**Current Issues in Pharmacy and Medical Sciences**
**Formerly** ANNALES UNIVERSITATIS MARIAE CURIE-SKLODOWSKA, SECTIO DDD, PHARMACIA

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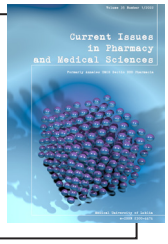

# Investigation the autoantibodies, IL-17 and IL-22 in rheumatoid arthritis patients

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**ARTICLE INFO**
Received 12 March 2024
Accepted 28 April 2025

***Keywords:***
rheumatoid arthritis (RA),
rheumatoid factor (RF),
anti-citrullinated protein antibodies (ACPA),
IL-17,
IL-22,
biological treatment,
disease stages.

**ABSTRACT**

Rheumatoid arthritis (RA) remains a prevalent and progressive autoimmune disease worldwide, associated with substantial medical, psychological, and economic burdens.
To evaluate the role of rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPA), and the proinflammatory cytokines interleukin-17 (IL-17) and interleukin-22 (IL-22) in the development of RA, and to assess their association with disease activity and response to treatment.
A case–control study was conducted involving 150 participants, including 120 patients with RA diagnosed by a specialist according to the 2010 ACR/EULAR criteria and 30 age- and sex-matched healthy controls. Serum levels of RF, ACPA, IL-17, and IL-22 were measured using enzyme-linked immunosorbent assay (ELISA).
Significantly higher serum levels of RF and ACPA were observed in patients with RA compared with the control group. Receiver operating characteristic (ROC) curve analysis identified a cut-off value of 22.95 U/mL for RF, with 97.4% sensitivity and 90% specificity, and a cut-off value of 22.45 U/mL for ACPA, with 100% sensitivity and 100% specificity. Serum levels of IL-17 and IL-22 were also significantly increased in patients with RA compared with controls. ROC analysis revealed cut-off values of 26.86 pg/mL for IL-17 and 30.16 pg/mL for IL-22, both showing high statistical significance. Stratification according to disease severity and treatment type demonstrated that IL-17 and IL-22 levels were significantly higher in patients at stage 4 and in untreated patients compared with those at earlier disease stages and those receiving chemical, biological, or combination therapies.
The present study demonstrates that RF and ACPA levels are significantly elevated in patients with RA and exhibit high diagnostic accuracy based on optimal cut-off values. In addition, IL-17 and IL-22 levels are markedly increased, particularly in patients with advanced disease and those who are untreated. These findings indicate a strong association between elevated autoantibody and cytokine levels, disease severity, and treatment response, supporting their potential utility as biomarkers in the clinical management of RA.

## INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by persistent synovial inflammation, progressive joint destruction, and systemic complications that contribute to significant morbidity and mortality [1]. The disease is driven by complex interactions among genetic, environmental, and immunological factors, leading to the activation of autoreactive immune cells and the production of autoantibodies—such as rheumatoid factor (RF), anti-citrullinated protein antibodies (ACPA), and anti-carbamylated protein antibodies (anti-CarP)—as well as pro-inflammatory cytokines [2]. In RA, autoantibodies are detected in both serum and synovial fluid (SF). Their accumulation within the joints promotes the recruitment and activation of immune cells through complement-dependent pathways or direct cellular interactions. This activation triggers the release of chemokines and pro-inflammatory cytokines, amplifying the local immune response and

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resulting in persistent synovial inflammation, accelerated tissue damage, and progressive bone loss [3].

Rheumatoid factors (RFs) are a heterogeneous group of immunoglobulins (Igs) of various isotypes and affinities that recognize the Fc portion of immunoglobulin G (IgG). Through the formation of immune complexes, RFs activate the complement system within the joint, increasing vascular permeability and stimulating the release of pro-inflammatory cytokines and chemotactic factors. This process promotes immune cell recruitment and sustains a destructive inflammatory cascade. Consequently, RFs exhibit high diagnostic value and are widely used as biomarkers in the diagnosis of RA [4]. Anti-citrullinated protein antibodies (ACPA) can stimulate fibroblasts and osteoclasts, leading to increased pain, more severe inflammation, and enhanced tissue damage. Their pathogenic activity contributes to synovial necrosis, the formation of rheumatoid nodules, and endothelial and synovial lining injury, thereby exacerbating disease progression in RA [5].

Interleukin-17 (IL-17) is a potent pro-inflammatory cytokine produced primarily by T helper 17 (Th17) cells, as well as by $CD8^+$ T cells, natural killer T (NKT) cells, and innate lymphoid cells. It plays a central role in sustaining chronic inflammation and contributes to the pathogenesis of autoimmune diseases, allergies, and certain malignancies, including autoimmune disorders such as RA [6]. In addition, IL-17 is essential for host defense against extracellular bacterial pathogens by promoting early neutrophil recruitment to sites of infection [7].

Interleukin-22 (IL-22) is produced by a variety of immune cell populations, including $CD4^+$ T cells (Th1, Th17, and Th22 subsets), $CD8^+$ T cells, and natural killer (NK) cells. As a member of the interleukin-10 cytokine family, IL-22 plays a crucial role in regulating tissue responses during inflammation and autoimmunity, acting both as a mediator of tissue protection and repair and as a driver of chronic inflammatory processes [8]. IL-22 functions as a homeostatic factor that promotes tissue integrity and regeneration; however, by enhancing innate immune responses and altering the tissue microenvironment, it may also contribute to pathological inflammation, depending on the disease context [9].

The aim of this study was to investigate the relationship between autoantibodies (RF and ACPA) and pro-inflammatory cytokines (IL-17 and IL-22) in patients with rheumatoid arthritis, and to evaluate their association with disease activity and response to treatment.

## MATERIALS AND METHODS

### Patients and control characterization

A case-control study was conducted between October 2022 and September 2023 and included a total of 150 participants. The study group comprised 120 patients with rheumatoid arthritis (RA), aged 20-79 years, of both sexes. All patients were evaluated by specialist rheumatologists at the Rheumatology Unit of Al-Sadder Teaching Hospital, Al-Najaf Province, Iraq. The diagnosis of RA was established according to the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria, based on clinical, radiological, and serological findings.

The control group consisted of 30 apparently healthy individuals, matched for age and sex, with ages ranging from 20 to 65 years.

### Inclusion and exclusion criteria

All patients diagnosed with rheumatoid arthritis (RA), irrespective of age or sex, were eligible for inclusion in the study. Patients with chronic systemic diseases, concomitant autoimmune disorders, or other forms of arthritis were excluded to ensure a homogeneous study population and to minimize potential confounding factors.

### Blood samples

Three milliliters (3 mL) of venous blood were collected from each patient and healthy control and transferred into gel-containing tubes. The samples were allowed to clot at room temperature for 30 minutes and were then centrifuged at 1,000 × g for 10 minutes to obtain serum. The separated sera were aliquoted and stored at −20 °C until analysis.

Serum IgM rheumatoid factor (IgM-RF) and anti-citrullinated protein antibodies (ACPA) were measured using commercial enzyme-linked immunosorbent assay (ELISA) kits (Alegria, Germany). Serum levels of interleukin-17 (IL-17) and interleukin-22 (IL-22) were determined using ELISA kits (MELSIN, China), in accordance with the manufacturers' instructions.

### Ethical approval

The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants prior to sample collection. The study protocol, participant information, and consent forms were reviewed and approved by the local ethics committee of the Faculty of Medicine. Ethical approval was granted on October 20, 2022 (approval number: HK/1052).

### Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 22.0. Descriptive statistics were used to summarize the data; continuous variables are presented as mean ± standard deviation (SD), whereas categorical variables are expressed as frequencies and percentages. An independent-samples t test was used to compare mean values between patients and control groups. One-way analysis of variance (ANOVA) was applied to compare means among more than two groups. Receiver operating characteristic (ROC) curve analysis was performed to assess diagnostic performance. Statistical significance was defined as a p value $\leq 0.0001$.

## RESULTS

### Demographic distribution of rheumatoid arthritis patients and control subjects

The study included 120 patients with rheumatoid arthritis (RA) and 30 healthy controls. Among the RA patients, 109 (90.8%) were female and 11 (9.2%) were male, whereas in

the control group, 26 (86.6%) were female and 4 (13.3%) were male. The difference in sex distribution between the two groups was not statistically significant (Table 1).

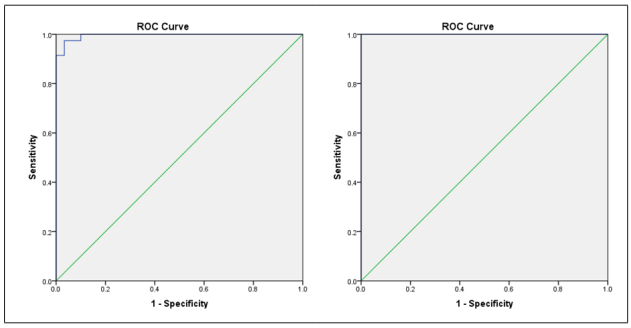
***Table 1.*** Distribution of study subjects according to gender, age and stage of disease

| Parameter | Rheumatoid arthritis patients n (%) | Control group n (%) |
|---|---|---|
| Sex | | |
| Male | 11 (9.2) | 4 (13.3) |
| Female | 109 (90.8) | 26 (86.6) |
| Age | | |
| Age mean | 47.75±14.20 | 35.9±8.36 |
| Age range | 20-79 | 20-65 |
| Stages of disease | | |
| Stage 1 | 9 (7.5%) | |
| Stage 2 | 39 (32.5%) | |
| Stage 3 | 57 (47.5%) | |
| Stage 4 | 15 (12.5%) | |

## Evaluation of RF and ACPA levels in RA patients and control group

The present study demonstrated significantly higher levels of RF and ACPA in RA patients compared with the control group ($p \leq 0.0001$). The mean RF level in RA patients was 120.57 ± 118.99 U/mL, compared with 9.33 ± 3.69 U/mL in controls. For ACPA, the mean levels were 170.12 ± 155.94 U/mL in RA patients versus 10.6 ± 3.59 U/mL in controls.

Receiver operating characteristic (ROC) curve analysis identified an optimal cut-off value of 22.95 U/mL for RF, yielding 97.4% sensitivity, 90% specificity, and an area under the curve (AUC) of 0.995. For ACPA, the cut-off value was 22.45 U/mL, with 100% sensitivity, 100% specificity, and an AUC of 1.000, as shown in Table 2 and Figure 1.




(a) RF (b) ACCP

***Figure 1.*** ROC curve analysis of (a) RF and (b) ACCP in RA patients versus control

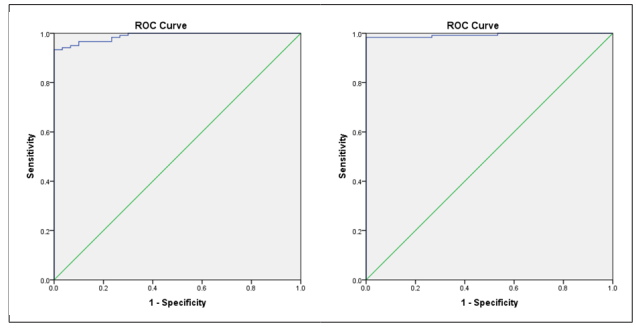
## Estimation of IL-17 and IL-22 levels in RA patients and healthy controls

Serum levels of IL-17 and IL-22 were significantly elevated in RA patients compared with healthy controls. The mean IL-17 level in RA patients was 41.36 ± 9.64 pg/mL, compared with 20.7 ± 1.04 pg/mL in controls. Similarly, the mean IL-22 level in RA patients was 46.28 ± 9.72 pg/mL, versus 21.28 ± 5.18 pg/mL in healthy controls ($p < 0.0001$ for both comparisons).

The optimal cut-off values for IL-17 and IL-22 were 26.86 pg/mL and 30.16 pg/mL, respectively, both showing high statistical significance ($p \leq 0.0001$). Their corresponding sensitivity, specificity, and area under the curve (AUC) values are presented in Table 2 and illustrated in Figure 2.

***Table 2.*** Sensitivity and specificity of RF, ACCP, IL-17 and IL-22 between RA patients and control

| Variable | AUC | P-value | Cut-off | Sensitivity | Specificity |
|---|---|---|---|---|---|
| RF | 99.5 | 0.0001 | 22.95 | 97.4% | 90% |
| ACCP | 1.000 | 0.0001 | 22.45 | 100% | 100% |
| IL-17 | 99.0 | 0.0001 | 26.86 | 97.0% | 99% |
| IL-22 | 99.3 | 0.0001 | 30.16 | 98.3% | 100% |




(a) IL-17 (b) IL-22

***Figure 2.*** ROC curve analysis of (a) IL-17 and (b) IL-22 in RA patients versus control

Analysis according to disease stage revealed that serum levels of IL-17 and IL-22 were significantly elevated in patients at stage 4 compared with earlier stages. The mean IL-17 level in stage 4 patients was 59.38 ± 8.12 pg/mL, and the mean IL-22 level was 62.61 ± 3.15 pg/mL ($p \leq 0.0001$) (Figure 3).

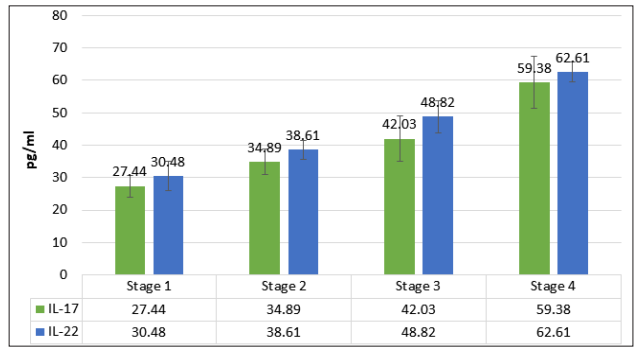



***Figure 3.*** IL-17 and IL-22 level in RA patients according to stages of disease

## Evaluation of IL-17 and IL-22 levels in RA patients according to treatment type

Serum levels of IL-17 and IL-22 were significantly higher in untreated RA patients compared with those receiving therapy. In untreated patients, the mean IL-17 level was 57.64 ± 10.21 pg/mL, and the mean IL-22 level was 59.06 ± 6.6 pg/mL.

In comparison, patients treated with chemical (conventional), biological, or combination therapy showed lower cytokine levels. For IL-17, the mean levels were 40.76 ±

5.62 pg/mL (chemical), 31.56 ± 6.12 pg/mL (biological), and 29.98 ± 10.21 pg/mL (combination therapy). For IL-22, the corresponding mean levels were 47.54 ± 6.51 pg/mL, 37.45 ± 3.06 pg/mL, and 30.48 ± 4.52 pg/mL, respectively. These differences were statistically significant ($p \leq 0.0001$).

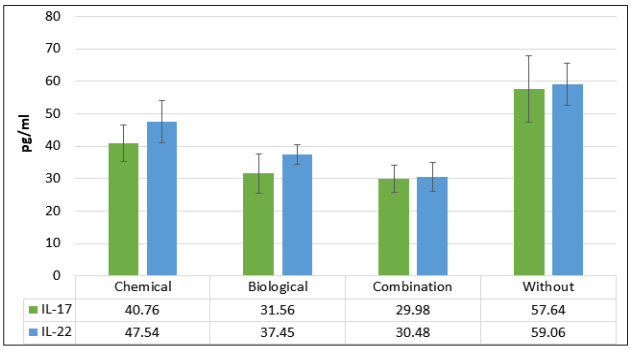



***Figure 4.*** IL-17 and IL-22 level in RA patients according to types of treatment

## DISCUSSION

The demographic characteristics of RA patients in this study (Table 1) are consistent with findings by Abd El-Ghany *et al*. [10], who reported that chronic autoimmune inflammatory RA predominantly affects females, with a female-to-male ratio ranging from 2:1 to 5:1. Similarly, the present study showed that women were more frequently affected than men. Nilsson *et al*. [11] reported that RA is two to three times more prevalent in women than in men, and that female patients often experience poorer prognoses, with higher disease activity and greater disability. Epidemiological studies also indicate that RA typically manifests in women around menopause or middle age, whereas men tend to develop the disease later. Male patients are also more likely to test positive for RF and to exhibit higher ACPA titers [12].

In the early stage of RA (stage I), swelling of affected joints and pain on movement are characteristic features of synovitis, an inflammation of the synovial membrane. According to van Boheemen *et al*. [13], synovitis represents the initial pathological hallmark of RA and contributes to progressive joint damage if left untreated. Moderate RA (stage II) is characterized by gradual degeneration of joint cartilage as inflammation extends from the synovial tissue into the joint cavity. Severe RA (stage III) involves the formation of pannus within the synovium, leading to progressive cartilage destruction and exposure of underlying bone. In the final stage (stage IV), inflammatory activity may subside, but joints become nonfunctional due to fibrous tissue formation or bony fusion [14].

Rheumatoid factor (RF) has long been used as a screening marker in patients with arthritis. Beyond its diagnostic role, RF also has prognostic value, and recent studies have shown that RF titers closely reflect disease activity in rheumatoid arthritis [15]. In a previous study by Al-Saffar *et al*. [16], all 60 RA patients tested positive for RF (100%), whereas only 10% of 60 healthy controls were RF positive. In the present study, RF antibody levels were elevated in RA patients, with higher titers observed in more severe cases and correlating with disease activity, supporting the concept that RF reflects inflammation-driven pathology. Similarly, Volkov *et al*. [17] reported that RF levels in early RA may fluctuate independently of clinical activity, yet still correlate with overall disease severity.

Anti-citrullinated peptide antibodies (ACPAs) are believed to play a pathogenic role in the development of RA, with approximately 50-60% of patients diagnosed in the early stages testing positive for these antibodies [18]. In a previous study by Al-Saffar *et al*. [16] in Baghdad, Iraq, the mean ACPA level was 0.504 ± 0.006 in RA patients compared with 0.244 ± 0.004 in healthy controls ($p = 0.0001$). These findings are consistent with the present study, which also demonstrated significantly elevated ACPA serum levels in RA patients relative to controls. Similarly, Chen *et al*. [4] reported that the mean ACPA concentration in RA samples was 182.10 ± 143.61 U, compared with 1.93 ± 1.93 U in healthy controls.

In addition, Mahdi *et al*. [19] reported that ACPA levels had a mean ± SD of 0.52 ± 0.18, with a cut-off value of 0.328, an area under the curve (AUC) of 0.987, and a specificity of 0.976, while the mean ± SD in RA patients was 0.902. Catrina *et al*. [20] further emphasized that the presence of ACPAs reflects pathogenic features and ongoing immunological activation. ACPAs have also been detected in individuals without synovial inflammation, suggesting that these antibodies contribute to bone remodeling independently and play a critical role in preclinical RA-related bone mass loss [21].

IL-17 is a potent pro-inflammatory cytokine with joint-destructive activity and plays a critical role in the development and progression of RA pathogenesis. It has therefore been identified as a promising target for biological therapy [22-23]. In the present study, IL-17 levels were significantly elevated in RA patients compared with healthy controls. These findings are consistent with a local study from Erbil by Albarzinji *et al*. [24], which highlighted the pivotal role of IL-17 in autoimmune diseases, particularly RA.

IL-17 promotes the stimulation of other pro-inflammatory mediators and facilitates the accumulation of dendritic cells, monocytes, neutrophils, and tumor necrosis factor-alpha (TNF-α), thereby driving inflammation and contributing to progressive joint destruction [25]. In RA, IL-17 induces synovial alterations that lead to synovitis and sustain local inflammation, playing a direct role in both the early induction and late chronic phases of the disease [26]. In stage IV RA, when the disease has progressed to chronic inflammation, the present study confirmed significantly higher mean serum IL-17 levels, consistent with previous reports that IL-17 production peaks in chronic inflammatory conditions.

During the early phases of RA, loss of self-tolerance triggers the activation of autoantibodies, which drive immune cell infiltration into the synovium. This process is mediated by multiple cytokines, including TNF-α and various interleukins, sustaining inflammation and promoting joint destruction [22]. In Egypt, Farag *et al*. [27] reported significantly higher serum and synovial fluid IL-17 levels in RA patients compared with those with osteoarthritis (OA) and healthy controls ($p = 0.001$). The strong correlation with DAS28 further suggests that serum IL-17 may serve

as an important marker of disease activity in RA. Similarly, Al-Saadany *et al*. [28] demonstrated that serum IL-17 levels were significantly correlated with DAS28, confirming its central role in the destructive and inflammatory processes characteristic of RA.

High serum IL-17 levels in untreated RA patients indicate disease progression, including synovial inflammation and joint damage [29]. Persistently elevated IL-17 has been reported in some methotrexate (MTX) non-responders, with risk factors including female sex, younger age, high BMI, smoking, elevated baseline DAS28, positive RF, and diabetes [30-31]. Approximately 25% of patients discontinue MTX within the first year, whereas biological therapies demonstrate significantly higher response rates.

The present study corroborates findings by Al-Ani *et al*. [32], who reported better outcomes in Iraqi RA patients treated with etanercept earlier rather than later. Similarly, Lopez-Pedrera *et al*. [33] confirmed that biologic disease-modifying antirheumatic drugs (bDMARDs), such as etanercept, are among the most effective therapies. While some bDMARDs directly inhibit pro-inflammatory cytokines, others act upstream in the inflammatory cascade by interfering with T-cell activation or inducing B-cell depletion. Conventional DMARDs, such as methotrexate and hydroxychloroquine, are often initiated as monotherapy, with methotrexate in particular blocking cytokine generation that promotes inflammation. When MTX fails to adequately control RA symptoms, bDMARDs—such as tumor necrosis factor (TNF) inhibitors—may be prescribed in combination with MTX [34]. Patients receiving combination therapy generally exhibit the best clinical responses [35]. As noted by Mutlu *et al*. [36], the enhanced efficacy of MTX plus anti-TNF treatment may result from MTX preventing anti-drug antibody formation and/or through synergistic anti-inflammatory effects, with both mechanisms likely contributing to improved outcomes in RA.

The present study's findings on IL-22 levels in RA patients compared with healthy controls are consistent with previous reports. In Diwaniyah, Iraq, Fakher *et al*. [37] observed significantly higher serum IL-22 levels in RA patients (129.30 ± 33.70 pg/mL) than in controls (8.18 ± 3.02 pg/mL; $p < 0.001$). Similarly, Almurshedi *et al*. [8] reported a markedly higher median (IQR) IL-22 concentration in RA patients [36.9 (28.6-63.7) pg/mL] compared with other patients with inflammatory arthritis [23.6 (19.8-26.8) pg/mL], with a highly significant difference ($p < 0.0001$).

Interleukin-22 (IL-22) plays a key role in inflammation, including chronic inflammatory and infectious diseases. In RA, IL-22 responses are elevated in both peripheral blood and joints and correlate with inflammatory markers, disease activity scores, and the extent of bone damage [38].

This study demonstrated lower mean serum IL-22 levels in early RA (stages I-II), reflecting initial immune activation, and higher levels in advanced stages (III-IV), which were associated with synovial hyperplasia, cartilage degradation, and bone erosion. These findings are consistent with previous reports by Yap *et al*. [39], confirming that IL-22 is elevated in chronic inflammatory disease alongside IL-17.

IL-22 contributes to the chronic inflammation characteristic of RA by promoting immune cell recruitment and stimulating the production of inflammatory cytokines, processes that ultimately drive tissue damage. According to Xuan *et al*. [40], multiple regulatory pathways in RA pathogenesis and the proliferation of fibroblast-like synoviocytes (FLSs), which mediate the transition from the inflammatory to destructive stages, can drive IL-22 production. Elevated IL-22 levels have been observed in patients with bone erosions, suggesting that IL-22 may serve as a potential biomarker of bone degradation in RA [21].

High serum IL-22 levels in untreated RA reflect disease progression, including ongoing joint damage and inflammation. Persistently elevated IL-22 in methotrexate non-responders further highlights its pathogenic role, whereas biological therapies, such as rituximab, are more effective in reducing IL-22 expression in affected joints [40].

## CONCLUSION

This study demonstrates that serum levels of RF and ACPA are significantly elevated in patients with rheumatoid arthritis, exhibiting high diagnostic accuracy based on receiver operating characteristic (ROC) curve analysis. In addition, serum levels of IL-17 and IL-22 were markedly increased, particularly in patients with stage 4 disease and in untreated individuals. These findings indicate a significant association between elevated autoantibody and cytokine levels, disease severity, and treatment response. Furthermore, the interaction among RF, ACPA, IL-17, and IL-22 suggests that these parameters may serve as valuable biomarkers in the clinical management of rheumatoid arthritis.

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