Clinical and Laboratory Characteristics and Risk Factors of Systemic Sclerosis Complicated by Sjögren' s Syndrome: A Postprint Study

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Abstract

Background: Systemic sclerosis (SSc) is a heterogeneous disease that frequently co-occurs with Sjögren' s syndrome (SS). As some symptoms of SSc patients resemble those of SS, SS is prone to be missed during clinical diagnosis and treatment.

Objective: To investigate the clinical and laboratory characteristics and risk factors for co-occurring SS in SSc patients.

Methods: SSc patients hospitalized at Li Huili Hospital of Ningbo Medical Center from 2019 to 2023 were retrospectively enrolled. Baseline data and laboratory test results were collected. Patients were divided into an SSc group (n=91) and an SSc with SS group (n=36) based on the presence of co-occurring SS. Multivariate logistic regression analysis was used to explore the risk factors for SSc with SS.

Results: The SSc with SS group exhibited higher proportions of females, longer disease duration, hematological involvement, limited cutaneous SSc (lcSSc), and autoimmune liver disease, but lower proportions of pulmonary involvement and cyclophosphamide use compared to the SSc group ($P<0.05$). The SSc with SS group also showed lower platelet distribution width, complement C4, and detection rate of anti-scleroderma 70 antibody, while demonstrating higher alkaline phosphatase, gamma-glutamyl transferase, immunoglobulin M (IgM), anti-centromere protein B antibody (anti-CENP-B antibody), anti-Sjögren' s syndrome A/Ro52 antibody (anti-SSA/Ro52 antibody), anti-Sjögren' s syndrome A/Ro60 antibody (anti-SSA/Ro60 antibody), anti-Sjögren' s syndrome B antibody (anti-SSB antibody), and anti-mitochondrial M2 antibody (anti-AMA-M2 antibody) detection rates compared to the SSc group. Multivariate logistic regression analysis revealed that elevated IgM (OR=3.796, 95%CI=1.021~14.115), positive anti-SSA/Ro52 antibody (OR=15.099, 95%CI=1.750~130.264), and

positive anti-CENP-B antibody (OR=11.681, 95%CI=1.662~82.097) were independent risk factors for SSc with SS (P<0.05).

Conclusion: Patients with SSc and SS exhibit characteristics of both conditions. When SSc patients present with elevated IgM, positive anti-Sjögren' s syndrome A antibodies, positive anti-CENP-B antibodies, and corresponding clinical symptoms, systematic and comprehensive examinations such as labial salivary gland biopsy should be performed to prevent missed diagnosis.

Full Text

Analysis of Clinical and Laboratory Characteristics and Risk Factors of Systemic Sclerosis Combined with Sjögren' s Syndrome

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Abstract

Background: Systemic sclerosis (SSc) is a heterogeneous disease often accompanied by Sjögren' s syndrome (SS). Some symptoms of SSc patients are similar to those of SS, leading to frequent missed diagnoses of SS in clinical practice.

Objective: To explore the clinical and laboratory characteristics of SSc combined with SS and identify risk factors for their co-occurrence.

Methods: We retrospectively enrolled SSc patients hospitalized at Ningbo Medical Center Lihuili Hospital from 2019 to 2023. Baseline data and laboratory test results were collected. Patients were divided into two groups based on the presence or absence of SS: the SSc group (n=91) and the SSc with SS group (n=36). Multivariate logistic regression analysis was used to identify risk factors for SSc combined with SS.

Results: The SSc with SS group had higher proportions of female patients, longer disease duration, blood involvement, limited cutaneous systemic sclerosis (lcSSc), and autoimmune liver disease compared to the SSc group, while the proportions of lung involvement and cyclophosphamide use were lower (P<0.05). The SSc with SS group also showed lower platelet distribution width, complement C4, and anti-Scl-70 antibody detection rates, but higher alkaline phosphatase, gamma-glutamyl transferase, immunoglobulin M (IgM), anti-centromere protein B antibodies (anti-CENP-B antibodies), anti-Sjögren' s syndrome A/Ro52 antibodies (anti-SSA/Ro52 antibodies), anti-Sjögren' s syndrome A/Ro60 antibodies (anti-SSA/Ro60 antibodies), anti-Sjögren' s syndrome B antibodies (anti-SSB antibodies), and anti-mitochondrial M2

antibodies (anti-AMA-M2 antibodies) compared to the SSc group. Multivariate logistic regression analysis revealed that elevated IgM (OR=3.796, 95%CI=1.021-14.115), positive anti-SSA/Ro52 antibodies (OR=15.099, 95%CI=1.750-130.264), and positive anti-CENP-B antibodies (OR=11.681, 95%CI=1.662-82.097) were independent risk factors for SSc combined with SS (P<0.05).

Conclusion: Patients with SSc combined with SS exhibit characteristics of both diseases. When SSc patients present with elevated IgM, positive anti-SSA and anti-CENP-B antibodies along with corresponding clinical symptoms, comprehensive examinations such as labial gland biopsy should be performed to prevent missed diagnosis.

Keywords: Scleroderma, systemic; Systemic sclerosis; Sjögren' s syndrome; Clinical characteristics; Laboratory characteristics; Risk factors

1. Introduction

Systemic sclerosis (SSc) is an autoimmune disease characterized by limited or diffuse skin thickening and fibrosis that can affect various organs. Epidemiological studies show that the global incidence of SSc is 0.6-5.6 per 100,000, with a prevalence of 7.2-44.3 per 100,000. The average age at diagnosis is 33.5-59.8 years, and patients are predominantly female with a male-to-female ratio of approximately 1:15 to 1:3.8. SSc has the highest mortality among connective tissue diseases, with a 5-year survival rate of 84% for diffuse cutaneous systemic sclerosis (dcSSc) and 93%-96% for limited cutaneous systemic sclerosis (lcSSc). SSc frequently coexists with other autoimmune diseases, with approximately one-third of SSc patients also developing Sjögren' s syndrome (SS). Among patients with overlapping syndromes, lcSSc accounts for 17%-29% of cases. Dryness symptoms such as xerostomia and xerophthalmia are common in SSc patients, and exocrine gland dysfunction is typically associated with glandular fibrosis, though some studies suggest it may result from the combined effects of SSc and SS. This retrospective study of SSc patients examines the clinical symptoms and laboratory findings in SSc combined with SS and analyzes the risk factors to assist clinicians in diagnosis and treatment.

1.1 Study Subjects

We retrospectively enrolled SSc patients hospitalized at Ningbo Medical Center Lihuili Hospital from 2019 to 2023. Inclusion criteria were: (1) meeting the 2013 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for SSc, with SSc combined with SS patients also meeting the 2017 ACR/EULAR classification criteria for SS; and (2) age >18 years. Exclusion criteria included history of head and neck radiation therapy, hepatitis C virus infection, sarcoidosis, amyloidosis, AIDS, graft-versus-host disease, and immunoglobulin G4-related disease. A total of

127 patients were ultimately included. Patients were divided into two groups based on the presence or absence of SS: the SSc group (n=91) and the SSc with SS group (n=36). This study was approved by the Ethics Committee of Ningbo Medical Center Lihuili Hospital (Ethics approval number: Lihuili Hospital Ethics Review 2024 Research No. 058), and informed consent was waived.

1.2 Data Collection and Diagnostic Criteria

Patient data were extracted from the electronic medical record system of Ningbo Medical Center Lihuili Hospital, including sex, age, age at disease onset, disease duration, hypertension, diabetes, smoking history, alcohol consumption history, medication history, clinical manifestations, and comorbid autoimmune diseases. Hypertension was defined as systolic blood pressure $ $140 mmHg (1 mmHg=0.133 kPa) and/or diastolic blood pressure $ $90 mmHg, or previously diagnosed hypertension or current use of antihypertensive medication. Diabetes was defined as fasting blood glucose $ $7 mmol/L and/or 2-hour postprandial blood glucose $ $11.1 mmol/L, or self-reported diabetes history or current use of hypoglycemic medication. Smoking history was defined as smoking $ $1 cigarette daily for over one year. Alcohol consumption history was defined as drinking at least once per month on average. lcSSc was diagnosed when skin involvement was limited to areas distal to the elbows/knees but could involve the face and neck. Joint involvement included arthralgia, joint swelling, or joint deformity. Neurological involvement indicated nerve damage shown by electromyography. Pulmonary involvement referred to pulmonary fibrosis or interstitial lung disease. Gastrointestinal involvement included esophageal dysmotility, abnormal esophageal manometry, or gastroesophageal reflux. Pulmonary arterial hypertension was defined as pulmonary artery systolic pressure $ $38 mmHg. Cardiac involvement included conduction abnormalities and arrhythmias due to myocardial fibrosis, pericardial effusion, or left ventricular systolic/diastolic dysfunction shown by echocardiography. Hematological involvement referred to anemia or reduced platelet and white blood cell counts after excluding drug effects or other diseases. Muscle involvement included myopathy or myalgia with elevated muscle enzymes.

1.3 Laboratory Examinations

Fasting venous blood samples were collected in the morning. Anticoagulated whole blood and serum/plasma obtained after centrifugation were used for various tests. Autoantibody detection was performed using immunoblot assay kits (Shenzhen Yhlo Biotech Co., Ltd.). Autoantibodies included anti-nuclear ribonucleoprotein (nRNP) antibodies, anti-Smith (Sm) antibodies, anti-Sjögren' s syndrome A/Ro60 (SSA/Ro60) antibodies, anti-Sjögren' s syndrome A/Ro52 (SSA/Ro52) antibodies, anti-Sjögren' s syndrome B (SSB) antibodies, anti-scleroderma-70 (Scl-70) antibodies, anti-polymyositis-scleroderma (PM-Scl) antibodies, anti-histidyl-tRNA synthetase (Jo-1) antibodies, anti-proliferating cell nuclear antigen (PCNA) antibodies, anti-double-stranded DNA (dsDNA)

antibodies, anti-nucleosome antibodies (AnuA), anti-histone antibodies (AHA), anti-ribosomal P protein antibodies (ARPA), anti-centromere protein B (CENP-B) antibodies, and anti-mitochondrial M2 antibodies (AMA-M2). Results were read using Yhlo' s fully automated immunoanalyzer. Quantitative detection of IgG (reference range: 7.51-15.60 g/L), IgM (reference range: 0.46-3.04 g/L), IgA (reference range: 0.82-4.53 g/L), complement C3 (reference range: 79.0-152.0 mg/dL), complement C4 (reference range: 16.0-38.0 mg/dL), and rheumatoid factor (RF) (reference range: <20.0 U/mL) was performed using test kits from Haier Biomedical Co., Ltd. (immunoturbidimetry). Complete blood count was performed using a Sysmex automated hematology analyzer to obtain white blood cell count (WBC) (reference range: $3.5\$\times10^{\{9\}/L-9.5\times10}\{9\}/L), red blood cell count (RBC) (reference range: male 4.30\times10^{\{12\}/L-5.80\times10}\{12\}/L, female 3.80\times10^{\{12\}/L-5.10\times10}\{12\}/L), hemoglobin (Hb) (reference range: male 130-175 g/L, female 115-150 g/L), red blood cell distribution width (RDW) (reference range: 12.2\times10^{\{9\}/L-350\times10}\{9\}\$/L), and platelet distribution width (PDW) (reference range: 10.0%-17.5%). Biochemical parameters included total protein (TP) (reference range: 65.0-85.0 g/L), albumin (Alb) (reference range: 40.0-55.0 g/L), alanine aminotransferase (ALT) (reference range: male 9-50 U/L, female 7-40 U/L), aspartate aminotransferase (AST) (reference range: male 15-40 U/L, female 13-35 U/L), alkaline phosphatase (ALP) (reference range: male 45-125 U/L, female 35-135 U/L), gamma-glutamyl transferase (GGT) (reference range: male 10-60 U/L, female 7-45 U/L), lactate dehydrogenase (LDH) (reference range: 120-250 U/L), and creatine kinase (CK) (reference range: male 50-310 U/L, female 40-200 U/L), measured using standard biochemical methods recommended by the International Federation of Clinical Chemistry and Laboratory Medicine.

1.4 Statistical Methods

SPSS 21.0 software was used for data analysis. Normally distributed continuous variables were expressed as mean ± standard deviation and compared between groups using independent samples t-test. Non-normally distributed continuous variables were expressed as median (P25, P75) and compared using non-parametric tests. Categorical variables were expressed as frequencies and compared using ^{2} test or Fisher' s exact test. Variables with statistical significance in univariate analysis were included in multivariate logistic regression analysis to explore risk factors for SSc combined with SS. P<0.05 was considered statistically significant.

2. Results

2.1 Comparison of Clinical Data Between Groups

The SSc with SS group had significantly higher proportions of female patients, longer disease duration, blood involvement, lcSSc, and autoimmune liver disease compared to the SSc group, while the proportions of lung involvement

and cyclophosphamide use were significantly lower (P<0.05). There were no significant differences between groups in age, age at onset, hypertension, diabetes, smoking history, alcohol consumption history, Raynaud' s phenomenon, skin rash, digital ulcers, joint involvement, neurological involvement, gastrointestinal involvement, pulmonary arterial hypertension, cardiac involvement, muscle involvement, or in the use of glucocorticoids, hydroxychloroquine, tacrolimus, methotrexate, mycophenolate mofetil, Tripterygium wilfordii, anti-fibrotic drugs, biologics and targeted therapies, or in the proportions of autoimmune inflammatory myopathy and rheumatoid arthritis (P>0.05) .

2.2 Comparison of Laboratory Results Between Groups

The SSc with SS group had significantly lower RDW, complement C4, and anti-Scl-70 antibody detection rates, but significantly higher ALP, GGT, IgM, anti-CENP-B antibodies, anti-SSA/Ro52 antibodies, anti-SSA/Ro60 antibodies, anti-SSB antibodies, and anti-AMA-M2 antibodies compared to the SSc group (P<0.05). There were no significant differences between groups in WBC, RBC, Hb, PLT, PDW, TP, Alb, ALT, AST, LDH, CK, IgA, IgG, complement C3, proportion of RF>20 U/mL, anti-nRNP antibodies, or anti-PM-Scl antibodies (P>0.05) .

2.3 Multivariate Logistic Regression Analysis of Risk Factors for SSc Combined with SS

Using the presence or absence of SS in SSc patients (assignment: no=0, yes=1) as the dependent variable, variables showing statistical significance in univariate analysis were included as independent variables in multivariate logistic regression. Categorical variable assignments are shown in , while other variables (disease duration, RDW, ALP, GGT, IgM, complement C4) were assigned as actual measured values. Multivariate logistic regression analysis showed that elevated IgM (OR=3.796, 95%CI=1.021-14.115), positive anti-SSA/Ro52 antibodies (OR=15.099, 95%CI=1.750-130.264), and positive anti-CENP-B antibodies (OR=11.681, 95%CI=1.662-82.097) were independent risk factors for SSc combined with SS (P<0.05) . The Hosmer-Lemeshow test indicated good model fit.

3. Discussion

SSc is a complex autoimmune disease that frequently occurs with other rheumatic diseases, including SS, systemic lupus erythematosus, rheumatoid arthritis, and inflammatory myopathy. Dryness symptoms are common in SSc (68%), but only about 14% of SSc patients meet the diagnostic criteria for SS. The main feature of SS is lymphocytic infiltration of salivary glands, while approximately half of SSc patients have salivary gland fibrosis. SSc patients with concurrent SS may experience more severe disease progression and higher mortality rates. Therefore, earlier diagnosis and appropriate symptomatic

treatment are crucial.

CENP-B is one of the earliest discovered centromere proteins. From a serological perspective, both SSc and SS patients have very high positive rates of anti-CENP-B antibodies. Previous studies have shown that approximately 10% of SS patients present with scleroderma-pattern nailfold capillaroscopy. Our results demonstrate that patients in the SSc with SS group predominantly had the lcSSc skin phenotype, consistent with the findings of BALDINI et al. In SS patients, anti-CENP-B antibodies may be present for several years before the onset of SSc. Our univariate analysis showed that the positive rate of anti-CENP-B antibodies in the SSc with SS group was significantly higher than in the SSc group, and logistic regression analysis identified anti-CENP-B antibodies as an independent risk factor for SSc combined with SS, suggesting that anti-CENP-B antibodies may play a crucial role in the pathogenesis of both SSc and SS. MENG et al. reported that primary SS patients positive for anti-CENP-B antibodies have distinct clinical and immunological features, including relatively low disease activity, elevated liver function indices, and susceptibility to autoimmune liver disease. RAMIREZ et al. demonstrated that approximately 30% of patients with autoimmune liver disease have elevated IgM levels. Our univariate analysis showed that the SSc with SS group had a higher prevalence of concurrent autoimmune liver disease, with significantly higher liver function parameters (ALP and GGT), IgM levels, and anti-AMA-M2 antibody positivity compared to the SSc group. Logistic regression results indicated that IgM is an independent risk factor for SSc combined with SS, suggesting that the target organ of anti-CENP-B antibodies may be the liver and that IgM may be involved in the pathological process.

Retrospective studies have shown that SS patients positive for anti-SSA/Ro52 antibodies have higher disease activity and more frequent manifestations such as anemia and leukopenia compared to antibody-negative patients. Our results demonstrated that the SSc with SS group had significantly higher positive rates of anti-SSA antibodies than the SSc group, and logistic regression identified anti-SSA/Ro52 antibodies as an independent risk factor for SSc combined with SS. However, the higher anti-SSA antibody positivity rate did not significantly increase organ involvement beyond the hematological system. Interstitial lung disease is the leading cause of death in SSc patients, and clinicians typically use immunosuppressants such as cyclophosphamide and mycophenolate mofetil to inhibit disease progression. Our univariate analysis also showed that the SSc group had significantly higher rates of lung involvement and cyclophosphamide use compared to the SSc with SS group. COTTIN et al. reported that dcSSc patients, Scl-70-positive patients, and patients without anti-centromere antibodies have a higher risk of developing interstitial lung disease. Our results showed that the SSc with SS group had a high positive rate of anti-CENP-B antibodies (77.8%) but a 0% positive rate of anti-Scl-70 antibodies, with lower rates of lung involvement compared to the SSc group. This suggests that CENP-B antibody-positive SSc may represent a distinct subtype that, while prone to concurrent SS, has relatively slower disease progression compared to other autoantibody-

positive SSc subtypes.

This study has several limitations. First, the number of enrolled patients was relatively small, and some patients may have received prior treatment at local hospitals, which could have altered their clinical symptoms and laboratory results. Additionally, as this was a retrospective analysis relying on medical record data, despite repeated verification and consistency checks, incomplete or inaccurate information may have introduced various biases and confounding factors, potentially affecting the results. Therefore, the conclusions require validation through larger prospective multicenter studies.

In summary, patients with SSc combined with SS are predominantly female, have longer disease duration, predominantly lcSSc clinical classification, common hematological involvement, and frequent concurrent autoimmune liver disease. These patients show decreased complement C4 levels, high positive rates of anti-SSA, anti-CENP-B, and anti-AMA-M2 antibodies, and elevated IgM and liver function parameters. Therefore, we recommend that clinicians perform comprehensive examinations such as labial gland biopsy when managing CENP-B antibody-positive SSc patients with dry mouth, dry eyes, decreased complement C4, and elevated IgM to prevent missed diagnosis.

Author Contributions: ZOU Songyan conceived the study, designed the research, conducted the investigation, and wrote and revised the manuscript. LI Xiaodong and ZHANG Riyi collected and organized data, performed statistical analysis, and prepared figures and tables. MU Yinyu was responsible for quality control, reviewed the manuscript, and provided overall supervision.

Conflict of Interest: The authors declare no conflict of interest.

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References: [1] CIAFFI J, MORABITO M F, RUSCITTI P, et al. Incidence, prevalence and mortality of systemic sclerosis in Italy: a nationwide population-based study using administrative health data[J]. Rheumatol Int, 2021, 41(1): 129-137. DOI: 10.1007/s00296-020-04733-8. [2] FAN Y N, BENDER S, SHI W Z, et al. Incidence and prevalence of systemic sclerosis and systemic sclerosis with interstitial lung disease in the United States[J]. J Manag Care Spec Pharm, 2020, 26(12): 1539-1547. DOI: 10.18553/jmcp.2020.20136. [3] BERGAMASCO A, HARTMANN N, WALLACE L, et al. Epidemiology of systemic sclerosis and systemic sclerosis-associated interstitial lung disease[J]. Clin Epidemiol, 2019, 11: 257-273. DOI: 10.2147/CLEP.S191418. [4] JERJEN R, NIKPOUR M, KRIEG T, et al. Systemic sclerosis in adults. Part I: Clinical features and pathogenesis[J]. J Am Acad Dermatol, 2022, 87(5): 937-954. DOI: 10.1016/j.jaad.2021.10.065. [5] BALDINI C, ARNAUD L, AVČIN T, et al. Sjögren' s syndrome and other rare and complex connective tissue diseases: an intriguing liaison[J]. Clin Exp Rheumatol, 2022, 40 Suppl 134(5): 103-112. DOI: 10.55563/clinexprheumatol/3y0hqs. [6] ZIMMERMANN F, ROBIN F, CADIOU S, et al. Should we really include systemic sclerosis specific anti-

bodies in the classification criteria of Sjogren' s disease?[J]. Semin Arthritis Rheum, 2023, 58: 152158. DOI: 10.1016/j.semarthrit.2022.152158. [7] CAN G, SARIOĞLU S, BIRLIK M, et al. The prevalence of Sjögren' s syndrome and sicca symptoms in patients with systemic sclerosis and alpha-smooth muscle actin expression in biopsy specimens from minor salivary glands[J]. Turk J Med Sci, 2021, 51(4): 1875-1882. DOI: 10.3906/sag-2012-25. [8] ZIMMERMANN F, ROBIN F, CAILLAULT L, et al. Sicca syndrome in systemic sclerosis: a narrative review on a neglected issue[J]. Rheumatology: Oxford, 2023, 62(SI): SI1-I11. DOI: 10.1093/rheumatology/keac412. [9] MARKETOS N, MAVRAGANI C P. Prevalence and clinical implications of scleroderma-specific autoantibodies in seronegative patients with sicca complaints[J]. Mediterr J Rheumatol, 2023, 34(3): 398-402. DOI: 10.31138/mjr.20230808.pa. [10] VAN DEN HOOGEN F, KHANNA D, FRANSEN J, et al. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative[J]. Ann Rheum Dis, 2013, 72(11): 1747-1755. DOI: 10.1136/annrheumdis-2013-204424. [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]. Arthritis Rheumatol, 2017, 69(1): 35-45. DOI: 10.1002/art.39859. [12] BECKER M O, RIEMEKASTEN G. Risk factors for severity and manifestations in systemic sclerosis and prediction of disease course[J]. Expert Rev Clin Immunol, 2016, 12(2): 115-135. DOI: 10.1586/1744666X.2016.1115712. [13] SCHERLINGER M, LUTZ J, GALLI G, et al. Systemic sclerosis overlap and non-overlap syndromes share clinical characteristics but differ in prognosis and treatments[J]. Semin Arthritis Rheum, 2021, 51(1): 36-42. DOI: 10.1016/j.semarthrit.2020.10.009. [14] BEYDON M, MCCOY S, NGUYEN Y, et al. Epidemiology of Sjögren syndrome[J]. Nat Rev Rheumatol, 2024, 20(3): 158-169. DOI: 10.1038/s41584-023-01057-6. [16] HYSA E, PIZZORNI C, SAMMORÌ S, et al. Microvascular damage in autoimmune connective tissue diseases: a capillaroscopic analysis from 20 years of experience in a EULAR training and research referral centre for imaging[J]. RMD Open, 2023, 9(3): e003071. DOI: 10.1136/rmdopen-2023-003071. [17] MENG Yanhong, CHEN Yifan, ZHOU Peiru. Clinical and immunological features of primary Sjögren' s syndrome patients positive for anti-CENP-B antibodies[J]. Journal of Peking University (Health Sciences), 2023, 55(6): 1088-1096. DOI: 10.19723/j.issn.1671-167X.2023.06.021. [18] RAMÍREZ F, URZÚA Á, ROBLERO JP, et al. Colangitis biliar primaria: experiencia de cinco años en el Hospital Clínico de la Universidad de Chile [Primary biliary cholangitis. Experience in 179 patients][J]. Rev Med Chile, 2022, 150(7): 889-895. Spanish. DOI: 10.4067/s0034-98872022000700889. [19] LEE A Y S, PUTTY T, LIN M W, et al. Isolated anti-Ro52 identifies a severe subset of Sjögren's syndrome patients[J]. Front Immunol, 2023, 14: 1115548. DOI: 10.3389/fimmu.2023.1115548. [20] COTTIN V, BROWN K K. Interstitial lung disease associated with systemic sclerosis (SSc-ILD)[J]. Respir Res, 2019, 20(1): 13. DOI: 10.1186/s12931-019-0980-7.

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Note: Figure translations are in progress. See original paper for figures.