BMC Pulmonary Medicine

RESEARCH Open Access

# Serum bilirubin levels in primary Sjögren's syndrome: an association with interstitial lung disease

You-Fan Peng[1*], Fei-Yan Lu[2] and Li-Ya Ma[1]



## Abstract

**Objective** We aimed to assess the association between serum bilirubin levels and interstitial lung disease (ILD) in patients with Primary Sjögren's syndrome (pSS).

**Materials and methods** The retrospectively analysis included 89 consecutive patients with pSS, we collected the clinical materials of pSS patients from the electronic medical records, and all pSS patients were divide into pSS with ILD group and pSS without ILD group.

**Results** Serum bilirubin levels were significantly lower in pSS patients with ILD than those without ILD (p = 0.010). Serum bilirubin levels showed a significant negative correlation with erythrocyte sedimentation rate (ESR) (r = -0.321, p = 0.002) in patients with pSS. A multivariable logistic regression analysis confirmed that serum bilirubin presented an independent association with ILD in patients with pSS (OR = 0.841, 95%CI:0.728–0.972, p = 0.019).

**Conclusion** Serum bilirubin is independently associated with ILD and therefore may be a promising marker of ILD in patients with pSS.

**Keywords** Serum bilirubin, Primary Sjögren's syndrome, Interstitial lung disease

## Introduction

Primary Sjögren's syndrome (pSS) is an autoimmune disorder with the lymphocytic infiltration in exocrine glands [1]. The clinical symptoms are mainly characterized by eyes and mouth dry [2], besides, interstitial lung disease (ILD) is a common extra-glandular manifestation in patients with pSS [3]. It has been reported that ILD is a risk factor of death in patients with pSS [4], thus, the early diagnosis and evaluation of ILD is important to improve the prognosis of pSS. Clinically, high-resolution computed tomography (HRCT) has been suggested as an effectively tool to diagnose and estimate ILD [5], nevertheless, the multiple detection methods have been lacking for ILD, especially laboratory markers, in patients with pSS.

Bilirubin as a main product of heme catabolism exhibits potent antioxidant and anti-inflammatory activity [6]. Over the recent years, accumulating evidences have suggested the associations between serum bilirubin and immune diseases, such as rheumatoid arthritis, systemic lupus erythematosus and ulcerative colitis [7–9]. Recent study demonstrated that decreased serum bilirubin may be a useful biomarker to evaluate the disease activity of pSS [10]. Moreover, pSS patients with high disease

*Correspondence:
You-Fan Peng
youfanpeng@hotmail.com
[1]Department of Respiratory and Critical Care Medicine, The Affiliated Hospital of Youjiang Medical University for Nationalities, No.18 Zhongshan Er Road, Baise, Guangxi 533000, China
[2]Clinical Pathological Diagnosis and Research Centre, The Affiliated Hospital of Youjiang Medical University for Nationalities, Baise, China

activity are more likely to develop into ILD [11]. Thus, in this study, we further evaluated whether serum bilirubin levels were associated with ILD in patients with pSS.

## Materials and methods

### Patients

A total of 89 consecutive patients with pSS who admitted The Affiliated Hospital of Youjiang Medical University for Nationalities were included in this retrospectively analysis. Patients with pSS were diagnosed according to the criteria of the American–European Consensus Group [12]. Patients who met the following diseases were excluded: cardiac disease, cerebral infarction, hepatobiliary disease, hemolytic disease, other autoimmune diseases and malignant tumors. The ILD was identified on the findings of chest HRCT in patients with pSS [13, 14], and then all pSS patients were divided into pSS with ILD group and pSS without ILD group. This study was approved by the Ethics Committee of The Affiliated Hospital of Youjiang Medical University for Nationalities, and was performed according to the Declaration of Helsinki. The informed consent of patients was waived by the Ethics Committee of The Affiliated Hospital of Youjiang Medical University for Nationalities due to the retrospective design of this study.

**Data collection**.

Clinical materials of pSS patients were collected from the electronic medical records, including demographic characteristics, clinical characteristics, laboratory tests and imaging examinations. Peripheral venous blood was taken for laboratory tests after an overnight fasting, the laboratory tests included complement C3, complement C4, immune globulin A, immune globulin G, immune globulin M, alanine aminotransferase, aspartate aminotransferase, serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and bilirubin, there into, serum bilirubin was total concentrations of serum direct bilirubin and serum indirect bilirubin. As regards the imaging examinations, HRCT was performed to assess the pulmonary lesion in patients with pSS.

### Statistical methods

Data were described as the median (interquartile range) for continuous variables with non-normally distribution and as frequencies (percentages) for categorical variables. The comparisons were performed by Mann-Whitney U test for continuous variables and Chi-squared test or Fisher's exact test for categorical variables. The correlation between continuous variables was detected by Spearman correlation test. The possible factors associated with dependent variable were analyzed by univariable and multivariable logistic regression analysis. A p value of $<0.05$ was defined as significant difference. The statistical analyses were conducted with SPSS 25.0 statistical software.

## Results

### The comparison of clinical materials between pSS patients with ILD and pSS patients without ILD

The clinical materials of pSS patients with ILD and without ILD are shown in Table 1. pSS patients with ILD showed significantly higher age and ESR than those without ILD (p=0.034; p=0.022). Of note, serum bilirubin levels were found to be significantly decreased in pSS patients with ILD compared to pSS patients without ILD(p=0.010).

**Table 1** The clinical materials of pSS patients with ILD and without ILD

| | pSS with ILD (n=30) | pSS without ILD (n=59) | p value |
|---|---|---|---|
| Female, n (%) | 27(90.0) | 55(93.2) | 0.684 |
| Age (years) | 57(50–67) | 52(45–61) | 0.034 |
| Disease history | | | |
| Diabetes mellitus, n (%) | 1(3.3) | 2(3.4) | 1.000 |
| Hypertension, n (%) | 4(13.3) | 5(8.5) | 0.479 |
| Medication use history | | | |
| Glucocorticoid, n (%) | 10(33.3) | 18(30.5) | 0.786 |
| Immunosuppressant, n (%) | 11(36.7) | 21(35.6) | 0.921 |
| Complement C3 (g/L) | 1.05(0.74–1.16) | 0.98(0.75–1.20) | 0.788 |
| Complement C4 (g/L) | 0.21(0.14–0.36) | 0.22(0.14–0.27) | 0.596 |
| Immune globulin A (g/L) | 2.74(2.42–3.47) | 2.94(2.17–3.93) | 0.979 |
| Immune globulin G (g/L) | 15.11(12.88–18.50) | 17.10(13.66–21.28) | 0.133 |
| Immune globulin M (g/L) | 1.20(1.00-2.10) | 1.43(1.03–1.97) | 0.570 |
| C-reactive protein (mg/L) | 10.72(1.96–41.96) | 6.00(1.60-20.41) | 0.265 |
| Erythrocyte sedimentation rate (mm/h) | 45(21–66) | 30 (12–55) | 0.022 |
| Alanine aminotransferase (U/L) | 14.4(9.0–20.0) | 15.0(12.0–19.0) | 0.211 |
| Aspartate aminotransferase (U/L) | 18.0(15.9–23.3) | 19.0(15.0–24.0) | 0.941 |
| Bilirubin (μmol/L) | 6.1(4.4–9.5) | 8.3(6.5–11.8) | 0.010 |

### The correlation of serum bilirubin with inflammatory and immune parameters in patients with pSS

Serum bilirubin levels were significantly and negatively correlated with ESR in patients with pSS (r=-0.321,p=0.002), while serum bilirubin had no significantly correlation with CRP in patients with pSS, and serum bilirubin levels were not significantly correlated with age, complement C3, complement C4, immune globulin A, immune globulin G, immune globulin M, alanine aminotransferase and aspartate aminotransferase in patients with pSS.

### Determinants of ILD for patients with pSS in logistic regression analysis

To explore which factors were significantly associated with ILD in patients with pSS, further univariable and multivariable analysis were employed. Multivariable logistic regression analysis adjusted by age, gender, medication use history, CRP and ESR revealed that serum bilirubin was independently associated with ILD in patients with pSS (OR=0.841, 95%CI:0.728–0.972, p=0.019), moreover, multivariable logistic regression analysis found that older age was a significantly risk factor of ILD in patients with pSS (OR=1.060, 95%CI: 1.009–1.114, p=0.021), as shown in Table 2.

## Discussion

In the present study, we analyzed the role of serum bilirubin in pSS patients with ILD, to date, there has been no study to investigate serum bilirubin levels in pSS patients with ILD. We confirmed that serum bilirubin levels were independently associated with ILD in patients with pSS.

Serum bilirubin was negatively related with ESR in patients with pSS [16], in accordance with our data, we also observed a significant negative correlation between serum bilirubin and ESR in patients with pSS. Notable, our study found a significant reduced serum bilirubin levels in pSS patients with ILD, and decreased serum bilirubin is an independent risk factor of ILD in patients with pSS. It is well known that chronic inflammation and fibrosis in lung are the main features of ILD, and inflammation is associated with many factors in ILD, the most common factor is autoimmune diseases [15]. Direct antibody-mediated injury may be an important driver for the development of interstitial inflammation and subsequent fibrosis in autoimmune diseases [16]. Early study has attested that bilirubin has a powerful antioxidant capacity, and only very low concentrations of bilirubin can significantly contribute to the plasma antioxidant capacity by scavenging hydrogen peroxide [17]. Besides this, the bilirubin also exhibits excellent anti-inflammatory effects [18], the bilirubin is able to alleviate smoking-induced lung injury by inhibiting the infiltration of inflammatory cells and secretion of inflammatory cytokines [19], and the bilirubin can meliorates bleomycin-induced pulmonary fibrosis by inhibiting lung inflammation partly [20]. Therefore, bilirubin likely is protective role against the occurrence and development of ILD by its antioxidant and anti-inflammatory effects in patients with pSS.

It has been demonstrated that older age is associated with the development of pSS patients with ILD [21], our study also found that older age was an significantly risk factor of ILD in patients with pSS. Indeed, aging increases the susceptibility of ILD [22]. The aged lung results in the functional and structural changes characterized by immunosenescence and inflammaging, which is associated with ILD [23]. Male and higher CRP levels have been suggested to be the significant risk factors of ILD in patients with pSS [21–24], however, Guo T et al. found that serum CRP levels have no significant difference between pSS with ILD and pSS without ILD [25], our present study did not observe the association of ILD with male and CRP in patients with pSS. The discrepant results may attribute to the following reasons: First, the sample size of male pSS patients with ILD is small, which may weaken the statistical efficacy of sex specific-morbidity. Second, the radiologic patterns of ILD main include nonspecific interstitial pneumonia, usual interstitial pneumonia, lymphocytic interstitial pneumonia and organizing pneumonia, while serum CRP levels are general determined by the degree of inflammatory response, so, the different radiologic patterns of ILD may affect the serum CRP levels in pSS patients in ILD.

**Table 2** The logistic regression analysis associated with ILD in patients with pSS

| | Univariable analysis | | Multivariable analysis | |
|---|---|---|---|---|
| | OR (95%CI) | *p* value | OR (95%CI) | *p* value |
| Sex | 1.528(0.319–7.316) | 0.596 | 3.798(0.468–30.839) | 0.212 |
| Age | 1.052(1.009–1.097) | 0.017 | 1.060(1.009–1.114) | 0.021 |
| Glucocorticoid | 1.139(0.445–2.915) | 0.786 | 1.243(0.366–4.226) | 0.727 |
| Immunosuppressant | 1.048(0.420–2.613) | 0.921 | 1.522(0.456–5.077) | 0.494 |
| C-reactive protein | 1.005(0.993–1.017) | 0.395 | 1.009(0.995–1.022) | 0.224 |
| Erythrocyte sedimentation rate | 1.016(1.000-1.031) | 0.044 | 1.011(0.992–1.029) | 0.258 |
| Bilirubin | 0.866(0.759–0.988) | 0.032 | 0.841(0.728–0.972) | 0.019 |

### Study limitations

Several limitations should be considered in the study. First, the sample size is small in this study. Second, the lung function was not measured in patients with pSS, especially for pSS patients with ILD, thus, it is not clear whether serum bilirubin levels are associated with the degree of pulmonary function damage in pSS patients with ILD. Third, we didn't investigate whether serum bilirubin had an association with prognosis of ILD in patients with pSS.

## Conclusion

In summary, decreased serum bilirubin is an independent risk factor of ILD in patients with pSS, suggesting that serum bilirubin may be considered as a promising marker for pSS patients with ILD.

**Acknowledgements**
Not applicable.

**Authors' contributions**
Y.F.P designed the study, Y.F.P wrote the main manuscript text; Y.F.P, F.Y and L.Y.M collected the data; Y.F.P analyzed the data. All authors reviewed the manuscript.

**Funding**
Not applicable.

**Data Availability**
The data are available from the corresponding author upon reasonable request.

## Declarations

**Competing interests**
The authors declare no competing interests.

**Ethical approval**
The study was approved by the Ethics Committee of The Affiliated Hospital of Youjiang Medical University for Nationalities, and was performed in accordance with the Declaration of Helsinki.

Received: 29 August 2023 / Accepted: 22 September 2023
Published online: 30 September 2023

**References**

1. Bowman SJ. Primary Sjögren's syndrome. Lupus. 2018;27(1suppl):32–5.
2. Negrini S, Emmi G, Greco M, et al. Sjögren's syndrome: a systemic autoimmune disease. Clin Exp Med. 2022;22(1):9–25.
3. Luppi F, Sebastiani M, Silva M, et al. Interstitial lung disease in Sjögren's syndrome: a clinical review. Clin Exp Rheumatol. 2020;38(Suppl 126):291–300.
4. Huang H, Xie W, Geng Y, Fan Y, Zhang Z. Mortality in patients with primary Sjögren's syndrome: a systematic review and meta-analysis. Rheumatology (Oxford). 2021;60(9):4029–38.
5. Jeny F, Brillet PY, Kim YW, Freynet O, Nunes H, Valeyre D. The place of high-resolution computed tomography imaging in the investigation of interstitial lung disease. Expert Rev Respir Med. 2019;13(1):79–94.
6. Kirkby KA, Adin CA. Products of heme oxygenase and their potential therapeutic applications. Am J Physiol Renal Physiol. 2006;290(3):F563–71.
7. Juping D, Yuan Y, Shiyong C, et al. Serum bilirubin and the risk of rheumatoid arthritis. J Clin Lab Anal. 2017;31(6):e22118.
8. Vítek L, Muchová L, Jančová E, et al. Association of systemic lupus erythematosus with low serum bilirubin levels. Scand J Rheumatol. 2010;39(6):480–4.
9. Schieffer KM, Bruffy SM, Rauscher R, Soltura MA, Yochum GS, Gallagher CJ. Reduced total serum bilirubin levels are associated with ulcerative colitis. PLoS ONE. 2017;12(6):e0179266.
10. Xie J, Zhang Z, Liang Y, Yang L. Decreased Serum Bilirubin is Associated with Disease Activity of primary Sjögren's syndrome. Arch Rheumatol. 2020;35(3):351–6.
11. Işık ÖÖ, Yazıcı A, Çefle A. The respiratory manifestations in patients with primary Sjögren's syndrome: is interstitial lung disease related to disease activity? Turk J Med Sci. 2022;52(5):1737–43.
12. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the european criteria proposed by the american-european consensus group. Ann Rheum Dis. 2002;61(6):554–8.
13. Bradley B, Branley HM, Egan JJ, et al. Interstitial lung disease guideline: the british thoracic society in collaboration with the thoracic society of Australia and New Zealand and the irish thoracic society. Thorax. 2008;63(Suppl 5):v1–58.
14. Cerasoli L, Giovannini I, Caronia G, et al. Chest high-resolution computed tomography in primary Sjögren's syndrome: an up-to-date primer for rheumatologists. Clin Exp Rheumatol. 2022;40(12):2450–62.
15. Wijsenbeek M, Suzuki A, Maher TM. Interstitial lung diseases. Lancet. 2022;400(10354):769–86.
16. Lega JC, Reynaud Q, Belot A, Fabien N, Durieu I, Cottin V. Idiopathic inflammatory myopathies and the lung. Eur Respir Rev. 2015;24(136):216–38.
17. Stocker R, Yamamoto Y, McDonagh AF, Glazer AN, Ames BN. Bilirubin is an antioxidant of possible physiological importance. Science. 1987;235:1043–6.
18. Nocentini A, Bonardi A, Pratesi S, Gratteri P, Dani C, Supuran CT. Pharmaceutical strategies for preventing toxicity and promoting antioxidant and anti-inflammatory actions of bilirubin. J Enzyme Inhib Med Chem. 2022;37(1):487–501.
19. Wei J, Zhao H, Fan G, Li J. Bilirubin treatment suppresses pulmonary inflammation in a rat model of smoke-induced emphysema. Biochem Biophys Res Commun. 2015;465(2):180–7.
20. Wang HD, Yamaya M, Okinaga S, et al. Bilirubin ameliorates bleomycin-induced pulmonary fibrosis in rats. Am J Respir Crit Care Med. 2002;165(3):406–11.
21. Lin W, Xin Z, Zhang J, et al. Interstitial lung disease in primary Sjögren's syndrome. BMC Pulm Med. 2022;22(1):73.
22. Cho SJ, Stout-Delgado HW. Aging and lung disease. Annu Rev Physiol. 2020;82:433–59.
23. Messina R, Guggino G, Benfante A, Scichilone N. Interstitial lung disease in Elderly Rheumatoid Arthritis Patients. Drugs Aging. 2020;37(1):11–8.
24. Weng L, Chen Y, Liang T, et al. Biomarkers of interstitial lung disease associated with primary Sjögren's syndrome. Eur J Med Res. 2022;27(1):199.
25. Guo T, Long Y, Shen Q, et al. Clinical profiles of SS-ILD compared with SS-NILD in a chinese population: a retrospective analysis of 735 patients. Ann Med. 2021;53(1):1340–8.

## Publisher's Note