# Correlation analysis of serum A-CCP, RF and CRP with Th1/Th2 immune balance and Treg and Th17 in patients with rheumatoid arthritis

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Introduction. To investigate the correlation between serum anti-cyclic citrullinated peptide antibody (A-CCP), rheumatoid factor (RF), and C-reactive protein (CRP) and their helper T-cell (Th)1/Th2 immune balance and Treg and Th17 in rheumatoid arthritis patients.
Methods. A regression analysis was used to analyze 40 patients with rheumatoid arthritis admitted to a tertiary hospital from December 2022 to June 2023, 40 patients in the non-rheumatoid arthritis group, and 40 healthy people were selected for control. Observe the immunological indexes, Th1/Th2, Treg/Th17 immune balance related indexes of patients in different groups and conduct correlation analysis.
Results. A-CCP, RF, CRP, interleukin (IL)-12, γ-interferon, rheumatoid arthritis necrosis factor-α (TNF-α), Th1 cell expression, and Th1/Th2 were significantly lower in the healthy control group than in the non-rheumatoid arthritis group ($P < 0.05$); IL-6, IL-10, IL-17 in the healthy control group, Th2 cell expression was higher than that in the non-rheumatoid arthritis group and rheumatoid arthritis group ($P < 0.05$), and the non-rheumatoid arthritis group was significantly higher than that in the rheumatoid arthritis group ($P < 0.05$).Pearson's correlation analysis showed a positive correlation between A-CCP and the patients' IL-12 and TNF-α levels, as well as the expression of Th1 cells and Th1/Th2 ($P < 0.05$) , RF was positively correlated with patients' IL-12, IFN-γ, and TNF-α levels and Th1 cell expression, Th1/Th2 ($P < 0.05$), and CRP was positively correlated with patients' IL-12, TNF-α levels and Th1 cell expression ($P < 0.05$); A-CCP, RF, CRP and IL-6, IL-10, IL-17 levels and Th2, Treg and Th17 cell expression were negatively correlated ($P < 0.05$).
Conclusion. Immunological indexes of rheumatoid arthritis patients were correlated with their Th1/Th2 immune balance and Treg, Th17, and with the change of immunological indexes of rheumatoid arthritis patients would cause the change of their Th1/Th2 immune balance and the expression level of Treg, Th17, and the Th1/Th2 immune balance of the patients with poorer immune status would be drifted to Th1, and the expression level of Treg, Th17 would be decreased, and the anti-inflammatory immune ability would be reduced. decreased, and anti-inflammatory immunity was weakened.
Keywords. Rheumatoid arthritis; Immunity, Helper T cell 1/helper T cell 2, Regulatory T cell, Helper T cell 17

## INTRODUCTION

Rheumatoid arthritis is an autoimmune disease, mainly characterized by erosive

arthritis, the pathological basis of which is synovitis, and the clinical manifestations are mainly morning stiffness, swelling, and pain in small joints such as the wrist and proximal interphalangeal joints, which can lead to joint deformities in patients in the late stage, seriously affecting the quality of life of the patients, so it is of great clinical significance to effectively improve the immunity of patients (Zhang, 2018). Immune balance is the basis for the normal functioning of the body's immune system, and it has been clearly reported that CD4+ T cells play a crucial role in the pathogenesis of rheumatoid arthritis, and their cell subpopulations can be categorized into Th1 (thelPer cell, Th) cells, Th2 cells, Treg (regulating Tcells) cells, and Th17 cells, etc., according to different functions (Min, 2013). A large number of clinical studies have pointed out (Cao,2019; Li,2014) that immune intervention for rheumatoid disease patients helps patients' immune function improve and promotes the restoration of their immune balance. It is hypothesized that the immune status of patients is correlated with their immune system function. However, most of the current studies are limited to immunologic interventions to improve the immune status of patients, and the correlation between the immune status and the immune function of patients has not yet been elucidated. The correlation between patients' immunologic indexes and immune balance has not been studied enough, and it is impossible to conclude the relationship between pure immunologic indexes and patients' immune balance. Therefore, this study focuses on the correlation between immunological indicators and the immune balance of Th1/Th2, Treg and Th17 in patients with rheumatoid arthritis, aiming to provide a theoretical basis for the early diagnosis of patients with rheumatoid arthritis, the development of immunology, and immune interventions in clinical rheumatoid arthritis.

## 1 INFORMATION AND METHODS

### 1.1 General information

The sample size of this study was calculated by the formula n=U2, ασ2/δ2, with α taking the value of 0.05, σ taking the value of 2, and δ taking the value of 0.01, which resulted in a sample size of 100 cases, and controlled the rate of dislocation and loss of visits to 20% or less, and finalized the sample size of 120 cases.

Forty cases of rheumatoid arthritis patients admitted to Lanxian People's Hospital from December 2022 to June 2023 were treated as the rheumatoid arthritis group, of which 9 cases were patients with low values of DAS28, 20 cases were patients with intermediate values, and 11 cases were patients with high values, and another 40 cases of other autoimmune diseases patients with non-rheumatoid arthritis admitted during the same period were retrospectively analyzed as the clinical data of the non-rheumatoid arthritis group, and the patients with other autoimmune diseases admitted as the non-rheumatoid arthritis group. rheumatoid arthritis group, 10 cases of ankylosing spondylitis, 16 cases of systemic lupus erythematosus, 9 cases of gout and 5 cases of scleroderma. Retrospectively analyze the physical examination data of 40 healthy people who came to the hospital for physical examination during the same period, and use them as a healthy control group. Inclusion criteria: patients in the

rheumatoid arthritis group met the relevant diagnostic criteria in Rheumatoid Arthritis (Li,2019), and the clinical manifestations were mainly morning stiffness, symmetric swelling and pain in the proximal interphalangeal joints, with the duration of morning stiffness lasting for at least 1h and the condition persisting for more than 6 weeks; patients in the non-rheumatoid arthritis group met the relevant diagnostic criteria in Clinical Disease Diagnostic and Effectiveness Determination Criteria (Sun,2014), and the morning stiffness lasted for at least 1h. The patients in the non-rheumatoid arthritis group all met the relevant diagnostic criteria in the Diagnostic and Efficacy Determination Criteria for Clinical Diseases (Sun,2014), and the duration of morning stiffness was <1h. Exclusion criteria: those with malignant rheumatoid arthritis of other systems; those with decreased immune function or joint deformities due to other reasons; those with severe damage to vital organs such as heart, liver, kidney, etc.; and those with abnormal coagulation functions. The study was reviewed and approved by the Medical Ethics Committee of the hospital, and all patients gave informed consent to participate voluntarily. The general information of each group is shown in Table 1.

Table 1 General information of the groups

| Groups | n | Sex (m/f, example) | Age (years, □±s) |
|---|---|---|---|
| Healthy control group | 40 | 21/19 | 42.73±5.41 |
| Non-rheumatoid arthritis group | 40 | 20/20 | 42.59±5.38 |
| Rheumatoid Arthritis Group | 40 | 22/18 | 42.80±5.45 |
| $F/x^2$ | | 0.201 | 0.016 |
| P | | 0.905 | 0.985 |

1.2 Research method

All patients were enrolled in the group to measure the relevant indicators before treatment. Immunological indexes: take 5mL of peripheral venous blood from the patients, centrifuge the serum at 3500r/min for 10min, and use electrochemiluminescence to detect the serum A-CCP level; use scattering turbidimetry to detect the serum RF level; and use immunoturbidimetric assay to detect the serum CRP level. Positive criteria: A-CCP >35 U/mL; RF >18 IU/mL; CRP >6 mgL (Hu, 2019).Th1/Th2-related indexes testing: samples were obtained as above, and patients were tested using enzyme-linked immunosorbent assay to detect interleukin-12 (IL)-12, IL-17, IL-6, IL-10, class rheumatoid arthritis necrosis factor-α (tumornecrosisfactor-α, TNF-α), and interferon-γ (IFN-γ) expression. Use flow cytometry to detect patients' Th1 and Th2 cell levels and calculate Th1/Th2; Treg/Th17 immune balance: samples were obtained as above, and patients' Treg and Th17 cell levels were detected using flow cytometry and Treg/Th17 was calculated.

1.3 Observation indexes

① Immunological indexes in each group; ② expression of Th1 and Th2 cytokines in each group, expression of Th1 and Th2 cells in each group, expression of Treg and

Th17 cells in each group; ③ correlation between immunological indexes and Th1/Th2 immune balance and expression of Treg and TH17.

1.4 Statistical methods

SPSS21.0 statistical software was used for data analysis. Measurement information was expressed as mean ± standard deviation (□±s), and one-way ANOVA test was used for comparison between groups; counting information was expressed as number of cases, and $\chi^2$ test was used for comparison; Pearson correlation analysis was used to observe the correlation between indicators. The difference was considered statistically significant at $P < 0.05$.

## 2 RESULTS

2.1 Comparison of immunological indexes among groups

A-CCP, RF and CRP of the healthy control group were lower than those of the non-rheumatoid arthritis group and the rheumatoid arthritis group, and the difference was statistically significant ($P < 0.05$); A-CCP, RF and CRP of the non-rheumatoid arthritis group were lower than those of the rheumatoid arthritis group, and the difference was statistically significant ($P < 0.05$). See Table 2.

Table 2 Comparison of serum A-CCP, RF, and CRP levels in the 2 groups of study subjects (□±s)

| Groups | cases | A-CCP(U/mL) | RF(U/mL) | CRP(mg/L) |
|---|---|---|---|---|
| Healthy control group | 40 | 15.22±0.54 | 5.45±1.11 | 2.17±0.58 |
| Non-rheumatoid arthritis group | 40 | 533.18±139.87[a] | 26.83±10.12[a] | 15.71±6.57[a] |
| Rheumatoid Arthritis Group | 40 | 7635.78±2684.33[ab] | 321.45±123.03[ab] | 34.51±15.24[ab] |
| F | | 301.136 | 247.197 | 11.4.785 |
| P | | <0.05 | <0.05 | <0.05 |

Note: [a]P<0.05 compared with healthy control group; [b]P<0.05 compared with non-rheumatoid arthritis group. a-CCP: anti-cyclic citrullinated peptide antibody; RF: rheumatoid factor; CRP: C-reactive protein.

2.2 Comparison of Th1 and Th2 cytokine expression in each group

IL-12, IFN-γ, and TNF-α in the healthy control group were lower than those in the non-rheumatoid arthritis group and the rheumatoid arthritis group, and the difference was statistically significant ($P < 0.05$); IL-12, IFN-γ, and TNF-α in the non-rheumatoid arthritis group were lower than those in the rheumatoid arthritis group, and the difference was statistically significant ($P < 0.05$); IL-6, IL-10 in the healthy control group, IL-17 were significantly higher than those in the non-rheumatoid arthritis group and the rheumatoid arthritis group, and the difference was statistically significant ($P < 0.05$). See Table 3.

Table 3 Comparison of Th1 and Th2 cytokine expression among groups （□±s）

| Groups | cases | Th1 | | | Th2 | | |
|---|---|---|---|---|---|---|---|
| | | IL-12（Pg/mg） | IFN-γ（ng/L） | TNF-α（ng/L） | IL-6（Pg/ml） | IL-10（Pg/ml） | IL-17（Pg/ml） |
| Healthy control group | 40 | 8.91±4.43 | 171.14±15.05 | 99.08±13.33 | 18.24±2.62 | 30.79±3.69 | 71.73±8.31 |
| Non-rheumatoid arthritis group | 40 | 16.56±3.89[a] | 179.35±16.21[a] | 105.80±9.04[a] | 14.04±4.15[a] | 26.71±4.11[a] | 64.66±12.61[a] |
| Rheumatoid Arthritis Group | 40 | 19.57±3.25[ab] | 190.44±14.45[ab] | 124.62±10.16[ab] | 9.64±5.78[ab] | 21.58±7.99[ab] | 55.56±10.99[ab] |
| F | | 79.974 | 16.127 | 58.000 | 38.598 | 27.088 | 212.604 |
| P | | ＜0.05 | ＜0.05 | ＜0.05 | ＜0.05 | ＜0.05 | ＜0.05 |

Note: [a]P<0.05 compared with the healthy control group; [b]P<0.05 compared with the non-rheumatoid arthritis group. IL: interleukin; TNF-α: rheumatoid arthritis necrosis factor-α; IFN-γ: gamma interferon.

2.3 Comparison of Th1, Th2, Treg and Th17 cell expression in each group

In the healthy control group, Th1 cell expression and Th1/Th2 were lower than those in the non-rheumatoid arthritis group and the rheumatoid arthritis group, and Th2, Treg, and Th17 cell expression were higher than those in the non-rheumatoid arthritis group and the rheumatoid arthritis group, with statistically significant differences (P < 0.05); in the non-rheumatoid arthritis group, Th1 cell expression and Th1/Th2 were lower than those in the rheumatoid arthritis group, and Th2, Treg and Th17 cell expression was significantly higher than that of rheumatoid arthritis group, and the difference was statistically significant (P < 0.05). See Table 4.

Table 4 Expression of Th1, Th2, Treg, Th17 cells in each group （□±s）

| Groups | cases | Th1(%) | Th2(%) | Th1/Th2 | Treg(%) | Th17(%) |
|---|---|---|---|---|---|---|
| Healthy control group | 40 | 7.33±3.32 | 5.24±1.20 | 1.54±2.37 | 12.22±2.21 | 6.73±1.17 |
| Non-rheumatoid arthritis group | 40 | 10.70±2.74[a] | 4.64±1.44[a] | 2.73±1.61[a] | 10.18±2.87[a] | 5.63±1.24[a] |
| Rheumatoid Arthritis Group | 40 | 12.68±2.17[ab] | 3.44±1.81[ab] | 4.18±0.94[ab] | 7.67±3.65[ab] | 4.39±1.53[ab] |

| | | | | | |
|---|---|---|---|---|---|
| F | 397.781 | 14.846 | 23.070 | 23.570 | 31.342 |
| P | ＜0.05 | ＜0.05 | ＜0.05 | ＜0.05 | ＜0.05 |

Note: [a]P<0.05 compared with healthy control group; [b]P<0.05 compared with non-rheumatoid arthritis group. th: helper T cells; Treg: regulatory T cells.

2.4 Correlation of immunological indexes with Th1/Th2 immune balance and Treg and Th17 expression

A-CCP was positively correlated with patients' IL-12, TNF-α levels and Th1 cell expression, Th1/Th2, and negatively correlated with IL-6, IL-10, IL-17 levels and Th2, Treg, Th17 cell expression; RF was positively correlated with patients' IL-12, IFN-γ, TNF-α levels and Th1 cell expression, Th1/Th2, and negatively correlated with IL-6, IL-10, IL-17 levels and Th2, Treg, and Th17 cell expression were negatively correlated; CRP was positively correlated with patients' IL-12, TNF-α levels and Th1 cell expression, and negatively correlated with IL-6, IL-10, IL-17 levels and Th2, Treg, and Th17 cell expression ($P < 0.05$). See Table 5.

Table 5 Correlation of serum markers with Th1/Th2 immune balance and Treg and Th17 expression (r values)

| Norm | IL-12 | IFN-γ | TNF-α | IL-6 | IL-10 | IL-17 | Th1 | Th2 | Treg | Th17 | Th1/Th2 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| A-CCP | 0.510[a] | 0.194[a] | 0.461[a] | -0.444[a] | -0.432[a] | -0.397[a] | 0.414[a] | -0.233[b] | -0.423[a] | -0.418[a] | 0.339[a] |
| RF | 0.483[a] | 0.337[a] | 0.383[a] | -0.361[a] | -0.313[a] | -0.269[a] | 0.326[a] | -0.221[b] | -0.368[a] | -0.307[a] | 0.328[a] |
| CRP | 0.270[a] | 0.134[b] | 0.382[a] | -0.287[a] | -0.307[b] | 0.355[a] | 0.195[b] | -0.214[a] | -0265[a] | -0.326[a] | 0.156[a] |

Note: aP<0.05, vs. bP<0.05. A-CCP: anti-cyclic citrullinated peptide antibody; RF: rheumatoid factor; CRP: C-reactive protein; Th: helper T cells; Treg: regulatory T cells.

## 3 DISCUSSION

Rheumatoid arthritis is an autoimmune disease, slow onset and insidious, in the latent period can appear to last several weeks of low-grade fever, some patients can appear high fever, fatigue, general malaise and body mass decline, etc., the early clinical symptoms can be accompanied by varying degrees of morning stiffness, the clinical treatment of the disease is mainly based on drug therapy, but can only control the patient's condition, and can not be completely cured of the disease, and the treatment of untimely can also be The disease can also lead to the lesion of the joint activity obstacle. Therefore, improving one's own immunity is a positive and effective means of treatment (Zhang, 2022). Therefore, in this study, we collected data from the patients before the immune intervention and analyzed only the effects of their immune status on their Th1/Th2 immune balance and Treg and Th17, aiming to improve the gap of the domestic research on the immunity of rheumatoid disease patients.

In this study, serum A-CCP, RF, and CRP levels were significantly higher in the rheumatoid arthritis group than in the non-rheumatoid arthritis group and the healthy control group, and serum A-CCP, RF, and CRP levels were significantly higher in the non-rheumatoid arthritis group than in the healthy control group, suggesting that serum A-CCP, RF, and CRP levels are all abnormally high in expression in rheumatoid arthritis patients. Serum A-CCP has high sensitivity and specificity in the diagnosis of rheumatoid arthritis, and can be used as a highly specific indicator for diagnosing rheumatoid arthritis (Wang, 2021). Relevant studies have pointed out that serum A-CCP is also highly sensitive for identifying non-invasive rheumatoid arthritis and invasive rheumatoid arthritis; at the same time, serum A-CCP-positive patients are more prone to joint bone destruction, which results in patients' osteoporosis, limited joint movement and deformity, aggravating patients' conditions (Zhuang, 2020).RF is a rheumatoid arthritis patient in the presence of infections, RF is a common serological indicator used to diagnose rheumatoid arthritis in patients with rheumatoid arthritis, which is induced by infection, trauma, and other factors, such as the denaturation of IgG molecules in the body, which stimulates the body to produce autoantibodies against the denatured IgG, and is a common serological indicator used to diagnose rheumatoid arthritis in the clinic. The diagnostic specificity of rheumatoid arthritis is not high (Sun, 2018). When the organism is infected or tissue injury, serum CRP level rises sharply, and at the same time enhances the phagocytosis function of phagocytes and activates complement, so as to remove pathogenic microorganisms and damaged, necrotic and apoptotic tissue cells in the organism, and its elevated level reflects the impairment of the organism's immune function, suggesting that the patient's disease is in the acute stage, which is also of great significance for the diagnosis of rheumatoid arthritis; relevant studies show that CRP is an inflammatory indicator with high sensitivity and low specificity, which is used to determine the level of inflammation and preliminary judgment of viral or bacterial infection (Liu, 2016).

In the development of rheumatoid arthritis, the body's anti-rheumatoid arthritis immunity plays an important role. IL-12, IFN-γ, and TNF-α are mainly secreted by a subpopulation of TH1 cells, and their main roles are to mediate cellular immunity, in which IFN-γ and TNF-α can effectively kill rheumatoid arthritis cells and have anti-rheumatoid arthritis effects (Liu, 2022). IL-6, IL-10, and IL-17, on the other hand, are mainly secreted by a subpopulation of Th2 cells, which mediate humoral immunity, have immunosuppressive effects, and promote the development of rheumatoid arthritis (Hu, 2022). Under normal conditions, the body's Th1/Th2 cells are in dynamic balance (Moret, 2013). However, under the influence of external stimuli and other factors, the Th1/Th2 homeostasis of patients is damaged, causing massive proliferation of Th2 cells, hyperfunction, and secretion of a large number of immunosuppressive factors causing immune dysfunction in patients (Chen, 2012). Related studies have pointed out that Th1/Th2 drift may cause an increase in microvessel density and affect the progression of their disease. The results of this study, on the other hand, showed that IL-12, IFN-γ, and TNF-α were significantly

lower in the healthy control group than in the non-rheumatoid arthritis group and the rheumatoid arthritis group; IL-12, IFN-γ, and TNF-α were significantly lower in the non-rheumatoid arthritis group than in the rheumatoid arthritis group; IL-6, IL-10, and IL-17 were significantly higher in the healthy control group than in the non-rheumatoid arthritis group and the Rheumatoid arthritis group; IL-6, IL-10, IL-17 in the non-rheumatoid arthritis group were significantly higher than that in the rheumatoid arthritis group, suggesting that the immune status of the patient can directly affect the secretion of Th1 and Th2 cytokines in the patient to improve their immune ability, at the same time, this study also found that the better the immune status of the patient, the higher the expression of its Th1/Th2 cells, the immune balance drifts to Th1, and this effect can improve the patients' own body anti-inflammatory ability and improve the patients' anti-inflammatory immune response. Correlation analysis also confirmed that A-CCP and RF were strongly correlated with patients' Th1 and Th2 cytokine levels and Th1/Th2 immune balance, which further validated the interpretation of the research related to the improvement of patients' immune function by immune supplementation.Treg and Th17 are not the main factors of anti-inflammatory immunity, but they can influence patients' disease development and progression through the secretion of signaling factors, cytokines and other physicochemical factors, which can be used in rheumatoid arthritis. In rheumatoid arthritis patients, the immunological indexes of patients are correlated with their Treg and Th17, further confirming the influence of patients' immune status on their disease development.

This study is insufficient: ① domestic for rheumatoid patients pure immunological indicators and its immune balance correlation study less, can not be compared with other scholars research results for argumentation; ② affected by the conditions of the hospital, can not be carried out by the cellular level experiments or animal experiments to further observe the role of various immune indicators of the molecular level of the immune cell mechanism, only through the patient's final expression of the analysis, the in-depth study is also the next step of work The in-depth study is also the next step; (3) The samples included in this study were relatively small, and all of them were patients of this hospital, which may lack universality, and we need to expand the samples included in the next step for deeper analysis. Although this study has the above shortcomings, as one of the few purely immunological and immune status analysis reports in China, the results of this study still have a certain reference value, and we hope to further improve it in the next step to provide help for the development of immunology of rheumatoid arthritis in China.

In summary, the immunological indexes of rheumatoid arthritis patients are correlated with their Th1/Th2 immune balance and Treg and Th17, and changes in their immunological indexes will cause changes in their Th1/Th2 immune balance and Treg and Th17 expression levels, and patients with poorer immune status will see a drift of their Th1/Th2 immune balance toward Th1, a decrease in Treg and Th17, and a weakening of their anti-inflammatory immune ability. Inflammatory immunity is weakened. However, due to the number of cases admitted to the hospital, the sample

included in this study is relatively small, coupled with the lack of such studies in China, it is not possible to compare and verify with similar studies, and this conclusion needs to be further confirmed and improved by multi-center and large-sample experiments.

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