Postprint of a Study on Clinical Characteristics and Influencing Factors in Patients with Primary Sjögren' s Syndrome of Dryness and Blood Stasis Intermingled Syndrome

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Abstract

Background Primary Sjögren' s disease (pSjD) is a chronic autoimmune disease characterized by lymphocytic infiltration of exocrine glands, mainly manifesting as dry mouth and dry eyes, and can involve multiple systems. Epidemiological surveys show its prevalence is approximately 0.06%~0.08%, and is increasing year by year. In recent years, a consensus among traditional Chinese medicine experts has proposed that the "dryness and stasis intermingled pattern" is one of the common pattern types, but its clinical characteristics, influencing factors, and prognosis lack systematic research.

Objective To explore the Chinese and Western medicine clinical characteristics, influencing factors, and prognosis of pSjD patients with dryness and stasis intermingled pattern.

Methods A total of 970 pSjD patients who visited China-Japan Friendship Hospital from 2017 to 2022 were included and divided into the pSjD-dryness and stasis intermingled group (185 cases) and the pSjD-non-dryness and stasis intermingled group (785 cases). Differences in general data, clinical symptoms, laboratory indicators, and disease activity (ESSDAI) scores between the two groups were compared, and multivariate Logistic regression was used to analyze the influencing factors of pSjD-dryness and stasis intermingled pattern. Survival outcomes (including all-cause death, malignant tumors, and interstitial lung disease) were analyzed using Kaplan-Meier survival curves, and differences between groups were evaluated using the Log-rank test.

Results Compared with the pSjD-non-dryness and stasis intermingled group, the pSjD-dryness and stasis intermingled group had a higher proportion of females, longer disease duration, and younger age at visit and age at onset

(P<0.05). In the pSjD-dryness and stasis intermingled group, the top five high-frequency chief complaint symptoms were dry mouth (75%), dry eyes (75%), arthralgia (55%), fatigue (43%), and rampant caries (34%). The pSjD-dryness and stasis intermingled group had higher incidence rates of dry mouth, arthralgia, Raynaud' s phenomenon, lymphadenopathy, cough, dyspnea, parotid gland enlargement, purpura-like rash, arthritis, and concurrent hemorrhage than the pSjD-non-dryness and stasis intermingled group, while the incidence rates of cough and dyspnea were lower than in the pSjD-non-dryness and stasis intermingled group, with statistically significant differences (P<0.05). Multivariate Logistic regression analysis showed that increased age at visit (OR=0.979, 95%CI=0.965~0.993, P=0.004) and elevated platelet count level (OR=0.997, 95%CI=0.994~0.999, P=0.007) were independent protective factors for the development of dryness and stasis intermingled pattern in pSjD patients, while positive anti-RNP antibody (OR=2.352, 95%CI=1.305~4.238, P=0.004), positive anti-CENP-B antibody (OR=2.490, 95%CI=1.404~4.415, P=0.002), positive anti-$ $2GP1 antibody (OR=2.269, 95%CI=1.057~4.872, P=0.036), and increased ESSDAI score (OR=1.037, 95%CI=1.011~1.064, P=0.006) were independent risk factors for the development of dryness and stasis intermingled pattern in pSjD patients. Kaplan-Meier survival curve analysis showed no statistically significant differences in overall mortality, tumor incidence, and new-onset interstitial lung disease incidence between the pSjD-dryness and stasis intermingled group and the pSjD-non-dryness and stasis intermingled group (P>0.05).

Conclusion pSjD patients with dryness and stasis intermingled pattern have protracted disease progression, higher ESSDAI scores, and more significant hematological system involvement, but a lower proportion of concurrent ILD. Increased age at visit and elevated platelet count level may be independent protective factors for the development of dryness and stasis intermingled pattern in pSjD patients, while positive anti-RNP antibody, positive anti-CENP-B antibody, positive anti-$ $2GP1 antibody, and increased ESSDAI score may be independent risk factors for the development of dryness and stasis intermingled pattern in pSjD patients. There were no statistically significant differences in overall mortality, tumor incidence, and new-onset ILD incidence between the pSjD-dryness and stasis intermingled group and the pSjD-non-dryness and stasis intermingled group.

Full Text

Clinical Characteristics and Influencing Factors of Primary Sjögren's Disease with Dryness and Blood-Stasis Syndrome

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Abstract

Background: Primary Sjögren' s disease (pSjD) is a chronic autoimmune disease characterized by lymphocytic infiltration of exocrine glands, presenting mainly with xerostomia and xerophthalmia, and potentially involving multiple systems. Epidemiological studies indicate a prevalence of approximately 0.06%-0.08%, with an increasing trend over time. In recent years, expert consensus in traditional Chinese medicine (TCM) has recognized the dryness and blood-stasis pattern as one of the common syndromes; however, its clinical characteristics, influencing factors, and prognosis have not been systematically investigated.

Objective: To explore the integrative clinical features, influencing factors, and prognostic outcomes of patients with pSjD of dryness and blood-stasis syndrome.

Methods: A total of 970 patients with pSjD treated at the China-Japan Friendship Hospital from 2017 to 2022 were enrolled, including 185 with pSjD of dryness and blood-stasis syndrome and 785 without pSjD of dryness and blood-stasis syndrome. General information, clinical symptoms, laboratory indicators, and disease activity scores (EULAR Sjögren's Syndrome Disease Activity Index, ESSDAI) were compared between groups. Multivariate logistic regression analysis was used to identify independent factors associated with pSjD of dryness and blood-stasis syndrome. Survival outcomes, including all-cause mortality, malignancy, and incident interstitial lung disease (ILD), were analyzed using Kaplan-Meier survival curves and compared by the Log-rank test.

Results: Compared with the non-DBSS group, patients with pSjD of dryness and blood-stasis syndrome were more frequently female, had longer disease duration, and were younger at disease onset and enrollment ($P<0.05$). The top five symptoms in the pSjD of dryness and blood-stasis syndrome group were xerostomia (75%), xerophthalmia (75%), arthralgia (55%), fatigue (43%), and rampant caries (34%). The proportions of xerostomia, arthralgia, Raynaud' s phenomenon, lymphadenopathy, parotid gland enlargement, purpura-like rash, arthritis, and bleeding were significantly higher in the pSjD of dryness and blood-stasis syndrome group, whereas cough and dyspnea were less frequent ($P<0.05$). Multivariate analysis identified older age at enrollment (OR=0.979, 95%CI=0.965-0.993, P=0.004) and higher platelet counts (OR=0.997, 95%CI=0.994-0.999, P=0.007) as independent protective factors for pSjD of dryness and blood-stasis syndrome, while anti-RNP positivity (OR=2.352, 95%CI=1.305-4.238, P=0.004), anti-CENP-B positivity (OR=2.490, 95%CI=1.404-4.415, P=0.002), anti-$ $2GP1 positiv-

ity (OR=2.269, 95%CI=1.057-4.872, P=0.036), and higher ESSDAI scores (OR=1.037, 95%CI=1.011-1.064, P=0.006) were identified as independent risk factors. Kaplan-Meier survival analysis showed no significant differences between groups in all-cause mortality, malignancy, or incident ILD (P>0.05).

Conclusion: Nearly 20% of pSjD patients had dryness and blood-stasis syndrome, and these patients exhibited a more chronic disease course, higher ESSDAI scores, and more prominent hematological involvement, although with a lower proportion of ILD. Older age at enrollment and higher platelet counts may be the independent protective factors for pSjD of dryness and blood-stasis syndrome, while anti-RNP positivity, anti-CENP-B positivity, anti-$ $2GP1 positivity, and higher ESSDAI scores may be identified as independent risk factors. No significant differences were observed in all-cause mortality, malignancy, or incident ILD between the two groups.

Keywords: Primary Sjögren' s disease; Dryness and blood-stasis syndrome; Clinical characteristics; Haematological involvement; Root cause analysis; Prognosis

Introduction

Primary Sjögren's disease (pSjD) is a chronic inflammatory autoimmune disease characterized by lymphocytic infiltration of exocrine glands [1], clinically presenting with xerostomia and xerophthalmia, and potentially involving multiple organs and systems in severe cases [2]. Epidemiological surveys indicate that the annual prevalence of pSjD is approximately 0.060%-0.077%, with a rising trend year by year [3-4]. Its pathogenesis has not been fully elucidated, but is generally considered to be related to genetics, infection, and autoimmune abnormalities [5-6]. Currently, there is a lack of targeted therapeutic measures; systemic involvement is often managed with reference to treatment protocols for rheumatoid arthritis and systemic lupus erythematosus, while glandular involvement largely relies on tear and saliva replacement therapy, which has limited efficacy [7].

In TCM, pSjD belongs to the category of "dryness bi-syndrome" [8]. Modern TCM practitioners generally believe that this disease is characterized by "yin deficiency as the root, dryness-heat as the branch," and clinically adopt methods of supplementing qi and nourishing yin, moistening dryness and generating fluids [9]. However, dryness bi-syndrome is protracted and difficult to cure, and treatment with yin-nourishing and dryness-moistening methods alone sometimes yields limited results and fails to fundamentally alleviate the condition. In 2023, the Rheumatology Branch of the China Association of Chinese Medicine led the development of the "Expert Consensus on TCM Syndrome Patterns of Sjögren's Syndrome" [10], which greatly standardized the TCM pattern differentiation and classification of pSjD and, for the first time, proposed dryness and blood-stasis syndrome as one of the common patterns. However, systematic research

on the clinical characteristics and related factors of patients with dryness and blood-stasis syndrome is still lacking.

To this end, this study enrolled consecutive pSjD cases treated at the China-Japan Friendship Hospital over the past five years, summarized and analyzed the clinical characteristics and related factors of pSjD patients with dryness and blood-stasis syndrome, and conducted long-term follow-up of patients to clarify the clinical manifestations and prognosis of pSjD patients with dryness and blood-stasis syndrome, providing a reference for clinical diagnosis and treatment of this disease.

Methods

1.1 Study Subjects

This study employed a cohort study design combining retrospective baseline data collection with prospective follow-up. All consecutive pSjD cases treated at the China-Japan Friendship Hospital from January 2017 to December 2022 were enrolled. Baseline data were collected retrospectively from patients' clinical information at their first visit. The time of patient enrollment served as the starting point for follow-up observation. All patients were prospectively followed up every six months via telephone or outpatient visits until an outcome event occurred or until the follow-up cutoff date. The follow-up cutoff date was February 1, 2024. Outcome events were defined as all-cause death, malignancy, or new-onset interstitial lung disease (ILD) (i.e., newly diagnosed ILD during follow-up in patients without ILD at baseline). This study was approved by the Ethics Committee of the China-Japan Friendship Hospital (No. 2021-144-K102). Informed consent was waived as the study did not involve patients' personal privacy information.

Inclusion criteria: (1) Meeting the 2016 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for pSjD [11]; (2) Complete case data recording patient diagnosis and treatment information.

Exclusion criteria: (1) Comorbid other connective tissue diseases, such as rheumatoid arthritis and systemic lupus erythematosus; (2) Pregnant or lactating women, patients with mental illness; (3) Patients with severe cardiovascular and cerebrovascular diseases, liver and kidney failure, or malignancy.

1.2 Diagnostic Criteria for Dryness and Blood-Stasis Syndrome

Referring to the 2023 "Expert Consensus on TCM Syndrome Patterns of Sjögren's Syndrome" by the Rheumatology Branch of the China Association of Chinese Medicine [10], patients with dryness and blood-stasis syndrome of Sjögren's syndrome met three diagnostic criteria: (1) Main symptoms: dry mouth without desire to drink, dry eyes with little tearing, and rough scaly skin or presence of ecchymosis and petechiae; (2) Secondary symptoms: dry nose, dry throat, joint

and muscle pain, extremities skin turning white or purple, persistent swelling of the cheeks or scrofula; (3) Tongue and pulse: dark tongue or with ecchymosis and petechiae, or sublingual veins tortuous and bluish-purple, scanty and dry coating, choppy or thin-choppy pulse.

Two TCM rheumatology specialists with rich clinical experience independently performed pattern differentiation according to the "Expert Consensus on TCM Syndrome Patterns of Sjögren' s Syndrome (2023)" and other standards. If the two physicians agreed, the pattern type was directly determined; if there was disagreement, a third senior physician reviewed the case and convened an expert panel discussion in the department to reach a final consensus based on the patient' s symptoms, signs, and previous medical records. Patients were thus divided into the pSjD-dryness and blood-stasis group and the pSjD-non-dryness and blood-stasis group.

1.3 Data Collection

1.3.1 Demographic and medical history data: Patient gender, age at enrollment, age at disease onset, and disease duration (defined as the time from first appearance of dryness symptoms to enrollment in this study) were recorded.

1.3.2 Clinical manifestations: Baseline clinical features were recorded as binary variables, including xerostomia, xerophthalmia, fever, night sweats, fatigue, Raynaud' s phenomenon, purpura-like rash, cough, dyspnea, lymphadenopathy, arthralgia, arthritis, morning stiffness, rampant caries, parotid gland enlargement, and bleeding complications.

1.3.3 ILD: Diagnosis of pSjD-related ILD was determined by clinicians based on comprehensive assessment of clinical symptoms, signs, and high-resolution CT (HRCT) imaging reports of the chest.

1.3.4 Splenomegaly diagnosis: Splenomegaly was determined by clinicians based on professional imaging reports showing splenic thickness exceeding 4 cm or maximum longitudinal diameter exceeding 11 cm, with the spleen palpable below the left costal margin.

1.3.5 Disease activity: The European League Against Rheumatism Sjögren' s Syndrome Disease Activity Index (ESSDAI) was used for assessment. Disease activity was classified into three levels based on scores: low activity (ESSDAI<5), moderate activity (5≤ESSDAI$ $13), and high activity (ESSDAI>13) [12].

1.3.6 Laboratory indicators: The following indicators were recorded as binary variables within the normal reference range: elevated immunoglobulin G (IgG) (>16.2 g/L), elevated immunoglobulin A (IgA) (>3.78 g/L), elevated immunoglobulin M (IgM) (>2.63 g/L), decreased complement 3 (C3) (<0.7 g/L), decreased complement 4 (C4) (<0.16 g/L), elevated C-reactive protein (CRP) (>8 mg/L), and elevated erythrocyte sedimentation rate (ESR) (female >20 mm/1h, male >15 mm/1h). Other laboratory parameters included white blood cell count (WBC), neutrophil count (NEUT), lymphocyte count (LYMPH),

red blood cell count (RBC), hemoglobin (Hb), platelet count (PLT), alanine transaminase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), creatinine (Cr), albumin (ALB), serum potassium, serum sodium, and serum chloride.

1.3.7 Baseline autoantibody detection: Antinuclear antibodies (ANA) were detected by indirect immunofluorescence assay (EUROIMMUN Medizinische Labordiagnostika AG, batch No. FA1800-101033). Anti-Sm, anti-SSA, anti-Ro52, anti-SSB, anti-ribonucleoprotein (RNP), anti-topoisomerase I (Scl-70), anti-centromere protein B (CENP-B), anti-AMA-M2, anti-PM-Scl, anti-cardiolipin antibody (aCL), anti-beta-2-glycoprotein 1 antibody ($ $2GP1), and anti-double-stranded DNA (dsDNA) antibodies were all detected by immunoblotting (EUROIMMUN Medizinische Labordiagnostika AG, batch No. DL1590-6401-3G).

1.4 Quality Control

This was a real-world cohort study of consecutive cases, enrolling all pSjD patients treated at the China-Japan Friendship Hospital from January 2017 to December 2022. No prior sample size calculation was performed; instead, consecutive enrollment was used to ensure completeness and representativeness of cases. The year 2017 was selected as the study start time primarily because the hospital' s electronic medical record system and follow-up database were unified and perfected from that year onward, ensuring complete case information and traceable follow-up data, thereby improving research data reliability. Study data were mainly sourced from the hospital' s electronic medical record system, with baseline case data extracted retrospectively from patients' first visits. All laboratory tests were completed in the hospital laboratory. To ensure data quality, the database was established using a dual independent entry with third-party verification model.

1.5 Statistical Analysis

This study used SPSS 26.0 software and R 4.2.3 software for data processing. Count data were expressed as cases (%) and compared between groups using ^{2} test or Fisher' s exact test. Normally distributed measurement data were expressed as ($\bar{x}\pm s$) and compared using two-sample independent t-test. Non-normally distributed measurement data were expressed as M(P25, P75) and compared using Mann-Whitney U test. Factors with $P<0.1$ in univariate analysis were included as independent variables in multivariate logistic regression analysis to explore independent influencing factors for dryness and blood-stasis syndrome in pSjD patients. Survival outcomes (including all-cause death, malignancy, and interstitial lung disease) were analyzed using Kaplan-Meier survival curves, with between-group differences assessed using Log-rank test. $P<0.05$ was considered statistically significant.

Results

2.1 Comparison of General Data Between pSjD-Dryness and Blood-Stasis Group and pSjD-Non-Dryness and Blood-Stasis Group

This study enrolled 970 pSjD patients, including 185 in the pSjD-dryness and blood-stasis group and 785 in the pSjD-non-dryness and blood-stasis group. Comparison of general data between the two groups showed statistically significant differences ($P<0.05$). Compared with the pSjD-non-dryness and blood-stasis group, the pSjD-dryness and blood-stasis group had a higher proportion of females, longer disease duration, and younger age at enrollment and disease onset, with statistically significant differences ($P<0.05$) .

2.2 Comparison of Clinical Symptoms Between pSjD-Dryness and Blood-Stasis Group and pSjD-Non-Dryness and Blood-Stasis Group

Chief complaints were recorded as binary variables including xerostomia, xerophthalmia, fever, night sweats, fatigue, Raynaud' s phenomenon, purpura-like rash, cough, dyspnea, lymphadenopathy, arthralgia, arthritis, morning stiffness, rampant caries, parotid gland enlargement, and bleeding complications. Symptoms were sorted by frequency from high to low. In the pSjD-non-dryness and blood-stasis group, the top five chief complaints were xerostomia (82.5%), xerophthalmia (76.2%), fatigue (49.1%), cough (36.2%), and arthralgia (32.9%). In the pSjD-dryness and blood-stasis group, the top five chief complaints were xerostomia (75%), xerophthalmia (75%), arthralgia (55%), fatigue (43%), and rampant caries (34%).

There were no statistically significant differences between the two groups in the proportions of xerophthalmia, fatigue, rampant caries, morning stiffness, fever, or night sweats ($P>0.05$). However, statistically significant differences were observed in the proportions of xerostomia, arthralgia, Raynaud' s phenomenon, lymphadenopathy, cough, dyspnea, parotid gland enlargement, purpura-like rash, arthritis, and bleeding complications ($P<0.05$). Specifically, the pSjD-dryness and blood-stasis group had higher proportions of xerostomia, arthralgia, Raynaud' s phenomenon, lymphadenopathy, parotid gland enlargement, purpura-like rash, arthritis, and bleeding complications, but lower proportions of cough and dyspnea compared with the pSjD-non-dryness and blood-stasis group, with statistically significant differences ($P<0.05$) .

2.3 Comparison of Laboratory Indicators Between pSjD-Dryness and Blood-Stasis Group and pSjD-Non-Dryness and Blood-Stasis Group

Laboratory indicator comparisons showed no statistically significant differences between the two groups in WBC, NEUT, ALT, AST, TBIL, ALB, serum potassium, serum sodium, serum chloride levels, or in the proportions of elevated IgA, elevated IgM, decreased C3, decreased C4, elevated CRP, elevated ESR, ANA$ $1:320, anti-Sm positivity, anti-SSB positivity, anti-Scl70 positivity,

anti-AMA_{M2} positivity, anti-PMScl positivity, anti-ACL positivity, or splenomegaly (P>0.05).

The pSjD-dryness and blood-stasis group had lower LYMPH, RBC, Hb, PLT, and Cr levels, and lower ILD proportion, but higher proportions of elevated IgG, ANA$ 1 : 160, $anti-SSApositivity$, $anti-Ro52positivity$, $anti-RNPpositivity$, $anti-CENP-Bpositivity$, $anti-$ $2GP1 positivity, and anti-dsDNA positivity, as well as higher ESSDAI scores compared with the pSjD-non-dryness and blood-stasis group, with statistically significant differences (P<0.05) .

2.4 Multivariate Logistic Regression Analysis of Influencing Factors for Dryness and Blood-Stasis Syndrome in pSjD Patients

In the multivariate logistic regression analysis, because there was significant linear correlation among age at enrollment, age at disease onset, and disease duration (duration = age at enrollment - age at disease onset), simultaneous inclusion in the model could cause collinearity interference. To ensure model stability and interpretability, only "age at enrollment," which is more clinically intuitive, was retained in the multivariate model, while "age at disease onset" was excluded. Additionally, considering that the diagnostic criteria for dryness and blood-stasis syndrome already encompassed clinical symptom characteristics, simultaneous inclusion of chief complaints in the model could cause explanatory redundancy and logical confusion. Therefore, this study did not include symptom variables in the multivariate analysis, but primarily selected objective quantitative indicators such as laboratory markers and disease activity (ESSDAI score) as independent variables for multivariate logistic regression analysis.

Using whether pSjD patients were diagnosed with dryness and blood-stasis syndrome as the dependent variable, factors with P<0.1 in univariate analysis were included as independent variables in the multivariate logistic regression analysis (variable assignment table shown in). The results showed that older age at enrollment (OR=0.979, 95%CI=0.965-0.993, P=0.004) and higher PLT level (OR=0.997, 95%CI=0.994-0.999, P=0.007) were independent protective factors for dryness and blood-stasis syndrome in pSjD patients, while anti-RNP positivity (OR=2.352, 95%CI=1.305-4.238, P=0.004), anti-CENP-B positivity (OR=2.490, 95%CI=1.404-4.415, P=0.002), anti-$ $2GP1 positivity (OR=2.269, 95%CI=1.057-4.872, P=0.036), and higher ESSDAI scores (OR=1.037, 95%CI=1.011-1.064, P=0.006) were independent risk factors .

2.5 Kaplan-Meier Survival Curve Analysis

During prospective follow-up, some patients experienced outcome events or were lost to follow-up. Among pSjD patients included in the survival analysis, 95 cases (10.5%) of death, 30 cases (3.4%) of new malignancy, and 21 cases (3.9%) of new-onset ILD were observed. Kaplan-Meier survival curve analysis showed

no statistically significant differences in overall mortality, malignancy incidence, or ILD incidence between the pSjD-dryness and blood-stasis group and the pSjD-non-dryness and blood-stasis group (P>0.05) [Figure 1: see original paper].

Discussion

Current clinical research on pSjD has mostly focused on immunology and clinical classification, while systematic description and research on TCM patterns, particularly dryness and blood-stasis syndrome, are almost blank. To clarify the clinical characteristics, laboratory indicators, and prognosis of pSjD patients with dryness and blood-stasis syndrome, this study enrolled 970 pSjD patients, aiming to provide evidence-based correlation between TCM patterns and modern medical indicators, and to enrich individualized management of pSjD patients.

The study findings revealed: (1) Compared with the pSjD-non-dryness and blood-stasis group, the pSjD-dryness and blood-stasis group had younger age at enrollment and disease onset, longer disease duration, and higher proportion of females; (2) In terms of clinical symptoms, the top five chief complaints in pSjD-dryness and blood-stasis patients were xerostomia, xerophthalmia, arthralgia, fatigue, and rampant caries; (3) In laboratory examinations, the pSjD-dryness and blood-stasis group more frequently showed decreased peripheral blood LYMPH, RBC, Hb, and PLT levels, elevated IgG, higher positive rates of ANA$ 1 : 160, $anti-SSA, anti-Ro52, anti-RNP, anti-CENP-B, anti-2GP1$, and $anti-dsDNA$ antibodies, and higher ESSDAI scores, while Crelevation and new-onset ILD were less common; (4) Multivariate logistic regression showed that older age at enrollment and higher P1 stasis syndrome in pSjD patients, while anti-RNP positivity, anti-CENP-B positivity, anti-$2GP1 positivity, and higher ESSDAI scores were independent risk factors; (5) Survival curve analysis indicated no significant differences in overall mortality, malignancy, or new-onset ILD incidence between the pSjD-dryness and blood-stasis group and the pSjD-non-dryness and blood-stasis group.

From a pathogenesis perspective, this study further confirms that the formation of dryness and blood-stasis syndrome is consistent not only with traditional TCM theories of "body fluids generating blood," "blood transforming into fluids," and "prolonged disease causing deficiency, deficiency leading to stasis," but also receives objective manifestation in modern immunological test results, such as decreased blood cells, elevated immunoglobulin levels, and increased disease activity. This preliminary reveals the connection between TCM pattern differentiation and objective material basis in pSjD. Sjögren' s syndrome has "dryness" as its core pathogenesis, which gradually forms "dryness and blood-stasis intermingling" during disease progression, emphasizing the simultaneous depletion of fluids and blood and the interweaving of deficiency and stasis. This pathological characteristic of "dryness" as the root and "stasis" as the branch may explain the unique clinical presentation of pSjD patients with concurrent

xerostomia/xerophthalmia and hematological abnormalities.

Worth further discussion is that the "dryness" and "stasis" characteristics manifested in pSjD differ from other autoimmune diseases. Regarding the "dryness" feature, pSjD' s "dryness" centers on exocrine gland dysfunction caused by fluid depletion, mainly manifesting as xerostomia, xerophthalmia, skin dryness, and reduced salivary and lacrimal secretion. Academician Wu Yiling integrated collateral disease theory with modern medicine to propose the theoretical system of "collateral-vascular system disease" [19]. Collaterals are tiny and intricate, with ocular collaterals called "eye collaterals" that have fine and deep structures with slow blood flow, making them prone to stasis. Over time, this can lead to eye dryness, reduced tear secretion, and in severe cases, develop into keratoconjunctivitis sicca and corneal epithelial erosion [20]. Regarding the "stasis" feature, pSjD' s "stasis" mainly results from long-term fluid depletion leading to poor blood circulation, and the presence of blood stasis further aggravates fluid distribution 障碍, making xerostomia and xerophthalmia symptoms protracted and difficult to resolve. Rheumatoid arthritis belongs to the category of "bi-syndrome" in TCM. The "Yi Lin Gai Cuo" (Corrections of Medical Errors) proposed: "Bi-syndrome has a theory of blood stasis." The "stasis" in rheumatoid arthritis mostly results from poor local qi and blood circulation and blocked meridians in joints, often manifesting as fixed joint pain and skin ecchymosis, i.e., "All shoulder pain, arm pain, waist pain, leg pain, or generalized pain are collectively called bi-syndrome." Current research has found that D-dimer is an independent factor associated with blood stasis syndrome in RA [21]. Professor Wang Qingguo believes that systemic lupus erythematosus can be summarized pathologically as "yin deficiency as the root, stasis-heat as the branch" [22], where "stasis" mostly results from intense heat-toxin scorching collaterals or yin deficiency with blood stasis, can involve multiple viscera and tissues, and manifests as skin petechiae, abdominal pain, hemoptysis, proteinuria, etc.

Additionally, pSjD patients with dryness and blood-stasis syndrome had a lower proportion of comorbid ILD, with their condition mainly manifesting as hematological and immunological abnormalities. This suggests that in clinical practice, for such patients, hematological function should be prioritized for assessment based on pattern differentiation, with timely intervention to prevent progression. Combining TCM theory, nourishing yin and moistening dryness, activating blood and resolving stasis may become an important treatment strategy to improve immunological abnormalities and hematological damage in these patients, warranting further clinical research validation.

During prospective follow-up, no significant differences were observed between the dryness and blood-stasis group and the non-dryness and blood-stasis group in overall mortality, new malignancy, or new-onset ILD incidence. This result may be closely related to the dynamic evolution of patterns. The dryness and blood-stasis pattern at patient enrollment may change over time. Therefore, the correlation between baseline pattern and outcomes may not fully reflect the true impact of pattern changes during follow-up on prognosis. This dynamic nature

may weaken the statistical power of survival analysis and is an important reason why this study' s survival analysis failed to yield positive results. This suggests that future research needs to dynamically assess pattern changes during long-term follow-up, combined with longitudinal data to further clarify their impact on prognosis.

In summary, pSjD patients with dryness and blood-stasis syndrome exhibit a protracted disease course, higher ESSDAI scores, more significant hematological involvement, but lower proportion of comorbid ILD. Older age at enrollment and higher PLT level may be independent protective factors for dryness and blood-stasis syndrome in pSjD patients, while anti-RNP positivity, anti-CENP-B positivity, anti-$ $2GP1 positivity, and higher ESSDAI scores may be independent risk factors. In clinical diagnosis and treatment, identifying the characteristics of dryness and blood-stasis syndrome can help detect potential high-risk patients early, prompting attention to blood routine and immunological indicator assessment and vigilance for hematological involvement, providing evidence-based support for individualized patient management. The treatment strategy of nourishing yin and moistening dryness combined with activating blood and resolving stasis is expected to improve disease activity and hematological damage in such patients, awaiting further clinical research validation. This study' s data were derived from a single-center study, and future multi-center, large-sample validation is still needed, combined with long-term follow-up to explore the long-term prognostic characteristics and comorbidity spectrum of pSjD patients with dryness and blood-stasis syndrome, providing basis and guidance for integrated Chinese and Western medicine individualized treatment.

References

[1] MARIETTE X, CRISWELL L A. Primary sjögren' s syndrome [J]. N Engl J Med, 2018, 378(10): 931-939. DOI: 10.1056/nejmcp1702514.

[2] MALEKI-FISCHBACH M, KASTSIANOK L, KOSLOW M, et al. Manifestations and management of sjögren's disease [J]. Arthritis Res Ther, 2024, 26(1): 43. DOI: 10.1186/s13075-024-03251-7.

[3] WENG M Y, HUANG Y T, LIU M F, et al. Incidence and mortality of treated primary Sjogren' s syndrome in Taiwan: a population-based study [J]. J Rheumatol, 2011, 38(4): 706-708. DOI: 10.3899/jrheum.100883.

[4] QIN B D, WANG J Q, YANG Z X, et al. Epidemiology of primary sjögren' s syndrome: a systematic review and meta-analysis [J]. Ann Rheum Dis, 2015, 74(11): 1983-1989. DOI: 10.1136/annrheumdis-2014-205375.

[5] LUO Xuelan, JIAN Wenyuan. Progress in the application of autologous serum in the treatment of dry eye disease [J]. Journal of Ophthalmology & Otolaryngology of Traditional Chinese Medicine, 2021, 11(1): 54-58.

[6] TONOYAN L, VINCENT-BUGNAS S, OLIVIERI C V, et al. New viral

facets in oral diseases: the EBV paradox [J]. Int J Mol Sci, 2019, 20(23): 5861. DOI: 10.3390/ijms20235861.

[7] RAMOS-CASALS M, BRITO-ZERÓN P, BOMBARDIERI S, et al. EULAR recommendations for the management of Sjögren' s syndrome with topical and systemic therapies [J]. Ann Rheum Dis, 2020, 79(1): 3-18. DOI: 10.1136/annrheumdis-2019-216114.

[8] JIANG Quan, ZHANG Huadong, CHEN Yi, et al. Experience of Lu Zhizheng in treating Sjögren' s syndrome [J]. Journal of Traditional Chinese Medicine, 2016, 57(6): 463-465. DOI: 10.3321/j.issn: 1001-1668.2016.06.005.

[9] WANG Wanru, YAN Xiaoping. Professor Yan Xiaoping' s experience in diagnosing and treating Sjögren' s syndrome [J]. World Journal of Integrated Traditional and Western Medicine, 2015, 10(4): 473-475, 592. DOI: 10.13935/j.cnki.sjzx.150408.

[10] ZHOU Xinyao, JIANG Quan, TANG Xiaopo, et al. Expert consensus on TCM syndrome patterns of Sjögren's syndrome [J]. Journal of Beijing University of Chinese Medicine, 2023, 46(3): 310-314.

[11] SHIBOSKI C H, SHIBOSKI S C, SEROR R, et al. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren' s syndrome: a consensus and data-driven methodology involving three international patient cohorts [J]. Ann Rheum Dis, 2017, 76(1): 9-16. DOI: 10.1136/annrheumdis-2016-210571.

[12] SEROR R, BOOTSMA H, SARAUX A, et al. Defining disease activity states and clinically meaningful improvement in primary Sjögren' s syndrome with EULAR primary Sjögren' s syndrome disease activity (ESSDAI) and patient-reported indexes (ESSPRI) [J]. Ann Rheum Dis, 2016, 75(2): 382-389. DOI: 10.1136/annrheumdis-2014-206008.

[13] CUI Xiangning, FENG Xinghua. Feng Xinghua' s experience in differential diagnosis and treatment of Sjögren' s syndrome [J]. Journal of Traditional Chinese Medicine, 2017, 58(3): 202-204, 213. DOI: 10.13288/j.11-2166/r.2017.03.007.

[14] (Jin Dynasty) LIU Wansu. Suwen Xuanji Yuanbingshi [M]. Facsimile edition. Beijing: People' s Medical Publishing House, 1956.

[15] (Ming Dynasty) ZHANG Jiebin. Jingyue Quanshu [M]. Beijing: China Press of Traditional Chinese Medicine, 1994.

[16] ZHANG Yan, YANG Jianying, WANG Qin, et al. Research progress on TCM diagnosis and treatment of primary Sjögren' s syndrome with cytopenia [J]. World Chinese Medicine, 2024, 19(2): 250-256.

[17] LI Ben, XUE Luan. Analysis of clinical characteristics of patients with dryness-toxin syndrome in primary Sjögren' s syndrome [J]. Journal of

Shanghai University of Traditional Chinese Medicine, 2019, 33(3): 19-23. DOI: 10.16306/j.1008-861x.2019.03.004.

[18] WANG Dan, XUE Luan, HU Jiandong, et al. Analysis of clinical characteristics of blood stasis syndrome in primary Sjögren' s syndrome [J]. Chinese Journal of Traditional Chinese Medicine, 2013, 31(5): 1108-1110. DOI: 10.13193/j.archtcm.2013.05.150.wangd.028.

[19] WEI Cong, CHANG Liping, ZHAO Shanshan. Theoretical exploration on the prevention and treatment of "collateral-vascular system disease" guided by collateral disease theory [J]. Journal of Difficult and Complicated Diseases, 2015, 14(11): 1101-1103.

[20] QI Wenxia, WANG Gang, YAN Yanfeng, et al. Exploration of the pathogenesis and treatment of Sjögren' s syndrome based on TCM blood stasis theory [J]. World Science and Technology - Modernization of Traditional Chinese Medicine, 2022, 24(11): 4279-4285.

[21] LI Xuemei, TAO Qingwen, XU Yuan, et al. Diagnostic value of six coagulation parameters in blood stasis syndrome of rheumatoid arthritis [J]. Journal of China-Japan Friendship Hospital, 2023, 37(4): 211-215.

[22] DU Weizhe, LIAN Yajun, TAN Ling, et al. Wang Qingguo' s approach to differential diagnosis and treatment and medication characteristics for systemic lupus erythematosus [J]. Acta Chinese Medicine, 2020, 35(6): 1221-1225. DOI: 10.16368/j.issn.1674-8999.2020.06.275.

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