

Analysis of Immunoinflammatory Characteristics in Primary Sjögren's Syndrome with Different Rheumatoid Factor Levels: Postprint

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Abstract

Background Rheumatoid factor (RF) is a common autoantibody in patients with primary Sjögren's syndrome (pSS), and its specific role in the disease is not fully understood. Objective To explore the clinical characteristics and significance of different RF levels in pSS. Methods A cross-sectional study was conducted, enrolling 262 pSS patients who visited the Department of Traditional Chinese Medicine Rheumatology, China-Japan Friendship Hospital from December 2018 to September 2022 as study subjects. Patients were divided into three groups based on RF levels: negative group (137 cases, RF<20 U/mL), low-titer positive group (47 cases, RF: 20-60 U/mL), and high-titer positive group (78 cases, RF>60 U/mL). Clinical data of the three groups of pSS patients were collected, including general information, clinical manifestations, symptom scores, and hematological indicators. Chi-square, non-parametric, and trend tests were used to analyze inter-group differences. Results The RF positive rate among the 262 pSS patients was 47.7% (125/262), including 14 males (5.3%) and 248 females (94.7%), with a median age of 57.0 (49.0, 63.0) years, mean disease onset age of (48.7±11.6) years, and median disease duration of 60.0 (24.0, 120.0) months. There were no statistically significant differences (P > 0.05). The top three common clinical manifestations in pSS patients were dry mouth (257 cases), dry eyes (247 cases), and fatigue (235 cases). The incidence of hematological system involvement in the high-titer positive group was higher than that in the negative group (P < 0.05). With increasing RF titers, the incidence of sicca syndrome (χ² trend = 6.992, P trend = 0.008) and arthritis (χ² trend = 10.918, P trend = 0.001) in pSS patients showed an upward trend. With increasing RF titers, the proportions of pSS patients with antinuclear antibody ≥ 1:160 (χ² trend = 40.691, P trend < 0.001), anti-Sjögren's syndrome-related antigen A antibody positivity (χ² trend = 26.138, P trend < 0.001), anti-Ro52 ribonucleoprotein antibody positivity (χ² trend = 31.426, P trend < 0.001), anti-Sjögren's syndrome-related antigen B antibody positivity (χ² trend = 23.682, P trend <

0.001), elevated erythrocyte sedimentation rate (χ^2 trend = 40.132, P trend < 0.001), elevated immunoglobulin (Ig) A (χ^2 trend = 7.508, P trend = 0.006), elevated IgG (χ^2 trend = 71.570, P trend < 0.001), decreased complement 3 (χ^2 trend = 7.452, P trend = 0.006), decreased neutrophil count (χ^2 trend = 8.364, P trend = 0.004), and decreased hemoglobin (χ^2 trend = 6.390, P trend = 0.011) all showed an upward trend. Conclusion With increasing RF titers, the proportion of serum immune abnormalities and extra-glandular involvement in pSS patients increased; elevated RF titers have predictive value for arthritis and hematological system involvement.

Full Text

The Immune-Inflammatory Characteristics of Primary Sjögren's Syndrome with Different Levels of Rheumatoid Factor

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Abstract

Background: Rheumatoid factor (RF) is a common autoantibody found in patients with primary Sjögren's syndrome (pSS), but its specific role in the disease is not fully understood. **Objective:** To explore the clinical characteristics and significance of different RF levels in pSS. **Methods:** This study employed a cross-sectional survey design, enrolling 262 pSS patients who visited the Department of Rheumatology of Traditional Chinese Medicine at China-Japan Friendship Hospital between December 2018 and September 2022. Patients were divided into three groups based on RF levels: negative group (RF < 20 U/mL, n = 137), low-titer positive group (RF: 20–60 U/mL, n = 47), and high-titer positive group (RF > 60 U/mL, n = 78). Clinical data were collected, including general information, clinical manifestations, symptom scores, and hematological indices. Inter-group differences were analyzed using chi-square tests, nonparametric tests, and trend tests. **Results:** The RF positivity rate among 262

pSS patients was 47.7% (125/262), including 14 males (5.3%) and 248 females (94.7%), with a median age of 57.0 (49.0, 63.0) years, mean age of onset of (48.7 \pm 11.6) years, and median disease duration of 60.0 (24.0, 120.0) months. No significant differences were observed among the three groups in terms of gender, age, age of onset, or disease duration ($P > 0.05$). The three most common clinical manifestations in pSS patients were dry mouth (257 cases), dry eyes (247 cases), and fatigue (235 cases). The incidence of hematological involvement and arthritis was higher in the high-titer positive group than in the negative group ($P < 0.05$). With increasing RF titer, the incidence of hematological involvement (χ^2 trend = 10.918, P trend = 0.001) and arthritis (χ^2 trend = 6.992, P trend = 0.008) showed an upward trend. As RF titer increased, the proportions of pSS patients with antinuclear antibody $\geq 1:160$ (χ^2 trend = 40.691, P trend < 0.001), anti-SSA antibody positivity (χ^2 trend = 26.138, P trend < 0.001), anti-Ro52 antibody positivity (χ^2 trend = 31.426, P trend < 0.001), anti-SSB antibody positivity (χ^2 trend = 23.682, P trend < 0.001), elevated erythrocyte sedimentation rate (χ^2 trend = 71.570, P trend < 0.001), elevated immunoglobulin (Ig) A (χ^2 trend = 7.508, P trend = 0.006), elevated IgG (χ^2 trend = 7.452, P trend = 0.006), decreased complement 3 (χ^2 trend = 8.364, P trend = 0.004), decreased neutrophil count (χ^2 trend = 6.390, P trend = 0.011), and decreased hemoglobin (χ^2 trend = 40.132, P trend < 0.001) all showed an upward trend.

Conclusion: With increasing RF titer, the proportion of pSS patients with serum immunological abnormalities and extra-glandular involvement increases. High RF titers have predictive value for arthritis and hematologic involvement.

Keywords: Sjögren's syndrome; Rheumatoid factor; Immune inflammation; Arthritis; Surveys and questionnaires; Beijing

Introduction

Primary Sjögren's syndrome (pSS) is a common autoimmune disease primarily affecting exocrine glands such as salivary and lacrimal glands, with dry mouth and dry eyes as its main symptoms. The disease predominantly affects middle-aged and elderly women, with a prevalence of approximately 2%–4.8% in the elderly population. As population aging intensifies, the disease burden of pSS is gradually increasing. Rheumatoid factor (RF) is a common autoantibody in pSS patients, though its role in pSS remains incompletely understood. Previous small-sample retrospective studies have preliminarily explored the clinical characteristics of RF-positive pSS patients, finding that those with high-titer RF positivity differ from RF-negative patients in terms of autoantibodies and extra-glandular organ involvement, though specific trends remain unclear. It is uncertain whether pSS patients exhibit certain trends in serum immunological abnormalities and organ involvement as RF titers increase. Based on this, our study aims to investigate the clinical characteristics of pSS patients with different RF levels and conduct trend tests to provide references for clinical diagnosis and treatment of pSS.

Methods

1.1 Study Subjects This cross-sectional survey collected clinical data from pSS patients who visited China-Japan Friendship Hospital between December 2018 and September 2022. The diagnosis of pSS was based on the 2016 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) classification criteria for pSS. Inclusion criteria were: (1) meeting pSS diagnostic criteria; (2) age 18–75 years; (3) signed informed consent. Exclusion criteria were: (1) coexisting diffuse connective tissue diseases such as rheumatoid arthritis or systemic lupus erythematosus; (2) coexisting hypersplenism; (3) coexisting liver cirrhosis; (4) coexisting malignancy; (5) pregnancy or lactation, or psychiatric illness; (6) poor compliance or inability to cooperate with follow-up. This study was approved by the Ethics Committee of China-Japan Friendship Hospital (2018-156-K112).

1.2 Data Collection **1.2.1 General Information:** Gender, age, age of onset, and disease duration were collected through questionnaire surveys.

1.2.2 Clinical Manifestations: Dry mouth, dry eyes, fatigue, arthritis, oral ulcers, parotid gland enlargement, rampant caries, Raynaud's phenomenon, lymphadenopathy, purpuric rash, interstitial lung disease, and hematological involvement.

1.2.3 Symptom Scores: Dry mouth Visual Analogue Scale (VAS) score, dry eye VAS score, and EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) score. Dry mouth and dry eye scores were categorized into four levels: none (0 points), mild (1–3 points), moderate (4–6 points), and severe (7–10 points). ESSPRI scores were divided into patient-acceptable status (<5 points) and patient-unacceptable status (≥5 points).

1.2.4 Hematological Indices: RF and C-reactive protein (CRP) were measured by immunoturbidimetry; erythrocyte sedimentation rate (ESR) by the Westergren method; antinuclear antibodies (ANA) by indirect immunofluorescence; anti-SSA, anti-Ro52, anti-SSB, anti-ribonucleoprotein (RNP), and anti-centromere protein B (CENP-B) antibodies by immunoblotting; anti-cyclic citrullinated peptide (CCP) antibody, immunoglobulin (Ig) G, IgA, IgM, complement (C) 3, and C4 by enzyme-linked immunosorbent assay; and blood cell counts including white blood cell (WBC), neutrophil (NEUT), hemoglobin (Hb), and platelet (PLT) counts. All tests were performed at China-Japan Friendship Hospital.

1.2.5 Grouping: Patients were divided into three groups based on RF levels: negative group (RF < 20 U/mL), low-titer positive group (RF: 20–60 U/mL), and high-titer positive group (RF > 60 U/mL). Differences in symptoms and hematological indices among groups and trend characteristics were analyzed.

1.3 Statistical Methods Two researchers independently entered data using Epidata 3.4 software. Statistical analysis was performed using SPSS 20.0 software, and graphs were created using GraphPad Prism 9.0.0. Normally distributed continuous data were expressed as ($\bar{x} \pm s$) and compared among groups using one-way ANOVA. Non-normally distributed data were expressed as $M(P_{25}, P_{75})$ and compared using nonparametric rank-sum tests. Categorical data were expressed as frequencies and percentages, with inter-group comparisons using chi-square tests, pairwise comparisons using Z-tests with Bonferroni correction, and trend chi-square tests to explore linear trends. All hypothesis tests were two-tailed, with $P < 0.05$ considered statistically significant.

Results

2.1 General Data A total of 262 pSS patients were enrolled, including 14 males (5.3%) and 248 females (94.7%). Patient age ranged from 23–75 years, with a median age of 57.0 (49.0, 63.0) years; age of onset ranged from 16–72 years, with a mean of (48.7 ± 11.6) years; disease duration ranged from 1–384 months, with a median of 60.0 (24.0, 120.0) months.

Based on RF levels, patients were divided into: negative group ($n = 137, 52.3\%$), low-titer positive group ($n = 47, 17.9\%$), and high-titer positive group ($n = 78, 29.8\%$). No significant differences were found among the three groups in gender, age, age of onset, or disease duration ($P > 0.05$).

2.2 Clinical Manifestations The most to least common clinical manifestations among 262 pSS patients were: dry mouth (257 cases), dry eyes (247 cases), fatigue (235 cases), rampant caries (140 cases), hematological involvement (109 cases), lymphadenopathy (53 cases), interstitial lung disease (49 cases), oral ulcers (41 cases), arthritis (38 cases), Raynaud’s phenomenon (30 cases), parotid enlargement (19 cases), and purpuric rash (9 cases).

No significant differences were observed among the three groups in the incidence of dry mouth, dry eyes, fatigue, rampant caries, lymphadenopathy, interstitial lung disease, oral ulcers, Raynaud’s phenomenon, parotid enlargement, or purpuric rash ($P > 0.05$). However, significant differences were found in the incidence of hematological involvement and arthritis ($P < 0.05$). Specifically, the high-titer positive group had higher rates of hematological involvement and arthritis than the negative group ($P < 0.05$).

Trend tests showed that with increasing RF titer, the incidence of hematological involvement (χ^2 trend = 10.918, P trend = 0.001) and arthritis (χ^2 trend = 6.992, P trend = 0.008) demonstrated an upward trend [Figure 1: see original paper].

2.3 Symptom Scores Among 262 pSS patients, dry mouth severity was: none in 5 cases, mild in 59 cases, moderate in 97 cases, and severe in 101 cases. Dry eye severity was: none in 17 cases, mild in 68 cases, moderate in 104

cases, and severe in 73 cases. ESSPRI classification showed 150 patients in the acceptable status and 112 in the unacceptable status.

Significant differences were found among the three groups in dry mouth VAS scores ($P < 0.05$), but not in dry eye VAS scores or ESSPRI scores ($P > 0.05$). Trend analysis revealed that dry mouth severity increased with rising RF levels (χ^2 trend = 3.957, P trend = 0.048).

2.4 Hematological Indicators No significant differences were found among the three groups in the positivity rates of anti-RNP antibodies, anti-CCP antibodies, elevated CRP, elevated IgM, decreased C4, decreased WBC, or decreased PLT ($P > 0.05$). However, significant differences were observed in the proportions of patients with ANA $\geq 1:160$, anti-SSA antibody positivity, anti-Ro52 antibody positivity, anti-SSB antibody positivity, anti-CENP-B antibody positivity, elevated ESR, elevated IgA, elevated IgG, decreased C3, decreased NEUT, and decreased Hb ($P < 0.05$).

Compared with the negative group, both the low-titer and high-titer positive groups had higher proportions of ANA $\geq 1:160$, anti-SSA antibody positivity, anti-Ro52 antibody positivity, anti-SSB antibody positivity, and elevated IgG ($P < 0.05$). The high-titer positive group also showed higher rates of elevated ESR, elevated IgA, decreased C3, decreased NEUT, and decreased Hb ($P < 0.05$). Compared with the low-titer positive group, the high-titer positive group had lower anti-CENP-B antibody positivity but higher rates of elevated ESR and elevated IgG ($P < 0.05$).

Trend tests demonstrated that with increasing RF titer, the proportions of pSS patients with ANA $\geq 1:160$ (χ^2 trend = 40.691, P trend < 0.001), anti-SSA antibody positivity (χ^2 trend = 26.138, P trend < 0.001), anti-Ro52 antibody positivity (χ^2 trend = 31.426, P trend < 0.001), anti-SSB antibody positivity (χ^2 trend = 23.682, P trend < 0.001), elevated ESR (χ^2 trend = 71.570, P trend < 0.001), elevated IgA (χ^2 trend = 7.508, P trend = 0.006), elevated IgG (χ^2 trend = 7.452, P trend = 0.006), decreased C3 (χ^2 trend = 8.364, P trend = 0.004), decreased NEUT (χ^2 trend = 6.390, P trend = 0.011), and decreased Hb (χ^2 trend = 40.132, P trend < 0.001) all showed an upward trend [Figure 2: see original paper] and [Figure 3: see original paper].

Discussion

RF is a common autoantibody initially discovered in rheumatoid arthritis patients, and subsequent studies have found it in many autoimmune diseases, including pSS. In this study of 262 pSS patients, we summarized clinical characteristics across different RF levels and innovatively employed trend tests to evaluate differential clinical features. We found that approximately 47.7% of pSS patients were RF-positive. Using three times the upper limit of normal RF as the cutoff, the proportions of low-titer and high-titer RF positivity were

17.9% and 29.8%, respectively, consistent with previous studies. The high-titer positive group showed higher rates of hematological involvement, arthritis, and dry mouth VAS scores compared with the negative group. With increasing RF titer, the incidence of hematological involvement and arthritis rose, and immunoinflammatory responses became more active.

RF includes multiple isotypes such as IgM, IgA, and IgG. IgM RF is associated with early-onset pSS, glandular dysfunction, complete atrioventricular block, and extra-glandular manifestations, with higher risks of hypergammaglobulinemia, hypocomplementemia, and lymphadenopathy. IgA RF correlates with more active autoimmune status, more severe salivary gland dysfunction, and renal disease in pSS patients, suggesting its potential clinical predictive value. Studies have indicated that RF positivity in early-onset pSS may relate to greater systemic involvement and higher disease activity, making RF an important predictive and assessment marker for these patients. Elevated RF titers have also been identified as a risk factor for interstitial lung disease in pSS, offering auxiliary diagnostic value. When anti-SSA and anti-SSB antibodies are negative, combined detection of RF and anti- α -fodrin antibodies may prevent missed pSS diagnoses. Furthermore, RF-positive pSS patients are more likely to develop other connective tissue diseases such as rheumatoid arthritis during follow-up. In summary, RF can assess pSS severity and prognosis, though its role as a disease-specific diagnostic marker remains controversial.

Our findings align with previous research, confirming that elevated RF titers affect pSS clinical manifestations and predict arthritis and hematological involvement, warranting clinical attention. Notably, none of our patients had coexisting primary iron-deficiency anemia.

The mechanism of RF in pSS can be summarized as follows: Reduced regulatory T cells in pSS peripheral blood enhance B cell activity, producing more RF. RF forms immune complexes with IgM, IgA, and IgG, depositing in tissues and activating the complement system to trigger inflammatory responses. RF also stimulates B cell proliferation and differentiation, promoting IgG production and exacerbating autoimmune inflammation. Thus, high RF levels and their isotypes are important indicators of immunoinflammatory responses like hypergammaglobulinemia and hypocomplementemia, as well as disease prognosis.

In conclusion, elevated RF titers predict arthritis and hematological involvement in pSS. For pSS patients with subtle symptoms and lacking specific autoantibodies, early diagnosis is challenging. Although RF is not disease-specific, RF positivity combined with glandular involvement should raise suspicion for pSS after excluding rheumatoid arthritis. Patients with high RF titers require vigilant monitoring for arthritis and hematological complications, necessitating early diagnosis, treatment, and regular follow-up to better control disease progression and improve prognosis.

Limitations: This single-center observational study requires validation through large-sample, multicenter, prospective cohort studies. We only

recorded clinical data at initial visits; future research should examine medication use and stratify patients by RF isotype levels to further explore RF's clinical significance in pSS.

Author Contributions

YANG Jianying and LUO Jing conceived and designed the study. ZHANG Yan, CHEN Jiaqi, WU Zihua, and ZHANG Xiya collected and organized data. YANG Jianying, HUANG Ziwei, and LEI Chunxin performed statistical analysis and created figures and tables. YANG Jianying wrote the manuscript. LUO Jing revised the manuscript. LUO Jing and TAO Qingwen were responsible for quality control, review, and overall supervision.

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