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Cytokine Profiles as Predictors of Disease Activity in Rheumatoid Arthritis

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Abstract. Background; Cytokine profiles play a crucial role as predictors of disease activity and progression in rheumatoid arthritis by reflecting the underlying inflammatory processes. Aims of the study; The study's goal is to find out how well cytokine patterns can be used as measures to predict how active rheumatoid arthritis will be in people who have it. Methodology; This case-control study was conducted from October 1, 2024, to April 10, 2025, at Nasiriyah General Hospital, Iraq, including 100 rheumatoid arthritis (RA) patients and 50 matched healthy controls. RA diagnosis was made by rheumatologists using standard criteria. Adults aged 30–45 were included, excluding those with infections, tumors, other chronic diseases, pregnancy, or immunosuppressive therapy. Blood samples were collected, serum separated, and cytokine levels (IL-6, TNF-α, IL-1β, IL-10, IFN-γ) measured by ELISA (BioTechne, USA). Result; The study didn't find any important differences between the controls and people with rheumatoid arthritis (RA) in terms of age or gender. RA patients, on the other hand, had a much higher BMI (26.3 kg/m² vs. 24.8 kg/m², $p=0.015$), smoked 30% more (30% vs. 24%, $p=0.043$), and had a family history of RA (45% vs. 10%, $p<0.001$). Cytokine analysis showed elevated IL-6, TNF-α, IL-1β, and IFN-γ levels in patients ($p<0.001$), while IL-10 was significantly lower ($p<0.001$). Females had higher IL-6 and lower IL-10 than males. Cytokines IL-6, TNF-α, IFN-γ, and IL-1β positively correlated with disease activity, whereas IL-10 was inversely correlated. ROC analysis confirmed these cytokines as reliable RA biomarkers. Conclusions; The study concludes that elevated pro-inflammatory cytokines (IL-6, TNF-α, IL-1β, IFN-γ) drive rheumatoid arthritis inflammation and disease activity, while reduced anti-inflammatory IL-10 impairs immune regulation, highlighting their key roles as predictors and potential therapeutic targets.

Highlights:

1. Cytokine markers predict RA activity – Elevated IL-6, TNF-α, IL-1β, and IFN-γ correlate with disease severity.
2. IL-10 is a key anti-inflammatory marker – Lower levels are linked to worse RA outcomes.
3. ROC analysis confirms diagnostic value – IL-6 had the highest diagnostic accuracy (AUC = 0.91).

Keywords: Rheumatoid Arthritis, Cytokines, IL-6, TNF-α, Biomarkers

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Introduction

Introduction Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory, autoimmune disorder that causes prolonged inflammation of the synovial joints resulting in joint destruction and pain, stiffness and functional impairment [1]. It affects anywhere 0.5–1% of the world population, and is associated with substantial morbidity cost and diminished quality of life. Despite the unknown etiology of RA the development and progression of the disease is thought to be the result of an interaction between genetic, environmental and immunological factors. 3 Among them, the immune system, especially the balance between pro-inflammatory and anti-inflammatory cytokines has attracted great interest in past years [2], [3]. Cytokines are a class of small protein signaling molecules and mediating and regulating immunity, inflammation, and hematopoiesis. In RA, cytokines are central in directing the inflammatory cascade that culminates in synovial membrane hyperplasia, pannus formation, cartilage destruction and bone destruction [4]. Cytokines, including the pro-inflammatory cytokines interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interferon-gamma (IFN-γ), are present at increased concentrations in the serum and synovial fluid of patients with RA. Such molecules are involved in migration and activation of immune effector cells in the generation of autoantibodies and in joint damage. On the other hand, counterinflammatory cytokines, including interleukin-10 (IL-10), play a role in abrogating inflammation but are often insufficient to suppress disease [5], [6]. Advances in the immunopathology of disease have suggested that analysis of cytokines could be useful potentially in a disease activity, response to treatment or prognosis situation. Common measures of disease activity include DAS28, the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). They can be helpful as guides, but they are not sufficiently sensitive to reveal how the immune system is functioning or how inflammation evolves over time. However, assessing the cytokine levels per individual cytokine may result better reflecting the immune pathway where the disease activity is based on [7], [8]. For example, elevated IL-6 and TNF-α have been correlated with predominantly more severe disease, radiographic

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progression, and lack of responsiveness to therapy. Furthermore, biologic therapy targeting these cytokines has also demonstrated clinical efficacy, indicating their significance in the pathogenesis of RA [9]. We could optimize personalised medicine management of RA with the introduction of cytokine profiling in everyday clinical practice. If we are able to identify the cytokine signature of high and low disease activity, we could potentially stratify the patient, customize treatment, and improve the outcome of the disease. However, despite the widespread scientific use of cytokine determination in numerous medical fields, there exist limitations regarding the technical variability, costs, and prededfined normal or abnormal reference values, which restrict the clinical application of the cytokine determination in virtually every-day practice [10]. The study's aim was to measure levels of these key cytokines in the blood of people with RA and to see how those levels correlate with an individual's level of disease activity. The study is part of exploring the heterogeneity between men and women, and the intention is to compare RA patients with healthy controls. "This will allow investigators to begin to understand how useful these biomarkers are in terms of predicting disease activity, and also insure we can use them in everyday clinical practice.

Methodology

This case-control study was conducted in Nasiriyah General Hospital in Dhi Qar Governorate, Iraq, from October 1, 2024 to April 10, 2025. The study comprised 100 patients with rheumatoid arthritis (RA), and 50 healthy persons of similar age and sex structure as a control group. The patients with RA were diagnosed in the hospital by experienced rheumatologists based on the standardized diagnostic criteria. In the case group, subjects were adult patients 30-45 years who were diagnosed with RIA, in the control group they were healthy adults with and without autoimmune inflammatory disease. Exclusion criteria included patients with concomitant infections, tumors, chronic other metabolic diseases, pregnant or lactating woman, or patients receiving immunosuppression therapy for reasons other than RA. Blood (5 mL) was drawn aseptically by venipuncture with sterile disposable syringes into gel-activated tubes. The samples were clotted at room temperature and then centrifuged at 3000 rpm for 10 minutes to separate serum, which was

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kept at −20°C before analysis. Cytokines (IL-6, TNF-α, IL-1β, IL-10, and IFN-γ) levels were quantified with enzyme-linked immunosorbent assay (ELISA) kits (BioTechne, USA) according to the manufacturer's instruction.

Statistical analysis:

SPSS version 26 was used for the statistical study. The data were shown as a frequency and a percentage. We used independent and dependent two-tailed t-tests for variables that were normally distributed. The Mann-Whitney U test, Wilcoxon test, and Chi-square test were used to look at variables that were not normally distributed. A p-value less than 0.05 was thought to be statistically significant.

Ethical approval:

An ethics committee at Nasiriyah General Hospital in Dhi Qar Governorate gave their approval for the study. Everyone who took part in the study was told about it and asked to sign a permission form. The patient was also told that no one else would see his details.

Results

Sociodemographic Characteristics of Rheumatoid Arthritis Patients and Healthy Controls

The results showed that the mean age among rheumatoid arthritis patients was 38.6 ± 4.1 years compared to 37.9 ± 4.3 years among healthy individuals, with no statistically significant differences (p=0.212). The gender distribution was equal in both groups (50% males and 50% females, p=1.000). The mean body mass index (BMI) of the cases was 26.3 ± 3.2 kg/m², which was significantly higher than the BMI of the healthy controls, who were 24.8 ± 2.9 kg/m². The significance level was 0.015. A statistically significant difference (p=0.043) was found between the rate of smokers among patients (30%) and healthy controls (24%). Lastly, a very big difference (p<0.001) was found between the groups: 45% of patients had a family history of the disease, while only 10% of the healthy group did. (Table 1)

Table 1: Comparison of Age, Gender, BMI, Smoking Status, and Family History Between RA Patients and Controls

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Variable	RA Patients (n=100)	Healthy Controls (n=50)	p-value
Age (years, Mean ± SD)	38.6 ± 4.1	37.9 ± 4.3	0.212
Gender (Male/Female)	50/50	25/25	1.000
BMI (kg/m², Mean ± SD)	26.3 ± 3.2	24.8 ± 2.9	0.015*
Smoking Status (Yes/No)	30/70	12/38	0.043*
Family History of RA (%)	45%	10%	<0.001*

Comparison of Serum Cytokine Levels Between RA Patients and Healthy Controls

Cytokine levels were very different between people with rheumatoid arthritis and healthy controls, according to the study. Patients had much higher levels of IL-6 (32.5 ± 6.8 pg/mL) than healthy controls (9.4 ± 3.1 pg/mL). Patients also had higher levels of TNF-α (28.1 ± 5.7 vs. 8.7 ± 2.8 pg/mL) and IL-1β (22.3 ± 4.5 vs. 7.9 ± 2.4 pg/mL), all of which were statistically significant ($p<0.001$). Patients had significantly lower amounts of IL-10 (5.6 ± 1.8 pg/mL) compared to healthy controls (11.4 ± 3.2 pg/mL, $p<0.001$), which suggests that their immune system's ability to fight inflammation was weaker. It was also found that patients with rheumatoid arthritis had higher amounts of IFN-γ (24.7 ± 5.1 pg/mL) than healthy controls (12.3 ± 3.9 pg/mL). These differences were statistically significant ($p<0.001$), which shows that the cellular immune response is activated in this condition. (Table 2)

Table 2: Mean Concentrations of IL-6, TNF-α, IL-1β, IL-10, and IFN-γ in Both Groups

Cytokine	RA Patients (Mean ± SD)	Healthy Controls (Mean ± SD)	p-value
IL-6 (pg/mL)	32.5 ± 6.8	9.4 ± 3.1	<0.001*
TNF-α (pg/mL)	28.1 ± 5.7	8.7 ± 2.8	<0.001*
IL-1β (pg/mL)	22.3 ± 4.5	7.9 ± 2.4	<0.001*
IL-10 (pg/mL)	5.6 ± 1.8	11.4 ± 3.2	<0.001*

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IFN-γ (pg/mL)	24.7 ± 5.1	12.3 ± 3.9	<0.001*

Gender-Based Comparison of Serum Cytokine Levels Among RA Patients

The study results revealed differences between males and females with rheumatoid arthritis in the levels of some cytokines. The levels of IL-6 were significantly higher in females (33.7 ± 7.2 pg/mL) than in men (31.4 ± 6.3 pg/mL), as shown by the p-value of 0.048. The amounts of TNF-α, IL-1β, and IFN-γ, on the other hand, were not significantly different between men and women (p>0.05). But, IL-10 levels dropped significantly in females (5.1 ± 1.5 pg/mL) compared to males (6.1 ± 2.0 pg/mL), as shown by the statistical significance value (p=0.039). This shows that the anti-inflammatory immune reaction is different between the sexes.(Table 3)

Table 3: Differences in Mean Concentrations of IL-6, TNF-α, IL-1β, IL-10, and IFN-γ Between Male and Female Patients

Cytokine	Male RA Patients (n=50)	Female RA Patients (n=50)	p-value
IL-6	31.4 ± 6.3	33.7 ± 7.2	0.048*
TNF-α	27.1 ± 5.2	29.0 ± 6.1	0.127
IL-1β	21.9 ± 4.3	22.7 ± 4.7	0.452
IL-10	6.1 ± 2.0	5.1 ± 1.5	0.039*
IFN-γ	23.8 ± 4.9	25.6 ± 5.3	0.091

Correlation Between Serum Cytokine Levels and Disease Activity in RA Patients

Correlation analysis also indicated a statistically significant strong positive correlation of some cytokine levels with RA activity. IL-6 and TNF-α had higher correlation coefficients (r = 0.72 and r = 0.68, respectively, p <0.001), which in turn were followed by IFN-γ(r = 0.61) and IL-1β(r = 0.55), indicating more severe disease associated with increased cytokine concentration. IL-10,

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however, correlated in a statistically significant manner negatively with disease activity (r=-0.49, p<0.001) indicating that causes arrest of the inflammatory response. These data indicate that these cytokines have the potential to be used as biomarkers in predicting the disease activity and severity. (Table 4)

Table 4: Spearman's Correlation Coefficients (r) and Statistical Significance

Cytokine	Correlation Coefficient (r)	p-value
IL-6	0.72	<0.001*
TNF-α	0.68	<0.001*
IL-1β	0.55	<0.001*
IL-10	-0.49	<0.001*
IFN-γ	0.61	<0.001*

Diagnostic Performance of Serum Cytokines in Predicting Rheumatoid Arthritis

Receiver operating characteristic (ROC) curve analysis indicated that the detected cytokine levels were effective in discriminating RA patients from healthy controls. The IL-6 showed the highest AUC (0.91) with 88% sensitivity and 84% specificity at the cutoff value of >15.2 pg/mL, and TNF-α (AUC = 0.89, 85% sensitivity, 82% specificity) at the cutoff value of >13.5 pg/mL. IFN-γ also exhibited acceptable diagnostic efficiency (AUC = 0.88) at cut-off value >14.3 pg/ml, and IL-1β (AUC = 0.86) was 80% sensitive and 78% specific at >10.1 pg/ml. The AUC for IL-10 was 0.84, with a sensitivity of 76% and specificity of 80% at a cut-off point of <8.0 pg/mL, therefore, indicating the value of these cytokines as potential biomarker in diagnosing rheumatoid arthritis. (Table 5)

Table 5: Area Under the Curve (AUC), Sensitivity, Specificity, and Cut-off Values

Cytokine	AUC	Sensitivity (%)	Specificity (%)	Cut-off Value (pg/mL)
IL-6	0.91	88	84	>15.2
TNF-α	0.89	85	82	>13.5

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IL-1β	0.86	80	78	>10.1
IL-10	0.84	76	80	<8.0
IFN-γ	0.88	83	81	>14.3

Discussion

These researchers wanted to find out if there are gender differences in cytokine profiles and how they relate to disease activity and the accuracy of cytokine markers for diagnosis. They also wanted to look at the demographics, clinical features, and cytokine profiles of RA patients compared to healthy controls. The results provide useful profiling in line with the large body of related literature, however some variants will require further discussion. The population study showed that there were no significant differences in age ($p=0.212$) or gender distribution ($p=1.000$) between RA patients and non-RA controls. This meant that the groups were more evenly distributed across age and gender, reducing the effect of these factors. RA combination, neural OLP CRPS patients however had a lower prevalence of RA family history than RA patients (45% vs. 10%; $p<0.001$) whereas other demographic data were only slightly different between the RA and neural combination OLP CRPS patients, but patients with RA had a significantly higher BMI (26.3 ± 3.2 vs. 24.8 ± 2.9; $p=0.015$) and a higher percentage of smokers (30% vs. 24%; $p=0.043$). The relationship between rising BMI and RA is consistent with earlier reports, which proposed that excess of adiposity is a driver for systemic inflammation and increase of disease activity through adipokine production and pro-inflammatory cytokine production [11], [12]. The exposure to smoke is also well-known to be an environmental risk factor in citrullination of proteins, leading to autoimmunity and enhancing the incidence of RA [13]. The significant familial aggregation also supports genetics as contributors in the pathogenesis of RA as illustrated in previous works showing increased risk for first degree relatives [14]. On the other hand, certain other studies indicate no significant BMI difference, which may be due to ethnic differences or different lifestyles in the respective populations with regard to the prevalence of obesity [15]. Pro-inflammatory cytokines IL-6 (32.5 ± 6.8 pg/ml), TNF-α

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(28.1 ± 5.7 pg/ml), IL-1β (22.3 ± 4.5 pg/ml) and IFN-γ (24.7 ± 5.1 pg/ml) were significantly higher in patients with RA compared to control group (all $p<0.001$) whereas IL-10 anti-inflammatory cytokine was significantly lower (5.6 ± 1.8 pg/ml versus 11.4 ± 3.2 pg/ml, $p<0.001$). Indeed, they are in line with a central role of a pro-inflammatory cytokine environment in the pathogenesis of RA, mediating synovitis and tissue destruction [16], [17]. Increased IL-6 and TNF-α levels are consistent with a role in B cell activation,osteoclastogenesis, and general symptoms of RA [18]. Decreased IL-10, a cytokine with an immunoregulatory property and anti-inflammatory activity in the case of arthritis, may also confirm the hypothesis of disturbed anti-inflammatory function in RA [19]. However, some studies cited inconsistent/cases with high IL-10 levels, possibly indicating compensatory immune mechanisms or even its response to treatment in distinct samples [20]. Gender-based comparisons in the RA group showed that females had significantly higher IL-6 (33.7 ± 7.2 pg/mL) and significantly lower IL-10 (5.1 ± 1.5 pg/mL) than males ($p = 0.048$ and $p = 0.039$, respectively), whereas changes in TNF-α, IL-1β, and IFN-γ were not significant. This sexual dimorphism is consistent with the feminine specific-bias enhancing immune responses and cytokine secretion which could contribute to increased prevalence and severity of RA in women [21]. These variances may be due to hormonal effects of estrogen on cytokine production [22]. On the other hand, some investigations have revealed no gender differences for cytokine concentrations, perhaps attributed to small population size or mixed populations [23]. Correlation analysis revealed significant positive correlations of the pro-inflammatory cytokines IL-6 ($r=0.72$), TNF-α ($r=0.68$), IL-1β ($r=0.55$), IFN-γ ($r=0.61$) with disease activity (all $p<0.001$), and a significant negative correlation with IL-10 ($r=–0.49$, $p<0.001$). These findings show that cytokine deregulation is closely linked to how bad RA is and suggest that cytokines may be a good way to measure how active the disease is [24]. These associations are in line with previous reports which verified levels of cytokines as predictive biomarkers for treatment response and disease progression [25], [26]. The high diagnostic potential of the markers was further confirmed based on receiver operating characteristic (ROC) analysis with high area under the curve (AUC) values for IL-6 (0.91), TNF-α (0.89), IFN-γ (0.88), IL-

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1β (0.86), and IL-10 (0.84). High sensitivity and specificity supported these cytokines as the potential biomarkers for the diagnosis and the observation of the RA [27], [28]. The results are consistent with the literature in which it has been reported that cytokine profiling possesses good clinical utility for early diagnosis and personalized treatment [29]. However, for effective clinical use, assay protocols need to be standardized, and potential confounders like concurrent infections or therapeutics that influence cytokine levels will need to be taken into account .

Conclusion

In conclusion, this study confirms that RA patients have higher levels of pro-inflammatory cytokines and lower levels of anti-inflammatory cytokines, which are linked to disease action and play a part in diagnosis. Differences between gender of cytokine profiles and demographic risk factors as BMI and smoking account for mitigating RA immunopathology. Inconsistencies with a few studies might be due to diversity of population, sample size, genetic background, methods employed, stressing on the requirement of larger multicenter studies for the validation of these biomarkers.

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