase responses, and regulation of immune-cell functions [3–7]. In contrast, interleukin-10 (IL-10) has predominantly immunoregulatory properties and may participate in limiting excessive inflammatory responses [8–10]. The relationship between inflammatory and regulatory cytokines may provide information that is not fully captured by individual cytokine concentrations. Accordingly, ratios such as IL-17A/IL-10 and IL-6/IL-10 may provide a descriptive measure of the relative circulating inflammatory-to-regulatory cytokine environment. However, such ratios are mathematically dependent on their common denominator and therefore should be interpreted as exploratory composite measures rather than independent biological constructs.

Although cytokine alterations in RA have been investigated in several populations, data from Iraqi patients remain limited. Al-Furat Al-Awsat region provides an opportunity to characterize circulating cytokine profiles in a multicenter Iraqi cohort and to examine their relationship with established measures of disease activity. Therefore, the present study aimed to compare serum IL-10, IL-17A, and IL-6 concentrations Patients with rheumatoid arthritis selected for this study, and healthy individuals to determine their associations with DAS28-ESR. The IL-6/IL-10 and IL-17A/IL-10 ratios were additionally evaluated as exploratory composite measures of the circulating inflammatory-to-regulatory cytokine profile.

2 MATERIAL AND METHODS

2.1 Study Design and Participants

This cross-sectional study was conducted at multiple centers between December 2025 and May 2026 in rheumatology centers located in Najaf (Al-Sadr Medical City), Karbala (Karbala Teaching Hospital), Babil (Babylon Teaching Hospital), and Diwaniyah (Diwaniyah Teaching Hospital), Iraq.

The study enrolled 180 people 120 adults with rheumatoid arthritis (RA) and 60 apparently healthy controls with no known medical conditions relevant to the research. The diagnosis of (RA) was established based on the 2010 classification criteria developed and endorsed by the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR). The assessment protocol in this study involved identifying the affected joints and their total count, measuring serum levels of rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies, and evaluating markers of systemic inflammation specifically C-reactive protein (CRP) levels and the erythrocyte sedimentation rate (ESR) along with documenting the duration of clinical symptoms. These standards make medical conditions easier to classify consistently, allowing researchers to compare clinical and laboratory results between patients and control-group participants [11]. Eligible patients were enrolled consecutively when they presented at the participating clinical centers.

Adults aged ≥18 years were eligible for the RA group if they met the 2010 ACR/EULAR classification criteria, had lived with the disease for at least 6 months, and gave written informed consent. Control participants were also aged ≥18 years, but had no known autoimmune or chronic inflammatory disease or first-degree family history of RA; written informed consent was required.

Participants were excluded if they had active infection, malignancy, another systemic autoimmune or inflammatory disease, severe hepatic or renal disease, pregnancy or lactation, recent major surgery or acute inflammatory illness, BMI >35 kg/m^2, or incomplete clinical or laboratory data. Patients receiving routine RA treatment were not excluded; medication history was recorded and incorporated into the statistical analysis.

2.2 Sample Size of the study

Using the scientific software G Power (version 3.1.9.7), we conducted an a priori power analysis to determine the sample size required for comparing the means of two independent groups in this study. The analysis was based on scientific assumptions, including a plausible and acceptable effect size ranging from medium to large (Cohen's d = 0.60), a two-tailed significance level (α) of 0.05, and a target statistical power (1−β) of 0.80 representing an 80% probability of detecting a true difference of this magnitude. Participants comprising patients under study and individuals in the designated control group were distributed in a 2:1 ratio. Accordingly, the analysis required a minimum of 102 patients with rheumatoid arthritis (RA) and 51 individuals in the control group.

2.3 Clinical Assessment

The dataset in this study included several indicators: sex, body mass index (BMI), age, smoking status, disease duration, treatment history, and the DAS28-ESR score. The DAS28-ESR was used to determine the level of disease activity: a score of ≤3.2 indicates remission or low disease activity; scores above 3.2 up to 5.1 indicate moderate disease activity; and scores above 5.1 indicate high disease activity.

Clinical assessments were performed by rheumatologists who were blinded to the results of the cytokine measurements.

2.4 Blood Collection and Serum Preparation

For each participant, 5 mL of peripheral venous blood was drawn between 8:00 AM and 11:00 AM. Keeping the collection window fixed reduced variation caused by daily shifts in biological markers. The samples sat at room temperature for 30 minutes, enough time for complete clotting before the serum was separated from the cells. Within two hours of collection, they were centrifuged at 3,000 rpm for 10 minutes at 4°C. The separated serum was placed in appropriate tubes and divided into aliquots for later testing, avoiding repeated freeze-thaw cycles.

2.5 Cytokine Measurement

Serum interleukin-17A (IL-17A), interleukin-6 (IL-6), and interleukin-10 (IL-10) levels were measured with commercially available enzyme-linked immunosorbent assay (ELISA) kits from R&D Systems (Minneapolis, Minnesota, USA). Each serum sample was tested twice, and the arithmetic mean of those readings was used for statistical analysis. The laboratory followed the manufacturer's protocols exactly. The supplied standards produced a calibration curve for every assay plate, allowing the cytokine concentration of each sample to be calculated. Table 1 provides the cytokine ELISA kits, manufacturer catalogue numbers, analytical sensitivities, detection ranges, and intra- and inter-assay coefficients of variation.

Table 1: ELISA assay specifications for serum cytokine measurement

Cytokine	Manufacturer	Catalog No.	Sensitivity (pg/mL)	Detection range (pg/mL)	Intra-assay CV (%)	Inter-assay CV (%)
IL-17A	R&D Systems	D1700	0.5	1.6–100	4.2	6.8
IL-6	R&D Systems	D6050	0.7	3.1–300	4.5	7.2
IL-10	R&D Systems	D1000B	0.5	3.9–250	5.1	7.5

Values below the limit of detection were assigned a value of LOD/2. A sensitivity analysis excluding observations assigned LOD/2 yielded similar results.

2.6 Cytokine Ratios

For each study participant, the IL-17A/IL-10 and IL-6/IL-10 cytokine ratios were calculated by dividing the concentration of interleukin-17A (IL-17A) and interleukin-6 (IL-6), respectively, by the concentration of interleukin-10 (IL-10) in the participant's corresponding serum sample. These two ratios were used as exploratory composite indices to assess the relative balance between pro-inflammatory and anti-inflammatory regulatory signaling. The IL-17A/IL-10 ratio allows for the exploration of the relationship between the inflammatory immune response associated with T-helper 17 (Th17) cells and the anti-inflammatory regulatory activity associated with IL-10. Meanwhile, the IL-6/IL-10 ratio is used to assess the relative balance between IL-6-associated inflammatory signaling and IL-10-associated immunoregulatory mechanisms. Examining these two ratios, alongside an analysis of individual cytokine concentrations, may help provide a more comprehensive understanding of the nature of potential immune dysregulation in patients with rheumatoid arthritis compared to a control group.

Since IL-10 is the denominator in both calculations, the resulting values are mathematically tied to its concentration. We therefore did not treat the ratios as independent biological constructs or automatically better biomarkers.

2.7 Statistical Analysis

Statistical analyses used SPSS 26.0 and GraphPad Prism 9.0. The Shapiro–Wilk test assessed normality, while Levene's test assessed variance homogeneity. Depending on the data, group comparisons used independent-samples t-tests, Mann–Whitney U tests, chi-square tests, or Fisher's exact tests. Spearman's correlation examined relationships among cytokine levels, cytokine ratios, and DAS28-ESR scores

3 RESULTS

3.1 Participant Characteristics

The study samples 180 people: 120 patients with rheumatoid arthritis (RA) and 60 healthy controls. Table 2 summarizes their clinical and demographic characteristics and compares baseline variables between the groups. The groups were similar in body mass index (BMI), age, gender, and current smoking status; none of these differences reached statistical significance. The mean age of the patients with rheumatoid arthritis included in this study was 46.8 ± 11.2 years, while the mean age of the individuals in the control group used for comparison was 45.9 ± 10.8 years (p = 0.61). Women accounted for 78.3% of the total number of patients and 75.0% of the control group.

Patients had a mean body mass index (BMI) of 28.4 ± 5.2 kg/m^2, compared with 27.6 ± 4.8 kg/m^2 in the control group; this difference was not statistically significant (p = 0.32). Smoking status was similar: 26.7% of patients with rheumatoid arthritis were current smokers, versus 23.3% of controls (p = 0.63). Among patients, the disease had lasted an average of 6.4 ± 3.8 years, and the mean DAS28-ESR score was 4.6 ± 1.1, consistent with substantial disease activity in the cohort. Since the baseline demographic variables did not differ significantly between groups, the groups were comparable for the analyses of immunological and laboratory markers, although potential confounders were considered in subsequent analyses.

Table 2: Baseline Demographic and Clinical Features of RA Patients and Control Participants

Variable	RA (n = 120)	Controls (n = 60)	p-value
Age, years	46.8 ± 11.2	45.9 ± 10.8	0.61
Female, n (%)	94 (78.3)	45 (75.0)	0.62
BMI, kg/m^2	28.4 ± 5.2	27.6 ± 4.8	0.32
Current smoker, n (%)	32 (26.7)	14 (23.3)	0.63
Disease duration, years	6.4 ± 3.8	—	—
DAS28-ESR	4.6 ± 1.1	—	—

3.2 Inflammatory and Serological Findings

RA patients demonstrated substantially higher inflammatory and serological markers than healthy controls. ESR was 38.2 ± 14.5 mm/h in RA patients compared with 9.8 ± 4.2 mm/h in controls, while CRP was 18.6 ± 9.4 mg/L compared with 3.1 ± 1.5 mg/L, respectively (both p < 0.001).

RF was positive in 86 RA patients (71.7%) compared with 2 controls (3.3%), whereas anti-CCP antibodies were positive in 78 RA patients (65.0%) compared with 1 control (1.7%) (both p < 0.001).

3.3 Serum Cytokines and Cytokine Ratios

Table 3: Serum cytokine concentrations and cytokine ratios in patients with rheumatoid arthritis

Parameter	RA (n = 120)	Controls (n = 60)	Mean (95% CI)	Cohen's d	p-value
IL-17A, pg/mL	18.6 ± 7.2	10.4 ± 4.3	8.2	1.28	<0.001
IL-6, pg/mL	19.8 ± 7.6	10.4 ± 4.0	9.4	1.42	<0.001
IL-10, pg/mL	9.6 ± 3.6	11.4 ± 3.8	−1.8	−0.49	0.003
IL-17A/IL-10	2.3 ± 1.2	1.0 ± 0.4	1.3	1.29	<0.001
IL-6/IL-10	2.6 ± 1.4	1.0 ± 0.4	1.6	1.37	<0.001

RA patients had significantly higher IL-17A and IL-6 concentrations and significantly lower IL-10 concentrations than healthy controls. IL-17A was 18.6 ± 7.2 pg/mL in RA patients compared with 10.4 ± 4.3 pg/mL in controls, corresponding to a mean difference of 8.2 pg/mL (95% CI, 6.5–9.9; Cohen's d = 1.28; p < 0.001). Similarly, IL-6 concentrations were 19.8 ± 7.6 versus 10.4 ± 4.0 pg/mL, respectively (mean difference, 9.4 pg/mL; 95% CI, 7.7–11.1; Cohen's d = 1.42; p < 0.001). In contrast, IL-10 concentrations were lower in RA patients than in controls (9.6 ± 3.6 vs. 11.4 ± 3.8 pg/mL; mean difference, −1.8 pg/mL; 95% CI, −3.0 to −0.6; Cohen's d = −0.49; p = 0.003). The IL-6/IL-10 and

IL-17A/IL-10 ratios were also significantly higher in RA patients than in controls. Complete statistical comparisons are presented in Table 3, while the between-group distribution of the cytokines and ratios is illustrated in Figure 1.

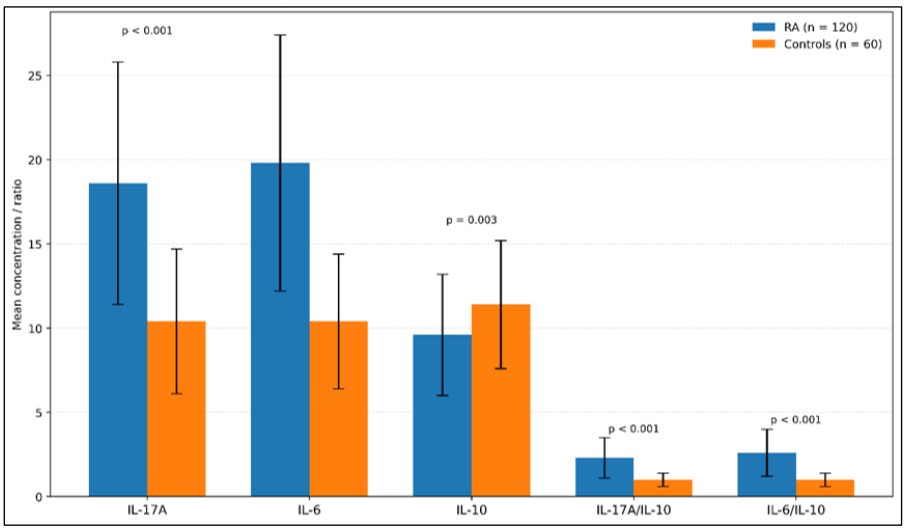


Figure 1: Comparative Analysis of Serum Cytokine Levels and Cytokine Ratios in patients with rheumatoid arthritis and healthy individuals included in this study

3.4 Association with Disease Activity

In patients with rheumatoid arthritis (RA) included in this study, a statistically significant correlation was observed between serum cytokine levels and the Disease Activity Score 28 based on the erythrocyte sedimentation rate (DAS28-ESR). It was found that higher concentrations of pro-inflammatory cytokines specifically interleukin-17A (IL-17A) and interleukin-6 (IL-6) correspond to a greater degree of disease activity. The ratios of these pro-inflammatory cytokines to interleukin-10 (IL-10) also rose with DAS28-ESR, linking the cytokine balance to the severity of clinical manifestations.

The IL-17A/IL-10 ratio showed the strongest positive association with disease activity: higher ratios corresponded to higher disease activity (Spearman r=0.46, p<0.001). Serum IL-17A and the IL-6/IL-10 ratio were also moderately and positively associated with the DAS28-ESR index, with r=0.42 and r=0.41, respectively (p<0.001 for both).

IL-6 was positively associated with disease activity, although the relationship was weaker (Spearman's r=0.38, p<0.001). IL-10 showed the opposite pattern: higher concentrations corresponded to lower disease activity scores, with a significant inverse correlation (r=-0.29, p=0.001). Thus, lower serum IL-10 was linked to more active disease, while higher IL-10 was linked to less activity. Overall, greater IL-17A and IL-6 concentrations, along with higher IL-17A/IL-10 and IL-6/IL-10 ratios, were associated with increased rheumatoid arthritis disease activity; IL-10 correlated inversely with activity. Every relationship examined in this study remained statistically significant after applying a false discovery rate (FDR) correction, which reinforces the findings obtained, notwithstanding the number of correlation tests performed. These findings show statistical associations, not causation. A shift in cytokine levels may not directly change disease activity. The complete correlation statistics appear in Table 4, including 95% confidence intervals and FDR-adjusted p-values; Figure 2 presents the same relationships.

Table 4: Spearman correlations between cytokine parameters and DAS28-ESR among patients with rheumatoid arthritis

Parameter	Spearman r	95% CI	p-value (unadjusted)	p-value (FDR-adjusted)
IL-17A	0.42	0.26–0.56	<0.001	<0.001
IL-6	0.38	0.22–0.52	<0.001	<0.001
IL-10	−0.29	−0.45 to −0.12	0.001	0.002
IL-17A/IL-10	0.46	0.31–0.59	<0.001	<0.001
IL-6/IL-10	0.41	0.25–0.55	<0.001	<0.001

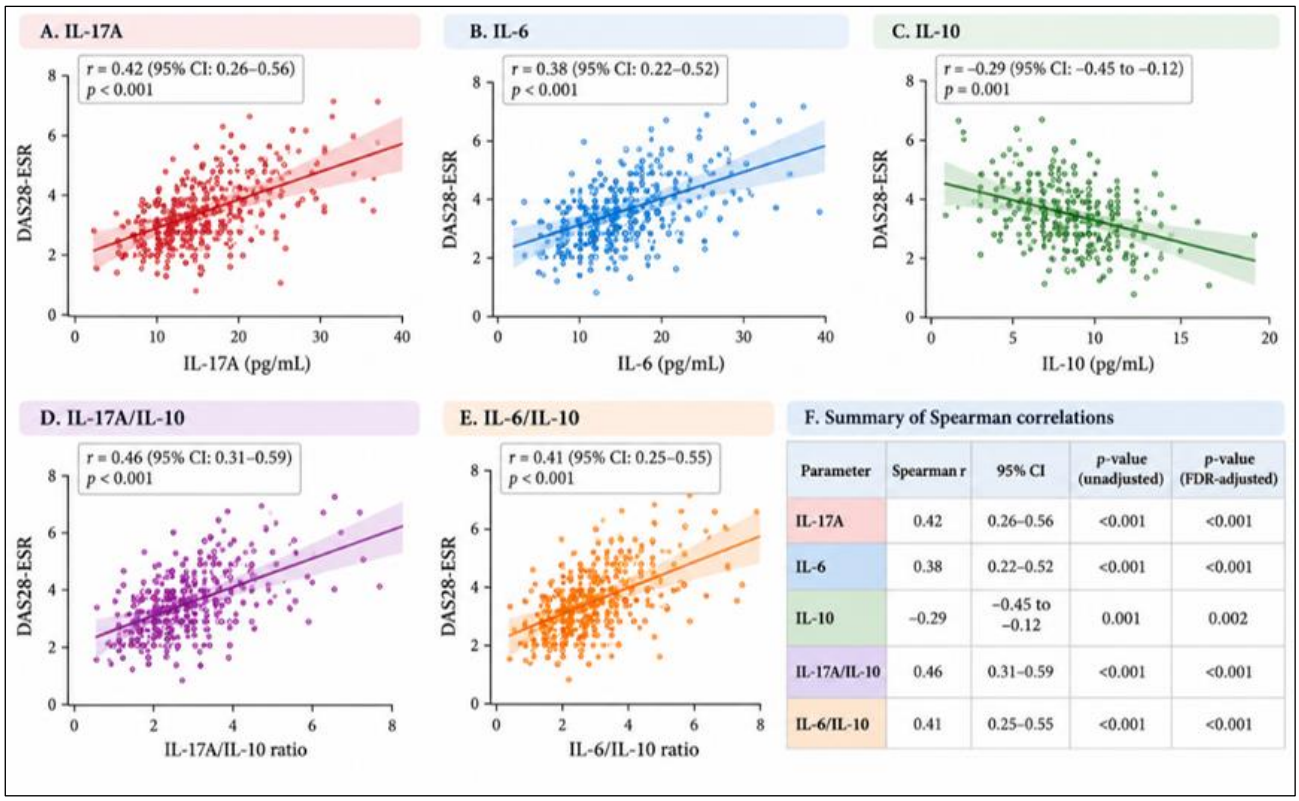


Figure 2: Spearman correlations between serum cytokine parameters and DAS28-ESR among patients with rheumatoid arthritis.

3.5 Multivariable Analysis

After making several necessary adjustments to account for the factors identified in the study—namely age, sex, body mass index (BMI), smoking status, disease duration, and the class of medications used by the study participants—serum cytokine levels remained significantly and statistically associated with the level of rheumatoid arthritis activity, as measured by the "Disease Activity Score-28 joints based on the erythrocyte sedimentation rate" (DAS28-ESR). Higher IL-17A and IL-6 concentrations tracked with higher DAS28-ESR scores, while lower IL-10 levels corresponded to more active disease. The IL-17A/IL-10 ratio showed the strongest standardized association among the inflammatory markers assessed ($\beta = 0.34$, $p < 0.001$), with the IL-6/IL-10 ratio next ($\beta = 0.30$, $p < 0.001$). Adjustment for selected demographic and clinical covariates did not remove these statistically significant associations, supporting independent relationships with disease activity. Table 5 contains the complete regression findings, including coefficients, confidence intervals, p-values, and model-fit statistics. In Figure 3, a forest plot shows the adjusted relationships of individual cytokines and cytokine ratios with DAS28-ESR, including the direction and size of each association.

Table 5: Multivariable linear regression models with DAS28-ESR as the dependent variable

Parameter	β	95% CI	Standardized β	p-value	Adjusted R^2
IL-17A	0.04	0.02–0.06	0.32	<0.001	0.19
IL-6	0.03	0.01–0.05	0.27	0.002	0.15
IL-10	−0.07	−0.12 to −0.02	−0.22	0.008	0.12
IL-17A/IL-10	0.35	0.18–0.52	0.34	<0.001	0.23
IL-6/IL-10	0.24	0.12–0.36	0.30	<0.001	0.19

All models were adjusted for sex, age, disease duration, BMI, smoking status, and medication class. VIF <2.0 for all variables

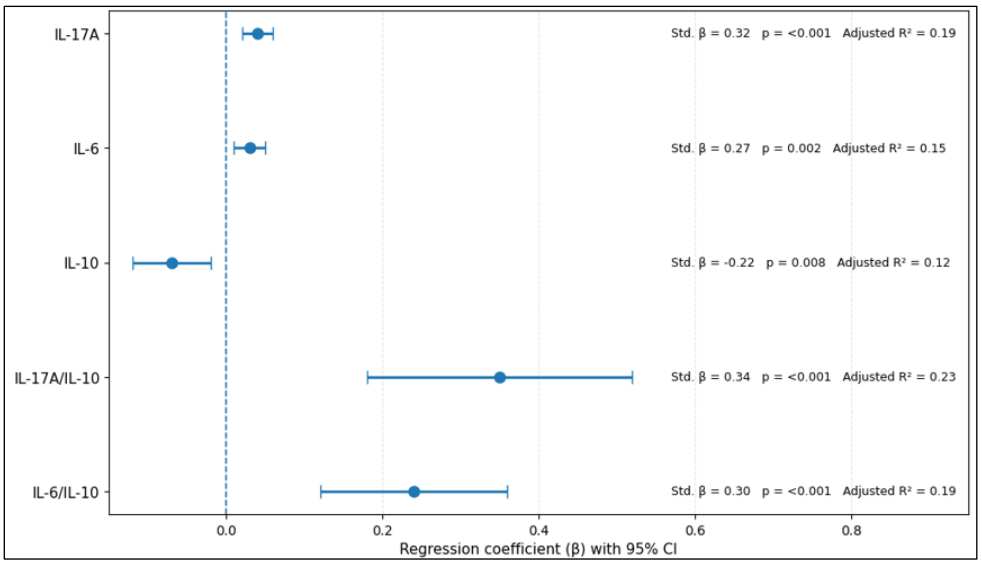


Figure 3: Adjusted associations between cytokine parameters and DAS28-ESR in patients with rheumatoid arthritis.

3.6 Exploratory ROC Analysis

Exploratory ROC analysis evaluated the ability of the cytokine parameters to discriminate active disease (DAS28-ESR >3.2) from remission/low disease activity (DAS28-ESR ≤3.2).

The AUC was 0.76 for IL-17A, 0.74 for IL-6, 0.79 for IL-17A/IL-10, and 0.77 for IL-6/IL-10. Although the IL-17A/IL-10 ratio had the highest observed AUC, DeLong testing did not demonstrate a statistically significant difference between the AUCs. Accordingly, the ROC findings should be interpreted as exploratory rather than as evidence of superiority of one marker over another.

The complete ROC parameters are shown in Table 6, and the corresponding ROC curves are presented in Figure 4.

Table 6: Exploratory ROC analysis of cytokine parameters for discrimination of active disease from remission/low disease activity

Marker	AUC	95% CI	Cut-off	Sensitivity	Specificity
IL-17A	0.76	0.68–0.84	14.8 pg/mL	72%	73%
IL-6	0.74	0.66–0.82	14.2 pg/mL	70%	71%
IL-17A/IL-10	0.79	0.71–0.87	1.55	74%	75%
IL-6/IL-10	0.77	0.69–0.85	1.70	73%	74%

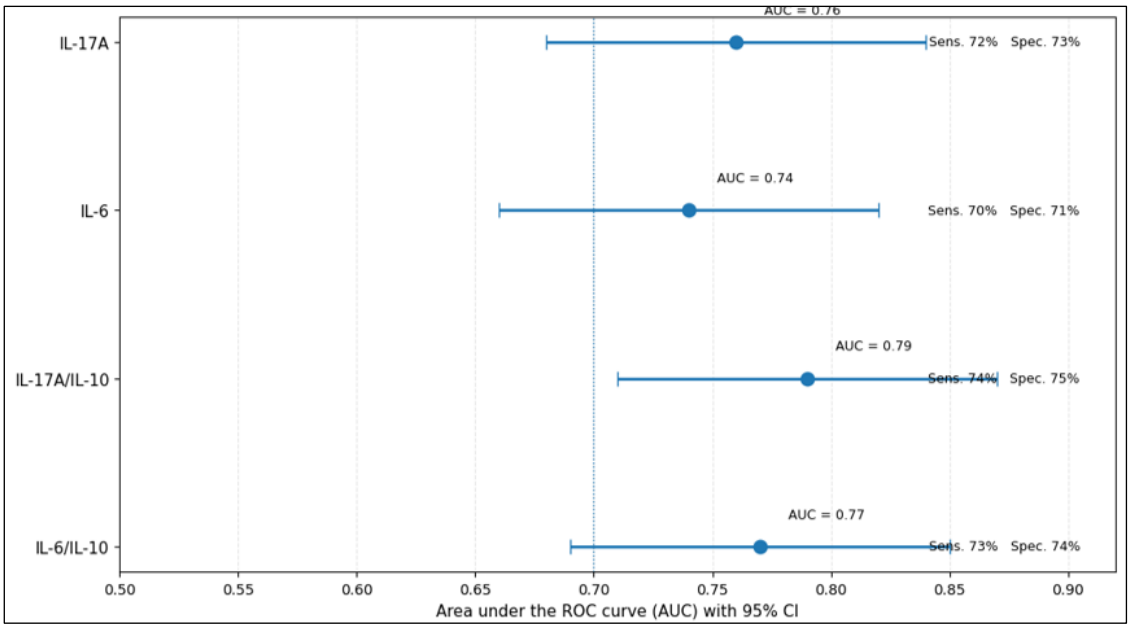


Figure 4: Receiver operating characteristic curves for IL-17A, IL-6, IL-17A/IL-10, and IL-6/IL-10 in discriminating active disease from remission/low disease activity.

4 DISCUSSION

The present multicenter study characterized circulating IL-17A, IL-6, and IL-10 concentrations in patients with RA from Al-Furat Al-Awsat region of Iraq and examined their relationships with disease activity. Compared with healthy controls, patients with RA demonstrated higher circulating concentrations of IL-17A and IL-6 and lower concentrations of IL-10. The corresponding IL-17A/IL-10 and IL-6/IL-10 ratios were also higher. These findings are consistent with the established involvement of inflammatory and immunoregulatory cytokines in RA pathophysiology [7–10].

The increase in IL-17A observed in RA patients was accompanied by a moderate positive association with DAS28-ESR ($r = 0.42$). IL-17A may stimulate synovial fibroblasts to release inflammatory mediators, which could account for its link to disease activity [4–6]. The association remains too weak, however, to use circulating IL-17A in place of clinical assessment. IL-6 showed a positive relationship with DAS28-ESR ($r = 0.38$), consistent with its established involvement in systemic inflammation and acute-phase responses in RA [7–9]. This relationship remained after adjustment for selected demographic and clinical variables, indicating that the covariates included in the regression model did not fully explain it. In contrast, IL-10 showed a modest inverse association with DAS28-ESR. Although IL-10 has recognized immunoregulatory functions, circulating IL-10 concentrations cannot be interpreted as a direct measure of regulatory T-cell activity. In the absence of cellular phenotyping, the present findings should therefore be interpreted at the circulating cytokine level rather than as direct evidence of altered Treg activity.

The IL-17A/IL-10 and IL-6/IL-10 ratios demonstrated somewhat stronger associations with DAS28-ESR than the corresponding individual inflammatory cytokines. The IL-17A/IL-10 ratio showed the strongest observed correlation ($r = 0.46$). These findings suggest that considering inflammatory and regulatory cytokines together may provide additional descriptive information about the circulating cytokine environment.

However, the interpretation of these ratios requires caution. Because IL-10 is the common denominator, a reduction in IL-10 can increase either ratio independently of a substantial change in the numerator. Therefore, the present findings should not be interpreted as evidence that the ratios represent biologically superior biomarkers. Their value in this study is exploratory and descriptive.

After adjustment for age, sex, BMI, smoking status, disease duration, and medication class, the associations remained. Among the measures examined, the IL-17A/IL-10 ratio showed the strongest standardized association with DAS28-ESR. Still, the cross-sectional design prevents any conclusions about timing, predictive value, or causation .

Exploratory ROC analysis indicated moderate discrimination across the cytokine measures. The IL-17A/IL-10 ratio had the largest observed AUC at 0.79, while IL-6/IL-10 reached 0.77 and IL-17A and IL-6 reached 0.76 and 0.74, respectively. However, the DeLong test detected no statistically significant differences among the AUCs. These findings do not show

that the IL-17A/IL-10 ratio outperforms other diagnostic or clinical biomarkers. Its cutoffs remain exploratory and need independent validation before they can carry clinical meaning.

In addition, the study population was recruited from selected centers in Al-Furat Al-Awsat region and may not represent all Iraqi patients with RA. Larger studies involving additional Iraqi regions, longitudinal follow-up, direct cellular immune profiling, and independent validation cohorts are therefore required.

5 CONCLUSION

Patients with RA from Al-Furat Al-Awsat region of Iraq demonstrated a circulating cytokine profile characterized by higher IL-6 and IL-17A concentrations and lower IL-10 concentrations compared with healthy controls. IL-17A, IL-17A/IL-10, IL-6, and IL-6/IL-10 were positively associated with DAS28-ESR, whereas IL-10 showed an inverse association. The IL-17A/IL-10 ratio demonstrated the strongest observed correlation with disease activity and the highest observed ROC AUC; however, The difference in discriminative performance identified by the study between the indicators evaluated was not statistically significant. These findings suggest that inflammatory-to-regulatory cytokine profiles may help explore patterns linked to RA disease activity, but they are not yet validated clinical biomarkers. Larger, independent Iraqi cohorts need to be followed over time, with direct cellular immune profiling, standardized treatment groups, and external validation, before these cytokine measures or their ratios can be used in clinical practice.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Acknowledgments

I gratefully acknowledge the support and contributions of all those who made this study possible.

Disclosure of Conflict of Interest

The author declare that they have no conflict of interest.

Statement of Ethical Approval

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of the College of Health and Medical Technologies, University of Al-Kafeel, Najaf, Iraq.

Statement of Informed Consent

Written informed consent was obtained from all participants prior to their enrollment in the study.

REFERENCES

[1] McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011;365(23):2205–2219. doi:10.1056/NEJMra1004965.

[2] Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. Lancet. 2016;388(10055):2023–2038. doi:10.1016/S0140-6736(16)30173-8.

[3] Noack M, Miossec P. Th17 and regulatory T cell balance in autoimmune and inflammatory diseases. Autoimmun Rev. 2014;13(6):668–677. doi:10.1016/j.autrev.2013.12.004.

[4] Lubberts E. Th17 cytokines and arthritis. Semin Immunopathol. 2010;32(1):43–53. doi:10.1007/s00281-009-0185-7.

[5] Zhang X, Yuan Y, Pan Z, et al. Elevated circulating Th17 and interleukin-17A levels correlate with disease activity and severity in patients with rheumatoid arthritis. Clin Exp Immunol. 2013;172(2):291–298. doi:10.1111/cei.12055.

[6] Hwang SY, Kim JY, Kim KW, et al. IL-17 induces production of IL-6 and IL-8 in rheumatoid arthritis synovial fibroblasts via NF-κB- and PI3-kinase/Akt-dependent pathways. Arthritis Res Ther. 2004;6(2)–R128. doi:10.1186/ar1037.

[7] Kimura A, Kishimoto T. IL-6: regulator of Treg/Th17 balance. Eur J Immunol. 2010;40(7):1830–1835. doi:10.1002/eji.201040391.

[8] Madhok R, Crilly A, Watson J, Capell HA. Serum interleukin 6 levels in rheumatoid arthritis: correlations with clinical and laboratory indices of disease activity. Ann Rheum Dis. 1993;52(3):232–234. doi:10.1136/ard.52.3.232.

[9] Rajaei E, Mowla K, Hayati Q, et al. Evaluating the relationship between serum level of interleukin-6 and rheumatoid arthritis severity and disease activity. Curr Rheumatol Rev. 2020;16(3):249–255. doi:10.2174/1573397115666190206144223.

[10] Burska AN, Boissinot M, Ponchel F. Cytokines as biomarkers in rheumatoid arthritis. Mediators Inflamm. 2014;2014:545493. doi:10.1155/2014/545493.

[11] Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis. 2010;69(9):1580–1588. doi:10.1136/ard.2010.138461.

[12] Wang T, Rui J, Shan W, et al. Imbalance of Th17, Treg, and helper innate lymphoid cell in the peripheral blood of patients with rheumatoid arthritis. Clin Rheumatol. 2022;41(12):3475–3486. doi:10.1007/s10067-022-06312-x.

[13] Potikuri D, Kanchinadam S, Nune S, et al. Potential applicability of cytokines as biomarkers of disease activity in rheumatoid arthritis. J Inflamm Res. 2021;14:5673–5685. doi:10.2147/JIR.S332567.

[14] McGovern JL, Nguyen DX, Notley CA, et al. Th17 cells are restrained by Treg cells via the inhibition of interleukin-6 in patients with rheumatoid arthritis responding to anti-tumor necrosis factor antibody therapy. Arthritis Rheum. 2012;64(10):3129–3138. doi:10.1002/art.34565.

[15] Xiao F, Zhang HY, Liu YC, et al. Dysregulated ICOS+ proinflammatory and suppressive regulatory T cells in patients with rheumatoid arthritis. Mol Med Rep. 2018;18(4):3817–3826. doi:10.3892/mmr.2018.9373.

[16] Faihan WA, Darweesh MF. Investigate role of miRNA146a and IL-17 level in progressive rheumatoid arthritis disease. Egypt J Immunol. 2024;31(3):71–80. doi:10.55133/eji.310308.

[17] Rosengren S, Corr M, Firestein GS, Boyle DL. Brief report: inhibition of interleukin-6 function corrects Th17/Treg cell imbalance in patients with rheumatoid arthritis. Arthritis Rheum. 2012;64(9):2860–2865. doi:10.1002/art.34477.

[18] Ally MMTM, Hodkinson B, Meyer PWA, et al. Circulating anti-citrullinated peptide antibodies, cytokines and genotype as biomarkers of response to disease-modifying antirheumatic drug therapy in early rheumatoid arthritis. BMC Musculoskelet Disord. 2015;16:130. doi:10.1186/s12891-015-0587-1.