Immune Interaction between Interleukin-22 and Interleukin-26 and Its Relationship with Rheumatoid Arthritis Disease Activity

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Abstract:

Rheumatoid arthritis (RA) is a chronic autoimmune condition in which persistent synovial inflammation gradually alters joint structure and function. Increasing attention has been directed toward Th17-related cytokines—particularly interleukin-22 (IL-22) and interleukin-26 (IL-26) because of their potential contribution to sustained inflammation and disease progression in RA. This study aimed to quantify serum IL-22 and IL-26 levels in patients with RA and to determine their relationship with disease activity assessed using the DAS28 score. A case-control study was conducted involving 50 RA patients and 35 age- and sex-matched healthy individuals. Serum IL-22 and IL-26 concentrations were measured using ELISA, while disease activity was assessed using DAS28. Appropriate statistical tests were applied to compare groups and examine correlations. Patients with RA exhibited markedly elevated IL-22 levels (178.5 ± 61.3 pg/mL) compared with controls (96.4 ± 39.7 pg/mL, $p < 0.001$). Likewise, IL-26 concentrations were significantly higher in RA patients (142.7 ± 55.9 pg/mL) than in controls (71.8 ± 28.6 pg/mL, $p < 0.001$). Serum IL-22 showed a moderate positive correlation with DAS28 ($r = 0.49$, $p < 0.001$), and IL-26 demonstrated a slightly stronger association ($r = 0.53$, $p < 0.001$). A notable correlation was also observed between IL-22 and IL-26 themselves ($r = 0.57$, $p < 0.001$). The clear elevation of IL-22 and IL-26 in RA patients, along with their strong correlations with disease activity, supports their potential role as useful supportive biomarkers for monitoring inflammatory burden and evaluating disease progression.

Keywords: Rheumatoid Arthritis, IL-22, IL-26, Cytokines, DAS28, Inflammatory.

1. Introduction

Rheumatoid arthritis (RA) can be described as a chronic systemic autoimmune disorder, which is characterised by the presence of chronic inflammation of the synovial membrane of the joints, which in a gradual progression result in joint pain, swelling and stiffness particularly of the small hands and feet joints. Unless this inflammation is managed, cartilage and bones are gradually and irreversibly damaged by the disease, which has a negative impact on the motor functions and quality of life (Xie et al., 2015; McInnes and Schett, 2011; Roeleveld and Koenders, 2015).

The disease arises as a result of a complex interaction between genetic predisposition, in particular alleles associated with HLA class II genes (HLA-DRB1), environmental factors such as smoking and some microbial stimuli, as well as disrupted immune regulatory mechanisms. This reaction leads to uncontrolled activation of the immune system and the occurrence of a chronic intra-articular inflammatory response.

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(Lundström et al., 2009; Too et al., 2012).

Clinically, rheumatoid arthritis manifests with morning stiffness that lasts more than an hour, with symmetrical injury to the joints, along with pain and swelling. It is also a systemic disease that may be associated with multiple extraarticular manifestations, including general fatigue and anaemia, and its effect may extend to the lungs and cardiovascular system (Smolen et al., 2016; Nadi et al., 2014). Epidemiological studies indicate that women are about three times more likely to contract the disease than men, indicating a possible role for hormonal factors, especially estrogen, along with genetic factors, in determining the severity and clinical course of the disease (Cross et al., 2014).

Traditional laboratory indicators like erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) still have limited sensitivity and quality and do not accurately reflect true inflammatory activity within the joints or immune alteration during disease progression, despite notable advancements in the diagnosis and treatment of the disease, including the introduction of biological therapies and targeted therapies. As a result, there is now more interest in studying cytokines as crucial components in the pathogenesis of rheumatoid arthritis and as possible indicators of disease activity (Tanaka et al., 2014; Kondo et al., 2022).

Cytokines play an essential role in the initiation and continuation of arthritis, as the imbalance between stimulating and inhibitory cytokines contributes to the infiltration of immune cells into the synovial membrane and the activation of synovial fibroblasts, leading to the formation of synovial granular tissue (Pannus) and progressive destruction of the joint (Kondo et al., 2022; Roeleveld & Koenders, 2015).

In this context, the axis of Th17 cells emerged as one of the main drivers of immunoinflammation in rheumatoid arthritis, as these cells secrete a group of inflammatory cytokines, most notably interleukin-22 (IL-22) and interleukin-26 (IL-26)(Roeleveld & Koenders, 2015; Firestein & McInnes, 2017). Interleukin-22 (IL-22) is also linked with bone erosion stimulation and synovial hyperplasia and could have a regulating effect in the early stages of the disease, and the pathogenic effects are also seen in the advanced stages (Ikeuchi et al., 2005).

Interleukin-26 (IL-26) is a potent inflammatory cytokine, and its roles in stimulating dendritic cells and mononuclear cells to promote the production of other inflammatory cytokines including tumour necrosis factor alpha (TNF-α) and interleukin- 6 (IL-6). It also participates in the magnification of the inflammatory pathway in the joint and can possibly contribute to the connection of the innate immunity to the acquired immunity (Corvaisier et al., 2012; Wang et al., 2023).

It was reported that the levels of both IL-22 and IL-26 in the serum were positively correlated with the disease activity, and these cytokines are rising along with the process of the inflammation and the changes in the deterioration of the joints, which can indicate that agglomerate them can be used as biomarkers to measure the disease activity and follow the disease progress (Altai, 2024; Wang et al., 2023). Up to now, the results remain incongruent across the various studies, and further research is required to establish the exact role of the IL-22 and IL-26 in the pathophysiology of RA (Firestein and McInnes, 2017; Xie et al., 2015).

Based on the findings indicated above, the current study is aimed at estimating the serum IL-22 and IL-26 levels of the patients with rheumatoid arthritis as well as to examine the relationship of the two with the disease activity with a view of contributing to the further explanation of the immune pathogenesis of the disease and selecting the possible candidates as biomarkers to help with monitoring the disease and guiding the future treatment techniques.

2. Materials and Methods

2.1 The Design and Location of The Study

Measurement of the serological levels of interleukin-22 (IL-22) and interleukin-26 (IL-26) in rheumatoid arthritis patients, as well as an analysis of the correlation between these levels and disease activity, were the objectives of this case-control study. The study included fifty patients diagnosed with rheumatoid arthritis, along with thirty-five healthy people who formed the control group, taking into account the convergence of age and

gender as much as possible to reduce the impact of confounding factors on the results. From November 2025 to January 2026, the study was carried out in Babylon Governorate's Marjan Medical City. The DNA Research Centre at the University of Babylon's Scientific Research Ethics Committee officially approved the study. Prior to their inclusion in the study, all participants provided written informed consent after being fully informed about the study's goals, methods, and possible risks.

2.2 Study Sample

The study included fifty patients diagnosed with rheumatoid arthritis according to the criteria of the American College of Rheumatology and the European Association for the Control of Rheumatism (ACR/EULAR), distributed to (38 females and 12 males), with an age proximity among the members of the group. The study also included thirty-five healthy people who formed the control group, by 25 females and 10 males, with a similar distribution of sex and no statistically significant difference in age between the two groups.

Patients with other autoimmune diseases, acute inflammatory conditions, or chronic systemic diseases that may affect cytokine levels were excluded to reduce the influence of confounding factors and ensure the validity of results. Sample size adequacy was assessed using G*Power software (version 3.1). Based on a medium effect size (d = 0.5), a two-tailed alpha of 0.05, and a desired power of 0.80, a minimum of 45 patients per group was required. The current sample of 50 RA patients and 35 controls was considered adequate for the primary objectives of this exploratory study.

2.3 Clinical Evaluation and Determination of Disease Activity

All patients underwent an organised clinical evaluation that included taking a detailed medical history and a full clinical examination of the joints by a rheumatologist. Disease Activity Was Evaluated Using the Disease Activity Index In 28 Joints (Disease Activity Score-28, DAS28), Which Is One of The Most Used Indicators to Estimate the Severity of Rheumatoid Arthritis Activity in Clinical Practice. This assessment was carried out at the time of sampling and before any change in the treatment plan was made, to ensure that the results reflected the actual medical condition of the patients.

2.4 Collection of Blood Samples and Preparation of Serum

(5 ml) of venous blood was drawn from each participant using anticoagulant-free sterile tubes. The samples were left to coagulate at room temperature, then the serum was separated by centrifuge at a speed of 3,000 rpm for 10 minutes. Divide the serum into small parts (Aliquots) and store at a temperature of -20°C until laboratory analyses are carried out, in order to avoid repeated freezing and thawing processes and maintain the stability of cytokines.

2.5 Measurement of Serous Cytokines

Serum concentrations of IL-22 and IL-26 were quantified using commercially available sandwich ELISA kits following the manufacturer's instructions. The Human IL-22 ELISA Kit (Abcam, Cambridge, UK; catalog no. ab100531; detection range: 15.6–1000 pg/mL; sensitivity: <10 pg/mL) and the Human IL-26 ELISA Kit (Abcam; catalog no. ab213074; detection range: 31.25–2000 pg/mL; sensitivity: <20 pg/mL) were used. Intra-assay and inter-assay coefficients of variation (CV%) were <8% and <12%, respectively, for both assays. Each sample was analyzed in duplicate, and the mean absorbance value was used for concentration calculations. Standard curves were generated using the recombinant protein standards supplied with each kit, and optical density was measured at 450 nm using a microplate spectrophotometer. All analyses were performed in a single analytical session at the Immunology Laboratory, DNA Research Centre, University of Babylon, to minimize inter-assay variability.

2.6 Correlation Analysis

The relationship between the serum levels of both IL-22 and IL-26 and the disease activity index (DAS28) was analysed using a cross-linkage analysis, with the aim of exploring the possible relationship between immune activity and severity of rheumatoid arthritis activity at the time of evaluation, without assuming a direct causal relationship.

3. Statistical Analysis

SPSS Version 26 (IBM, USA) was used to statistically analyze

the data. Whereas categorical data were reported as percentages and frequencies, continuous variables were shown as mean ± standard deviation. The Shapiro-Wilk test was used to establish the normality of cytokine distributions prior to performing parametric testing. This test supported the use of parametric methods by confirming approximate normality for both IL-22 ($W = 0.961$, $p = 0.089$) and IL-26 ($W = 0.957$, $p = 0.071$) in the patient group. The cytokine levels of the patients and the control group were compared using an independent samples t-test. Pearson's correlation coefficient was applied to assess the associations between serum cytokine concentrations and DAS28 scores. Multivariate linear regression analysis was performed to assess the independent contribution of IL-22 and IL-26 to DAS28 variability after adjusting for age and sex. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of each cytokine in distinguishing patients with rheumatoid arthritis from the control group, with the area under the curve (AUC) reported as a measure of discriminatory ability. Statistical significance was defined as $p < 0.05$ for all analyses.

4. Results and Discussion

4.1 Results

4.1.1 Demographic and Clinical Characteristics of the Participants

50 rheumatoid arthritis patients and 35 age- and sex-matched healthy controls participated in the study. There was no statistically significant difference between the two groups ($p = 0.68$), with the mean age of patients being 45.2 ± 9.1 years and that of the control group being 44.6 ± 8.7 years.

Additionally, the distribution of sex between patients and controls did not differ significantly (male/female: 12/38 vs. 10/25, respectively; $p = 0.74$) (Table 1).

Rheumatoid arthritis patients' DAS28 values varied from 2.4 to 6.8, with a mean of 4.6 ± 1.2, suggesting that the study population's disease activity varied (Table 1).

Table 1. Demographic and Clinical Characteristics of Participants.

Variable	RA Patients (N =50)	Controls (N = 35)
Age (years), mean ± SD	45.2 ± 9.1	44.6 ± 8.7
Sex (male/female), n	12/38	10/25
DAS28, mean ± SD	4.6 ± 1.2	-
DAS28 range (min–max)	2.4-6.8	-

Note: DAS28 scores were assessed only in patients with rheumatoid arthritis, as this index is not applicable to healthy controls.

4.1.2 IL-22 levels

The results demonstrated a significant increase in serum interleukin-22 (IL-22) levels in patients with rheumatoid arthritis compared to the healthy control group. The mean IL-22 concentration in patients was 178.5 ± 61.3 pg/mL, whereas in healthy individuals it was 96.4 ± 39.7 pg/mL. This difference was highly statistically significant ($p < 0.001$) (Figure 1A, Table 2).

4.1.3 IL-26 levels

Similarly, rheumatoid arthritis patients' serum levels of interleukin-26 (IL-26) were considerably higher than those of controls. Patients had a mean IL-26 concentration of 142.7 ± 55.9 pg/mL, while healthy persons had a mean of 71.8 ± 28.6 pg/mL. The difference was statistically significant ($p < 0.001$) (Figure 1B, Table 2).

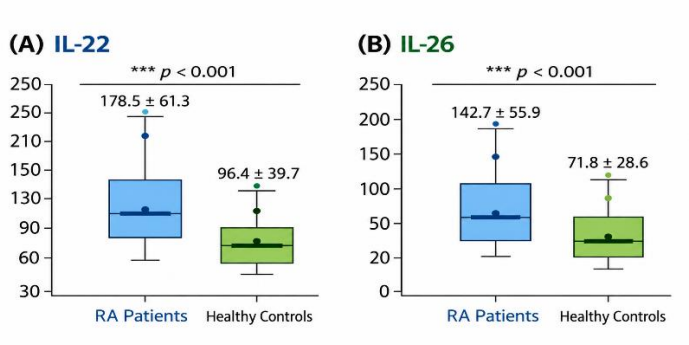

Figure 1. Box plots comparing rheumatoid arthritis patients' serum levels of interleukin-22 (IL-22) (A) and interleukin-26 (IL-26) (B) to the control group.

The first and third quartiles are represented by the boxes, the

median is shown by the line inside each box, and the minimum and maximum values are displayed by the whiskers. The mean ± standard deviation is indicated by the points. The findings show that there are substantial differences between the two groups ($p < 0.001$).

Table 2. Serum Levels of Interleukin-22 and Interleukin-26.

The Variable	RA Patients No. (50)	Control No. (35)	P Value
IL-22 (pg/mL)	178.5 ± 61.3	96.4 ± 39.7	0.001
IL-26 (pg/mL)	142.7 ± 55.9	71.8 ± 28.6	0.001

4.1.4 Relationship Between Cytokine Levels and Disease Activity

Correlation analysis revealed a significant positive association between serum interleukin-22 (IL-22) levels and DAS28 scores in patients with rheumatoid arthritis ($r = 0.49$, $p < 0.001$) (Figure 2A).

In addition, serum interleukin-26 (IL-26) levels were significantly positively correlated with DAS28 scores ($r = 0.53$, $p < 0.001$) (Figure 2B).

4.1.5 ROC Curve Analysis

ROC Curve Interpretation With an AUC of 0.82 (95% CI: 0.73–0.91, $p < 0.001$), ROC curve analysis showed that serum IL-22 performed well in discriminating RA patients from healthy controls. The sensitivity was 78% and the specificity was 80% at an ideal cut-off of 128.6 pg/mL. With an AUC of 0.79 (95% CI: 0.69–0.89, $p < 0.001$), serum IL-26 also demonstrated respectable diagnostic capacity; at a cut-off of 98.4 pg/mL, sensitivity was 74% and specificity was 77%. These results validate the potential value of both cytokines as additional diagnostic markers in the evaluation of RA activity.

4.1.6 Multivariate Regression Analysis

Multivariate linear regression analysis, after adjusting the results for age and sex, confirmed that both IL-22 ($\beta = 0.38$, $p < 0.001$) and IL-26 ($\beta = 0.41$, $p < 0.001$) were independent predictors of the DAS28 score, together accounting for approximately 34% of the variance in disease activity ($R^2 = 0.34$, $p < 0.001$). These results suggest that the associations between these cytokines and disease severity are not attributable to demographic confounding factors.

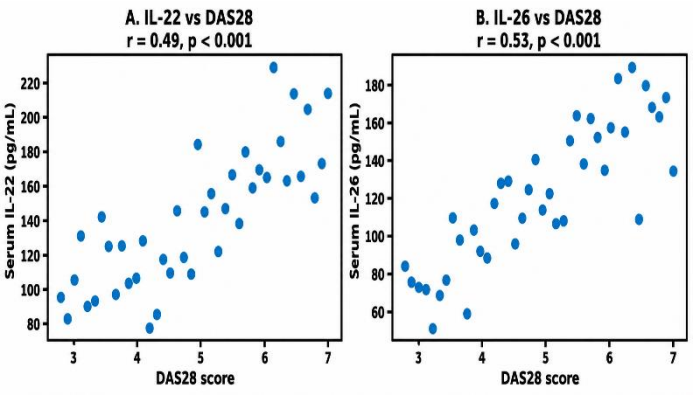

Figure 2. Correlation between serum cytokine levels and disease activity (DAS28) in patients with rheumatoid arthritis. (A) Correlation between interleukin-22 (IL-22) and DAS28. (B) Correlation between interleukin-26 (IL-26) and DAS28. Each dot represents an individual patient, and correlation coefficients with corresponding p-values are indicated.

4.1.7 Correlation between IL-22 and IL-26

Statistical analysis revealed a significant positive correlation between serum interleukin-22 (IL-22) and interleukin-26 (IL-26) levels in patients with rheumatoid arthritis ($r = 0.57$, $p < 0.001$) (Figure 3).

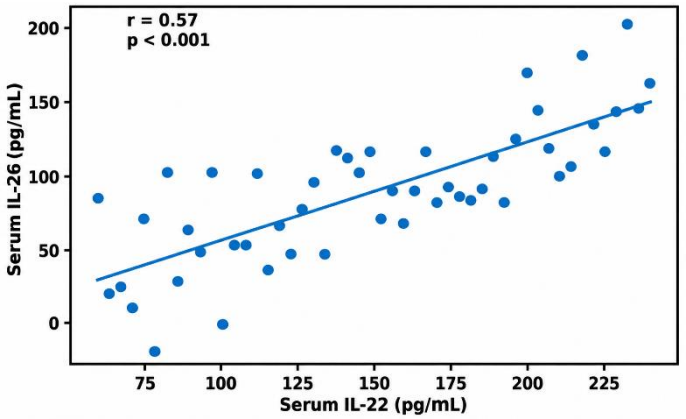

Figure 3. Correlation between serum interleukin-22 (IL-22) and interleukin-26 (IL-26) levels in patients with rheumatoid arthritis. Each dot represents an individual patient. The solid line indicates the linear regression trend. The correlation coefficient (r) and corresponding p-value are shown.

4.2 Discussion

The findings of the present research indicated a significant increase in interleukin-22 (IL-22) as well as interleukin-26 (IL-26) in the serum of patients with rheumatoid arthritis as compared to the control group, highlighting the crucial role of the two cytokines in the inflammatory and immune processes involved in the pathogenesis of rheumatoid arthritis. The findings correlate with the modern understanding of the disease which holds that rheumatoid arthritis is a chronic immune-mediated inflammatory disease with an imbalance between inflammatory and regulatory pathways within and outside the joint accompanied by excessive immune cell activation and persistent secretion of pro-inflammatory cytokines (McInnes & Schett, 2011; Firestein and McInnes, 2017).

Interleukin-22 is a Th17-related cytokine that exhibits stage-specific and context-dependent effects in inflammation. In rheumatoid arthritis, there are increasing data on the role of IL-22 in stimulating the growth of synovial fibroblasts, increasing the synthesis of inflammatory mediators and extracellular matrix remodeling enzymes, and indirectly contributing to bone erosion by modulating the osteoblast–osteoclast balance (Sonnenberg et al., 2011; Choy & Panayi, 2001; Mitra et al., 2012). The high level of IL-22 in the current study is in line with other publications that have associated this cytokine with increased disease activity, intense inflammation of the synovia, and progressive joint erosion (Ma et al., 2019; Pan et al., 2013).

Interleukin-26 (IL-26), another pro-inflammatory cytokine, that is linked to the Th17 axis characterized by its ability to activate the innate and adaptive immune response. It has already been proven that IL-26 can directly stimulate phagocytes and dendritic cells and cause the release of key inflammatory cytokines, such as IL-6, TNF-α, and IL-1β, as well as directly affect synovial cells within the joint (Corvaisier et al., 2012; Biedermann et al., 2015). The fact that IL-26 is very high in patients with rheumatoid arthritis in the study may be the indication that IL-26 contributes to the enhancement of the intra-articular inflammatory cascade that supports the hypothesis that IL-26 is a productive molecular bridge between cellular immunity and the maintenance of chronic inflammation in the disease.

It is important to mention that the relationship between interleukin-22 (IL-22) and interleukin-26 (IL-26) serum levels with the disease activity scores (DAS28) was statistically significant with a positive correlation, which illustrates how close the two cytokines are to the severity of the inflammation in the joints. This result is in line with the data provided in the scientific literature that suggested that the activation of cytokine T17 axis was directly related to high disease activity and inefficient clinical mechanisms among patients with rheumatoid arthritis (McInnes & Schett, 2017; Chen et al., 2020; Lubberts, 2015).

These data support the possibility of adopting IL-22 and IL-26 as complementary biomarkers for assessing disease activity and following up on the development of the disease, alongside established standard clinical measures. This interpretation is further supported by the ROC curve analysis, which demonstrated AUC values of 0.82 and 0.79 for IL-22 and IL-26, respectively, indicating acceptable diagnostic performance. Moreover, multivariate regression analysis confirmed that both cytokines independently predicted DAS28 scores after adjusting for age and sex (R^2 = 0.34), strengthening the evidence for their role as disease activity biomarkers beyond simple correlation.

Moreover, an analysis of the correlation showed that there was a strong positive relationship between serum IL-22 and IL-26, indicating the possibility of a synergistic effect of the two cytokines in stimulating inflammatory reactions. This interdependence can be explained by the fact that both of them belong to the Th17 axis and rely on similar intracellular signaling pathways, especially the STAT3 pathway, which is the central mechanism in the amplification and maintenance of chronic inflammation in rheumatoid arthritis (Gaffen et al., 2014; Corvaisier et al., 2012; Ouyang et al., 2008). This type of immune synergy will most probably lead to the maintenance of the inflammatory microenvironment in the joint and to progressive joint tissue damage.

Several limitations of the present study should be acknowledged. First, the sample size, while adequate for the primary exploratory objectives, is relatively modest (50 patients and 35 controls), which may limit the generalizability of the findings. Second, cytokine levels were measured in peripheral

serum only, without corresponding assessment of synovial fluid or tissue expression, which would provide more direct insight into intra-articular inflammatory dynamics. Third, detailed clinical information including disease duration, RA subtype, rheumatoid factor (RF) status, anti-citrullinated protein antibody (anti-CCP) levels, and treatment regimen were not fully incorporated into the analysis; inclusion of these variables in future studies would enable more rigorous subgroup analyses and confounder adjustment. Fourth, the cross-sectional design precludes causal inference, and the observed associations should be interpreted as correlational. Despite these limitations, this study provides meaningful evidence for the coordinated involvement of IL-22 and IL-26 in RA disease activity and establishes a foundation for future prospective and mechanistic investigations.

5. Conclusion

The results of this study revealed a significant increase in serum levels of IL-22 and IL-26 in patients with rheumatoid arthritis, which is consistent with the hypothesis of sustained activation of the Th17 axis in this disease. Both cytokins have been positively associated with DAS28 scores, which supports the argument that their serum levels reasonably reflect the severity of joint inflammatory activity. In addition, the interconnection between IL-22 and IL-26 indicated the possibility of a synergistic effect in enhancing the inflammatory response, most likely to be mediated by the combined STAT3 pathway, although verifying this role requires customised experimental studies.

At the level of clinical application, IL-22 and IL-26 can be seen as biological indicators helping to assess disease activity, not a substitute for approved indicators. However, there are limitations that must be taken into account when interpreting these results; the cross-sectional design of the study is limited to serological measurements without evaluating gene expression in the synovial membrane or monitoring the therapeutic response, which are aspects that deserve attention in future research. Therefore, longitudinal studies of larger ocular sizes, supported by histological analysis of the joints, remain necessary to determine the actual role of these two cytokins in the clinical context.

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