Journal of Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/cmcg7v23

PRO- AND ANTI-INFLAMMATORY CYTOKINE PROFILES (IL-6, TNF-A, IL-10) IN INFLAMMATORY BOWEL DISEASE AND RHEUMATOID ARTHRITIS: A COMPARATIVE CLINICAL STUDY

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ABSTRACT

Background: Inflammatory bowel disease (IBD) and rheumatoid arthritis (RA) are chronic immune-mediated inflammatory disorders characterized by dysregulated cytokine networks. While both conditions share common inflammatory pathways, comparative analyses of cytokine profiles between these diseases remain limited. Understanding differential cytokine expression may provide insights into disease-specific pathogenesis and therapeutic targeting.

Methods: This cross-sectional comparative study enrolled 200 participants: 60 patients with inflammatory bowel disease (30 Crohn's disease, 30 ulcerative colitis), 60 patients with rheumatoid arthritis, and 80 age- and sex-matched healthy controls. Serum levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-10 (IL-10) were measured using enzyme-linked immunosorbent assay. Disease activity was assessed using standardized indices. Statistical comparisons utilized ANOVA, independent t-tests, and correlation analyses.

Results: Both IBD and RA patients demonstrated significantly elevated pro-inflammatory cytokines compared to controls. IL-6 levels were highest in RA patients (42.68 ± 18.74 pg/mL) followed by IBD (28.94 ± 12.36 pg/mL) and controls (6.82 ± 3.14 pg/mL) ($p<0.001$). TNF-α levels were comparable between IBD (34.52 ± 14.28 pg/mL) and RA (31.86 ± 13.42 pg/mL), both significantly exceeding controls (8.24 ± 3.68 pg/mL) ($p<0.001$). IL-10 levels were reduced in both disease groups compared to controls ($p<0.001$). The IL-6/IL-10 ratio was significantly higher in RA (4.82 ± 1.94) versus IBD (3.24 ± 1.56) ($p<0.001$).

Conclusion: Distinct cytokine signatures exist between inflammatory bowel disease and rheumatoid arthritis, with IL-6 predominance in RA and comparable TNF-α elevation in both conditions. These differential profiles may guide personalized therapeutic approaches in immune-mediated inflammatory diseases.

Keywords: Ureteral stone, Holmium YAG laser, Pneumatic lithotripsy, Lithotripsy efficacy, Stone migration

INTRODUCTION

Chronic immune-mediated inflammatory diseases represent a significant global health burden, affecting millions of individuals worldwide with substantial morbidity and healthcare costs [1]. Among these conditions, inflammatory bowel disease (IBD) and rheumatoid arthritis (RA) stand as prototypical disorders characterized by persistent inflammation and tissue destruction in distinct anatomical compartments [2]. Despite affecting different organ systems, these diseases share

fundamental immunopathogenic mechanisms involving dysregulated innate and adaptive immune responses [3].

The cytokine network plays a central role in orchestrating inflammatory responses in both IBD and RA [4]. Pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), drive disease pathogenesis through multiple mechanisms including immune cell activation, endothelial dysfunction, and tissue remodeling [5]. Conversely, anti-inflammatory cytokines such as interleukin-10 (IL-10) serve regulatory functions that normally limit excessive inflammation [6]. The balance between pro- and anti-inflammatory mediators ultimately determines disease activity and progression. Tumor necrosis factor-alpha has been extensively studied in both conditions and represents a validated therapeutic target [7]. Anti-TNF biologics have revolutionized treatment outcomes in IBD and RA, confirming the pathogenic importance of this cytokine [8]. Similarly, IL-6 has emerged as a critical mediator, particularly in rheumatoid arthritis, where IL-6 receptor blockade demonstrates significant clinical efficacy [9]. The therapeutic success of targeting these cytokines underscores the need for comprehensive understanding of cytokine profiles across inflammatory diseasesInterleukin-10, a potent anti-inflammatory cytokine, plays essential regulatory roles in maintaining immune homeostasis **[10]**. Defective IL-10 signaling has been implicated in both IBD and RA pathogenesis, with genetic polymorphisms affecting IL-10 production associated with disease susceptibility **[11]**. The ratio between pro-inflammatory and anti-inflammatory cytokines may better reflect the overall inflammatory state than individual cytokine levels alone **[12]**.

Previous investigations have primarily examined cytokine profiles within individual diseases rather than across different inflammatory conditions **[13]**. Comparative studies are essential for identifying disease-specific inflammatory signatures that may explain differential therapeutic responses and guide treatment selection **[14]**. Furthermore, understanding shared and distinct cytokine patterns may reveal common pathogenic pathways amenable to intervention.

A significant research gap exists in the direct comparison of comprehensive cytokine profiles between IBD and RA populations. Most existing comparative data derive from meta-analyses of separate studies conducted under different conditions, limiting the validity of cross-disease comparisons **[15]**. Additionally, the relationship between cytokine imbalance and disease activity across these conditions requires systematic evaluation.

The aim of this study was to compare serum levels of IL-6, TNF-α, and IL-10 between patients with inflammatory bowel disease and rheumatoid arthritis, to evaluate cytokine ratios as indicators of inflammatory imbalance, and to correlate cytokine profiles with disease activity measures in both conditions.

Materials and Methods

Study Design and Setting

This cross-sectional comparative study was conducted at the Departments of Gastroenterology and Rheumatology, University Medical Center, from March 2022 to February 2024.

Study Population

A total of 200 participants were enrolled into four groups. Group A comprised 30 patients with Crohn's disease (CD). Group B included 30 patients with ulcerative colitis (UC). Group C consisted of 60 patients with rheumatoid arthritis. Group D included 80 healthy controls matched for age and sex distribution.

Inclusion Criteria

For IBD patients, inclusion criteria were established diagnosis according to European Crohn's and Colitis Organisation (ECCO) guidelines based on clinical, endoscopic, histological, and radiological findings; age 18-70 years; and disease duration of at least 6 months. For RA patients, criteria included diagnosis fulfilling American College of Rheumatology/European League Against

Rheumatism (ACR/EULAR) 2010 classification criteria, age 18-70 years, and disease duration of at least 6 months. Healthy controls had no history of chronic inflammatory, autoimmune, or infectious diseases.

Exclusion Criteria

Exclusion criteria for all participants included active infections, malignancy within 5 years, chronic liver or kidney disease, pregnancy or lactation, use of systemic corticosteroids exceeding 10 mg prednisolone equivalent within 4 weeks, and current participation in clinical trials. Patients with overlap syndromes or concurrent autoimmune diseases were also excluded.

Clinical Assessment

Comprehensive clinical evaluation was performed for all participants including demographic data, medical history, current medications, and physical examination. Disease activity in Crohn's disease was assessed using the Crohn's Disease Activity Index (CDAI), with remission defined as CDAI <150, mild activity 150-220, moderate activity 220-450, and severe activity >450. Ulcerative colitis activity was evaluated using the Mayo Score, with remission defined as score 0-2, mild 3-5, moderate 6-10, and severe 11-12.

Rheumatoid arthritis disease activity was determined using the Disease Activity Score-28 with C-reactive protein (DAS28-CRP), classified as remission (<2.6), low activity (2.6-3.2), moderate activity (3.2-5.1), and high activity (>5.1). Joint counts, patient global assessment, and CRP levels were recorded.

Laboratory Measurements

Venous blood samples were collected from all participants after overnight fasting between 8:00 and 10:00 AM to minimize circadian variation. Samples were processed within 2 hours of collection. Serum was separated by centrifugation at 3000 rpm for 15 minutes and stored at -80°C until batch analysis.

Serum IL-6 levels were measured using a high-sensitivity enzyme-linked immunosorbent assay (ELISA) kit with a detection range of 0.5-200 pg/mL and intra-assay coefficient of variation of 3.8%. TNF-α was quantified using ELISA with sensitivity of 0.5 pg/mL and intra-assay CV of 4.2%. IL-10 was measured using high-sensitivity ELISA with detection limit of 0.2 pg/mL and intra-assay CV of 3.5%. All assays were performed in duplicate according to manufacturer protocols.

Additional laboratory parameters including complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), liver and renal function tests, and rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) for RA patients were measured using standard automated methods.

Statistical Analysis

Sample size calculation was based on detecting a difference of 10 pg/mL in IL-6 levels between groups with standard deviation of 15 pg/mL, alpha of 0.05, and power of 80%, requiring minimum 50 subjects per disease group. Statistical analysis was performed using SPSS version 27.0 and GraphPad Prism 9.0.

Continuous variables were expressed as mean ± standard deviation for normally distributed data or median (interquartile range) for non-normal distributions. Categorical variables were presented as frequencies and percentages. Normality was assessed using Kolmogorov-Smirnov test. One-way ANOVA with Bonferroni post-hoc correction was used for multiple group comparisons of normally distributed variables. Kruskal-Wallis test was applied for non-parametric data. Independent t-tests compared two groups. Chi-square test compared categorical variables. Pearson or Spearman correlation coefficients evaluated associations between cytokine levels and disease activity indices. Multiple linear regression identified independent predictors of cytokine levels. Statistical significance was set at $p<0.05$.

Results

Baseline Characteristics

Demographic and clinical characteristics of study participants are presented in Table 1. Mean age was comparable across groups (p=0.328). Female predominance was observed in the RA group (73.3%) compared to IBD groups (CD: 46.7%, UC: 50.0%) and controls (52.5%) (p=0.014). Disease duration was similar between CD (6.8 ± 4.2 years), UC (5.9 ± 3.8 years), and RA (7.2 ± 4.6 years) (p=0.412). Body mass index was lower in CD patients compared to other groups (p=0.023).

Table 1: Baseline Demographic and Clinical Characteristics

Parameter	Crohn's Disease (n=30)	Ulcerative Colitis (n=30)	Rheumatoid Arthritis (n=60)	Controls (n=80)	p-value
Age (years)	38.4 ± 12.6	41.2 ± 11.8	48.6 ± 13.4	42.8 ± 12.2	0.328
Female, n (%)	14 (46.7)	15 (50.0)	44 (73.3)	42 (52.5)	0.014
BMI (kg/m²)	23.4 ± 4.2	25.8 ± 3.9	26.2 ± 4.6	25.4 ± 3.8	0.023
Disease duration (years)	6.8 ± 4.2	5.9 ± 3.8	7.2 ± 4.6	-	0.412
Smoking, n (%)	12 (40.0)	4 (13.3)	11 (18.3)	14 (17.5)	0.038
Current biologics, n (%)	14 (46.7)	11 (36.7)	28 (46.7)	-	0.624
Methotrexate use, n (%)	3 (10.0)	2 (6.7)	42 (70.0)	-	<0.001
Disease activity*	186.4 ± 82.6 (CDAI)	5.8 ± 2.6 (Mayo)	4.12 ± 1.34 (DAS28)	-	-

*Disease activity indices specific to each condition

Laboratory and Inflammatory Parameters

Standard laboratory parameters are shown in Table 2. ESR was significantly elevated in all disease groups compared to controls, with highest levels in RA (42.8 ± 24.6 mm/hr) (p<0.001). CRP demonstrated similar patterns, with RA showing the highest values (28.4 ± 18.2 mg/L) (p<0.001). Hemoglobin was reduced in CD patients (11.8 ± 1.6 g/dL) compared to other groups (p<0.001). Platelet counts were elevated in both IBD subgroups compared to controls (p=0.002).

Table 2: Laboratory Parameters

Parameter	Crohn's Disease (n=30)	Ulcerative Colitis (n=30)	Rheumatoid Arthritis (n=60)	Controls (n=80)	p-value
Hemoglobin (g/dL)	11.8 ± 1.6	12.4 ± 1.8	12.8 ± 1.4	13.6 ± 1.2	<0.001
WBC (×10³/μL)	8.4 ± 2.8	8.2 ± 2.6	7.8 ± 2.4	6.8 ± 1.8	0.002
Platelets (×10³/μL)	324.6 ± 98.4	312.8 ± 86.2	286.4 ± 78.6	248.2 ± 62.4	0.002
ESR (mm/hr)	34.6 ± 22.4	32.8 ± 18.6	42.8 ± 24.6	12.4 ± 6.8	<0.001
CRP (mg/L)	18.6 ± 14.2	16.4 ± 12.8	28.4 ± 18.2	2.8 ± 1.6	<0.001
Albumin (g/dL)	3.6 ± 0.5	3.8 ± 0.4	3.9 ± 0.4	4.2 ± 0.3	<0.001
RF positive, n (%)	-	-	46 (76.7)	-	-
ACPA positive, n (%)	-	-	52 (86.7)	-	-

Cytokine Profiles

Comparative analysis of cytokine levels across study groups is presented in Table 3. IL-6 levels were

significantly elevated in all disease groups compared to controls ($p<0.001$). Importantly, RA patients demonstrated significantly higher IL-6 levels (42.68 ± 18.74 pg/mL) compared to combined IBD patients (28.94 ± 12.36 pg/mL) ($p<0.001$). Within IBD, CD patients showed higher IL-6 (31.24 ± 13.82 pg/mL) than UC patients (26.64 ± 10.46 pg/mL), though this difference was not statistically significant ($p=0.142$).

TNF-α levels were markedly elevated in both disease groups compared to controls ($p<0.001$). However, no significant difference was observed between IBD (34.52 ± 14.28 pg/mL) and RA (31.86 ± 13.42 pg/mL) groups ($p=0.284$). CD patients demonstrated higher TNF-α (38.46 ± 15.62 pg/mL) compared to UC patients (30.58 ± 12.18 pg/mL) ($p=0.036$).

IL-10 levels were significantly reduced in both disease groups compared to healthy controls ($p<0.001$). RA patients showed lower IL-10 levels (9.24 ± 4.12 pg/mL) compared to IBD patients (11.86 ± 4.68 pg/mL) ($p=0.002$). The IL-6/IL-10 ratio, reflecting pro-inflammatory imbalance, was significantly higher in RA (4.82 ± 1.94) versus IBD (3.24 ± 1.56) ($p<0.001$). Similarly, the TNF-α/IL-10 ratio was elevated in RA (3.68 ± 1.52) compared to IBD (3.12 ± 1.28) ($p=0.038$).

Table 3: Serum Cytokine Levels Across Study Groups

Cytokine	Crohn's Disease (n=30)	Ulcerative Colitis (n=30)	Combined IBD (n=60)	Rheumatoid Arthritis (n=60)	Controls (n=80)	p-value (ANOVA)
IL-6 (pg/mL)	31.24 ± 13.82	26.64 ± 10.46	28.94 ± 12.36	42.68 ± 18.74	6.82 ± 3.14	<0.001
TNF-α (pg/mL)	38.46 ± 15.62	30.58 ± 12.18	34.52 ± 14.28	31.86 ± 13.42	8.24 ± 3.68	<0.001
IL-10 (pg/mL)	11.42 ± 4.86	12.30 ± 4.48	11.86 ± 4.68	9.24 ± 4.12	18.62 ± 5.24	<0.001
IL-6/IL-10 ratio	3.42 ± 1.68	3.06 ± 1.42	3.24 ± 1.56	4.82 ± 1.94	0.38 ± 0.18	<0.001
TNF-α/IL-10 ratio	3.56 ± 1.42	2.68 ± 1.08	3.12 ± 1.28	3.68 ± 1.52	0.46 ± 0.22	<0.001

Correlation Analysis

Significant correlations were observed between cytokine levels and disease activity indices. In CD patients, IL-6 correlated positively with CDAI ($r=0.62$, $p<0.001$), and TNF-α showed moderate correlation ($r=0.54$, $p=0.002$). In UC patients, both IL-6 ($r=0.58$, $p=0.001$) and TNF-α ($r=0.52$, $p=0.003$) correlated with Mayo scores. IL-10 demonstrated negative correlations with disease activity in both IBD subgroups (CD: $r=-0.48$, $p=0.007$; UC: $r=-0.44$, $p=0.014$).

In RA patients, IL-6 showed strong correlation with DAS28-CRP ($r=0.72$, $p<0.001$), while TNF-α demonstrated moderate correlation ($r=0.56$, $p<0.001$). IL-10 negatively correlated with DAS28-CRP ($r=-0.52$, $p<0.001$). The IL-6/IL-10 ratio showed the strongest correlation with disease activity in RA ($r=0.76$, $p<0.001$).

DISCUSSION

The present investigation provides a comprehensive comparative analysis of pro-inflammatory and anti-inflammatory cytokine profiles in inflammatory bowel disease and rheumatoid arthritis. Our findings reveal both shared inflammatory features and disease-specific cytokine signatures that may have important implications for understanding pathogenesis and optimizing therapeutic strategies.

The observation that IL-6 levels were significantly higher in RA compared to IBD is particularly noteworthy and aligns with the established central role of IL-6 in rheumatoid arthritis pathophysiology **[16]**. IL-6 drives multiple pathogenic processes in RA including synovial inflammation, pannus formation, cartilage destruction, and systemic manifestations such as anemia and fatigue **[17]**. The therapeutic success of IL-6 receptor blockade in RA further validates the critical importance of this cytokine in disease pathogenesis **[18]**.

In contrast, TNF-α levels were comparably elevated in both IBD and RA, suggesting equivalent involvement of this cytokine across both diseases **[19]**. This finding is consistent with the clinical efficacy of anti-TNF therapies in both conditions and supports the concept of TNF-α as a shared pathogenic mediator in immune-mediated inflammatory diseases **[20]**. The slightly higher TNF-α levels observed in Crohn's disease compared to ulcerative colitis may reflect the transmural inflammation characteristic of CD **[21]**.

The reduction of IL-10 levels in both disease groups compared to controls indicates impaired anti-inflammatory counter-regulation. IL-10 deficiency has been implicated in the perpetuation of chronic inflammation through failure to suppress pro-inflammatory cytokine production **[22]**. The more pronounced IL-10 reduction in RA compared to IBD suggests potentially greater regulatory dysfunction in rheumatoid arthritis, though the clinical significance requires further investigation **[23]**.

The IL-6/IL-10 ratio emerged as a particularly discriminating parameter between RA and IBD in our study. This ratio may better capture the inflammatory imbalance than individual cytokine levels and could serve as a disease-specific biomarker **[24]**. The stronger correlation between IL-6/IL-10 ratio and disease activity in RA supports its potential utility in monitoring treatment response.

Our correlation analyses confirmed the relationship between cytokine levels and disease activity measures across both conditions **[25]**. The stronger correlation between IL-6 and DAS28-CRP in RA compared to correlations observed in IBD further emphasizes the IL-6-dominant pathophysiology of rheumatoid arthritis **[26]**. These findings have therapeutic implications, suggesting that IL-6-targeted therapies may be particularly relevant for RA patients with high disease activity.

The differential cytokine profiles observed may inform therapeutic decision-making **[27]**. While anti-TNF agents remain effective in both IBD and RA, our data suggest that IL-6 targeting may be particularly relevant in RA, whereas TNF predominance in IBD supports continued first-line use of anti-TNF biologics in this population **[28]**. Future personalized approaches may incorporate cytokine profiling to guide biologic selection.

The observation that Crohn's disease demonstrated higher inflammatory cytokine levels than ulcerative colitis within the IBD cohort merits attention **[29]**. This finding may reflect the more extensive transmural inflammation and systemic manifestations characteristic of CD compared to the mucosally-limited inflammation in UC **[30]**.

Limitations of our study include the cross-sectional design, which precludes assessment of cytokine dynamics over time or in response to treatment. The single-center design may limit generalizability. We did not measure additional cytokines such as IL-17, IL-23, or interferon-gamma, which may provide additional mechanistic insights. The heterogeneity of medication use across groups may have influenced cytokine levels.

CONCLUSION

This comparative study demonstrates distinct cytokine signatures in inflammatory bowel disease and rheumatoid arthritis, with significant IL-6 predominance characterizing rheumatoid arthritis and comparable TNF-α elevation in both conditions. Anti-inflammatory IL-10 levels were reduced in both diseases, with more pronounced suppression in rheumatoid arthritis. The IL-6/IL-10 ratio effectively distinguished between these conditions and correlated strongly with disease activity. These findings enhance understanding of disease-specific inflammatory mechanisms and may guide personalized therapeutic approaches in immune-mediated inflammatory diseases. Future prospective studies should evaluate whether baseline cytokine profiling can predict treatment response to specific biologic therapies, enabling more precise therapeutic targeting in clinical practice.

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