

Original Article

Clinical features and independent predictors of interstitial lung disease in systemic lupus erythematosus

Fan Lian¹, Jun Zhou¹, Yu Wang², Wei Cui², Dongying Chen¹, Hao Li¹, Qian Qiu¹, Zhongping Zhan¹, Yujin Ye¹, Liuqin Liang¹, Xiuyan Yang¹, Hanshi Xu¹

Departments of ¹Rheumatology & Clinical Immunology, ²Interventional Oncology, The First Affiliated Hospital of Sun Yat-sen University, No. 58, Zhongshan 2nd Road, Guangzhou 510080, China

Received September 10, 2015; Accepted December 30, 2015; Epub February 15, 2016; Published February 29, 2016

Abstract: Objective: Respiratory manifestations were commonly seen in systemic lupus erythematosus. Systemic lupus erythematosus (SLE) associated interstitial lung disease (ILD) is one of the major respiratory complications, which increases morbidity and mortality. The objective of this paper is to observe the clinical characteristics of lung involvements for SLE in a population of South China and identify the risk factors contributing to the SLE-ILD. Methods: This is a retrospective study conducted in a population of south China between 2002 and 2012. SLE patients with respiratory involvements were reviewed. Demographic information, clinical features, laboratory findings and imaging characteristics were documented. Univariate and multivariate logistic regression models were applied to examine the predictors contributing to interstitial lung disease in SLE. Results: During the study period, 4038 SLE patients were reviewed, and 1536 cases with respiratory involvements were documented. Lupus pleuritis were the most commonly investigation in SLE-related respiratory disorders, followed by SLE induced ILD. Of all the 379 cases of SLE-ILD patients, the demographic features and most extrapulmonary symptoms were not significantly different from other SLE patients without ILD. Only dry eyes/months were exceptionally frequent in SLE-ILD. The single-breath carbon monoxide diffusing capacity (DLCO) decreased at the earlier time point than other indexes. Ground glass opacities were the most frequent manifestation on High resolution computed tomography (HRCT), followed by consolidation. Honeycombing was not very common. According to logistic regression analysis, positive SSA, positive SSB, positive anti-Scl-70 and dry eyes/mouth were significant and considered to be the predictors for interstitial lung disease in SLE. Conclusions: The study observed a population of SLE with lung involvements and summarized the clinical characteristics in these cases. The results of this study show that anti-SSA/anti-SSB/anti-Scl-70 and dry eyes/mouth were predictive associated factors for the occurrence of SLE-ILD. We recommend HRCT and pulmonary function test (PFT) scan in these SLE patients. As most ILD lesions are sensitively observed in HRCT, it is not absolutely apply lung biopsy.

Keywords: Systemic lupus erythematosus, interstitial lung disease, logistic regression, high resolution computed tomography

Introduction

Respiratory manifestations could be commonly investigated in systemic lupus erythematosus (SLE), involving up to 50% of patients [1]. A large area of pulmonary abnormalities presents in many SLE patients. These disorders vary from slight pleuritis to some life threatening situations, such as severe alveolar hemorrhage or end stage interstitial lung disease. SLE associated respiratory symptoms may slight or unnoticeably, and sometimes pulmonary function test (PFT) and High resolution computed

tomography (HRCT) are required for detecting the abnormalities [2-5]. SLE associated interstitial lung disease (ILD) is one of the major respiratory complications with high morbidity and mortality, as well as variety of the prognosis. In fact, ILD is a potentially fatal condition during the course of SLE. Different histopathological patterns of SLE-ILD may share similar clinical manifestations, such as dry cough and gradually progressive dyspnea [6-9].

The underlying mechanisms of SLE-ILD remain almost unknown, yet limited therapeutic options

were seem to be available. Dyspnea may be gradually developed and not quickly realized. Prompt and accurate assessment of SLE associated ILD is benefit to a more favorable prognosis. The diagnosis of ILD is currently based on clinical, radiological and pathological data. Histological examination is a sensitive and specific method. However, this procedure is performed in less than 15% of patients due to the invasive injuries [10, 11], and sometimes biopsy is not absolutely necessary if clinical and radiological exams are quite enough for diagnosis. Previous studies have been carried out to describe the clinical features of SLE associated ILD [12]. However, the clinically associated factors for the prediction of the SLE-ILD occurrence were not specifically analyzed.

In this research work, we conducted a retrospective observational study to describe the prevalence, causes, differential diagnosis of SLE in a population of south China, as well as the related clinical features of respiratory disorders. The associated risky factors contributing to occurrence of SLE-ILD were explored, which helped to set up a quick diagnosis for the situation and thus to improve therapeutic strategies.

Materials and methods

Patients

A retrospective study was carried out to analyze all cases of systemic lupus erythematosus with respiratory involvements between 2002 and 2012 recorded in the first affiliated hospital of Sun Yat-sen University, Guangzhou, China. And a total of 4038 SLE patients were retrospectively reviewed.

SLE was defined by the 1997 revised ACR classification criteria [13], and the SLE activity was evaluated by The SLE Disease Activity Index (SLEDAI) [14]. Systemic Sclerosis was defined by the ACR-EULAR Criteria for the classification of Systemic Sclerosis [15]. Interstitial lung disease was diagnosed according to the American Thoracic Society/European Respiratory Society International Society (ATS/ERS) consensus classification [16], based on respiratory symptoms and radiological findings.

Patients satisfying ACR-EULAR Criteria for the classification of systemic sclerosis, but unsatis-

fying the 1997 revised ACR classification criteria of SLE, would be considered as systemic sclerosis patients. If the patients simultaneously satisfied both SLE and systemic sclerosis criteria, they would be considered as having overlap syndrome and excluded from the present study.

Patients were classified as acute/subacute or chronic ILD according to the ATS/ERS criteria. Rapidly progressive ILD showing deterioration within one month was classified as acute ILD [17], and progressive ILD showing deterioration within three months was classified as subacute ILD [18]. Slowly progressive ILD presented with gradual deterioration over more than three months was classified as chronic ILD [19, 20]. Deterioration was considered if two or more of the following manifestations were presented: 1) symptomatic exacerbation (dyspnea upon exertion); 2) an increase in the severity of parenchymal abnormality under high-resolution computed tomography (HRCT) scan; and 3) at least one of the following physiological changes: >10% decrease in forced vital capacity (FVC), or >10 mmHg decrease in arterial oxygen tension (PaO₂) [19-21].

Other known causes of ILD, such as primary lung diseases and smoking history, were excluded. Patients with left ventricular failure and respiratory injuries due to environmental exposure were all excluded. The patients were also excluded if they had a history of taking drugs associated with presence of ANA and other extractable nuclear antigen (ENA), such as hydralazine, procainamide, isoniazid, minocycline, calcium channel blockers, angiotensin-converting enzyme inhibitors, thiazide diuretics, terbinafine and tumor necrosis factor (TNF)-alpha antagonists, etc.

Diagnosis of secondary Sjögren's syndrome (SS) was based on AECG criteria for SS. The presence of item I (ocular symptoms), or item II (oral symptoms) plus any 2 from among items III (objective evidence of ocular involvement), IV (histopathology) and V (objective evidence of salivary gland involvement), may be considered as indicative of secondary SS [22].

Demographic information, clinical manifestations, laboratory and immunological parameters, high resolution CT (HRCT) scanning and pulmonary function test (PFT) were documented.

Table 1. Diagnosis of lupus patients presented with respiratory involvements

Final Diagnosis	Number (%)
SLE induced	968 (24.0)
Pleuritis	937 (23.2)
Interstitial lung disease	379 (9.4)
Pulmonary hemorrhage	178 (4.4)
Pulmonary thromboembolism	123 (3.0)
Pulmonary hypertension	157 (3.9)
Lupus pneumonitis	88 (2.2)
Infection	1029 (25.5)
Virus	325 (8.5)
Fungus	249 (6.2)
Bacteria	697 (17.3)
Tuberculosis	126 (3.1)
Primary Respiratory Disease	118 (2.9)
Chronic obstructive pulmonary disease	68 (1.7)
Bronchiectasia	29 (0.7)
Asthma	13 (0.3)
Lung cancer	8 (0.2)
Total	5492 (100)

SLE: Systemic lupus erythematosus.

High resolution computed tomography (HRCT) scan

CT scans of 1.0 thick section were collected throughout the lungs. CT characteristics for the ILD diagnosis include ground glass opacities, consolidation, irregular linear opacities, sub-pleural curvilinear shadows, traction bronchiectasis, honeycombing, etc [23]. The HRCT scans were reviewed by two independent radiologists blind to this study and prognosis.

Pulmonary function test (PFTs)

Pulmonary function was assessed according to American Thoracic Society recommendations [24]. Forced expiratory volume at the first second (FEV₁), forced vital capacity (FVC), total lung capacity (TLC), and single-breath carbon monoxide diffusing capacity (DLCO) was measured accordingly.

Statistical analysis

Descriptive statistics were used for baseline data. Continuous and ordinal data are presented as mean \pm standard deviation (SD), while categorical data are presented as the absolute

count and percentage. The Mann-Whitney U test and t test were used to compare continuous variables, and the chi-square test was used to compare categorical variables. Logistic regression model was built to determine associated factors contributing to SLE-ILD. Statistical analyses were performed using the SPSS 16.0 package. A *P* value less than 0.05 was considered statistically significant.

Results

The profile of lupus patients with respiratory involvements

Lupus patients presented with respiratory involvements were listed in **Table 1**. During the study period, 4038 SLE patients were reviewed. Among them, a total of 1536 cases with respiratory involvements, including 968 cases of SLE- or non-SLE-induced respiratory complications, were documented.

Lupus pleuritis were the most commonly morbidity in SLE-related respiratory disorders (23.2%, 937/968), followed by SLE induced interstitial lung diseases (ILD) (9.4%, 379/968). Infection was very common in SLE patients, which occupies more than 60% (1029/1536) cases of all the lupus related respiratory involvements. Pulmonary involvements could affect pleura, pulmonary vasculature, and parenchyma. Some patients had more than one clinical presentation. Primary respiratory disease was rare in population for our study.

Clinical features of SLE-related interstitial lung disease

Based on the previous described ACR (American College of Rheumatology) criteria of SLE and ILD ATS/ERS consensus classification, 379 patients were diagnosed as SLE-related ILD. The demographic and clinical features of SLE-ILD were shown in **Table 2**. In all 379 cases of SLE-ILD, there were 251 cases (66.1%) of female and 128 cases (33.9%) of male. However, female SLE patients were much more than male ones, 3169 versus 869 respectively. Hence, 7.9% (251/3169) of female SLE patients were diagnosed as SLE-ILD, while that for male SLE patients was 14.7% (128/869), indicating relatively more common ILD in males SLE than that in females. The mean age at diag-

Clinical features and predictors of SLE-ILD

Table 2. Demographic and clinical features of patients with SLE-related interstitial lung disease and SLE patients without or with non-ILD respiratory involvements

Characteristics	SLE-ILD (n=379) N (%)	SLE without or with non-ILD respiratory involvements (n=3659) N (%)
Age at onset (years)	22.3±14.3 (range 14.3~67.2)	26.6±16.5 (range 11.3~68.6)
Age at diagnosis (years)	25.3±12.1 (range 3.8~72)	32.1±16.7 (range 12.1~74)
Disease duration (months)	43.8±52.3 (range 3.3~384.6)	
Female	251 (66.1%)	2918 (70.1%)
Male	128 (33.9%)	741 (29.9%)
Form of ILD		
Acute	4 (1.1%)	
Subacute	41 (10.8%)	
Chronic	334 (88.1%)	
Respiratory symptoms		
Cough	299 (78.9%)	
Sputum	94 (24.8%)	
Chest pain/Chest discomfort	195 (51.4%)	
Dyspnea	146 (38.5%)	
Hemoptysis	41 (11.0%)	
Other symptoms		
Skin rash	233 (61.5%)	2411 (65.9%)
Arthritis	202 (53.3%)	1752 (47.9%)
Serositis	198 (52.3%)	1486 (40.6%)
Raynaud's phenomenon	94 (24.8%)	731 (20.0%)
Fever	115 (30.3%)	1412 (38.6%)
Dry eyes/mouths	251 (66.2%)	1327 (36.3%)
Neurological involvements	87 (22.9%)	912 (24.9%)
Renal involvements	167 (44.0%)	1793 (49.0%)
Hematological involvements	125 (33.0%)	1391 (38.0%)
SLEDAI	14.3±7.8	11.7±8.5

ILD: interstitial lung disease; SLEDAI: systemic lupus erythematosus disease activity index.

nosis was (25.3±12.1) years. The median time between the diagnosis of SLE and ILD was 6 months, ranging from 3 to 187 months. Acute ILD with rapidly progressive deterioration within one month (4/379, 1.1%) and subacute ILD with progressive deterioration within three months (41/379, 10.8%) were relatively small population in our study. Acute/subacute ILD patients usually presented dry cough and progressive dyspnea, as well as bilateral, multifocal or diffuse radiographic opacities on HRCT. Chronic SLE-ILD was much more than acute/subacute SLE-ILD (334/379, 88.1%). Cough, chest pain/discomfort and progressive dyspnea were the dominating complaints. Although the demographic features and most extrapulmonary symptoms were not significantly different from other SLE patients without interstitial

lung disease, it could be identified in SLE-ILD cases for frequent dry eyes/months.

Dry eyes/mouths were investigated in above 60% of the SLE-ILD cases, while only 39.1% (1578/4038, data not shown) in the whole SLE population. Altogether 117 cases (30.8%, 117/379) with SLE-ILD satisfied the criteria for secondary Sjogren's syndrome, while 15.3% (560/3659) in SLE patients without ILD. Totally, 18.0% (727/4038) satisfied the above criteria in the whole SLE population. Eleven patients were asymptomatic and the diagnosis of ILD was based on HRCT and pulmonary function test (data not shown). Acute respiratory insufficiency is not very common in our study. Most patients were gradually exacerbated. Three patients were mainly involved with ILD, and no multisystem diseases were found.

Clinical features and predictors of SLE-ILD

Table 3. Comparison of laboratory findings and activity score between SLE-ILD and SLE with non-ILD respiratory involvements

	SLE-ILD (n=379) N (%)	SLE with non-ILD respiratory involve- ments (n=1157) N (%)	P- value
ANA	375 (98.9)	1152 (99.6)	>0.05
Anti-ds-DNA	372 (98.2)	1071 (92.6)	>0.05
ACL	167 (44.0)	279 (24.1)	<0.05*
Anti-Sm	91 (23.9)	356 (31.1)	>0.05
Anti-SSA	292 (77.1)	523 (45.2)	<0.05*
Anti-SSB	230 (60.6)	411 (35.5)	<0.05*
Anti-U1RNP	195 (51.4)	345 (29.8)	<0.05*
Anti-Scl-70	216 (56.9)	259 (22.4)	<0.05*
RF	111 (29.4)	415 (35.9)	>0.05
ANCA	56 (14.7)	127 (11.0)	>0.05
Decreased C3	271 (71.6)	935 (80.8)	>0.05
Decreased C4	285 (75.2)	885 (76.5)	>0.05
Elevated ESR	188 (49.5)	634 (54.8)	>0.05
Elevated CRP	219 (57.8)	487 (42.1)	>0.05
Disease activity (SLEDAI), mean \pm SD	14.3 \pm 7.8	15.6 \pm 8.2	>0.05

*P<0.05, *: statistical significance, SLE-ILD versus SLE with non-ILD respiratory involvements (Chi-square).

SSA was found in more than 70% SLE-ILD patients, compared to 45.2% in SLE patients without ILD, while anti-SSB was found in more than 60% SLE-ILD patients, compared to 35.5% in SLE patients without ILD. SLE-ILD patients also had a significant higher frequency of anti-Scl-70 (216/379, 56.9%) comparing to SLE patients without ILD (259/1157, 22.4%). ACL and anti-U1RNP are two other indexes more frequently observed in SLE-ILD. No significant difference of activity score SLEDAI was found between SLE-ILD and the patients with non-ILD respiratory involvements.

Pulmonary function test

Table 4. Pulmonary function test of SLE-ILD presented a restrictive ventilatory defect

% of predicted	SLE-ILD
FEV1	62.2 \pm 15.3
FVC	68.5 \pm 17.1
DLCO	58.2 \pm 18.7
FEV1/FVC	83.7 \pm 19.6

FVC: forced vital capacity; FEV1: forced expiratory volume; DLCO: diffusing capacity of the lung for carbon monoxide. Values are expressed as mean \pm SD.

Abnormalities in pulmonary function test (PFT) were shown in **Table 4**. PFT changes could be unnoticeably at the first place but recognized during follow up. PFT pattern was a restrictive ventilatory defect. FEV1/FVC increased during the course of progression. DLCO decrease appeared at the earlier time point than other indexes.

HRCT findings

High resolution computed tomography (HRCT) images were summarized in **Table 5**. Ground glass opacities were the most frequent findings, followed by consolidation. Honeycombing (15.6%) and traction bronchiectasis (12.8%) were not very common in our research. Respiratory lesions usually predominated in the peripheral lung regions and bilaterally distributed. Massive destruction of lung structure was rarely found.

Table 5. HRCT findings of SLE-ILD

Characteristics	Number (%)
Ground glass opacities	320 (84.4)
Consolidation	80 (21.1)
Honeycombing	59 (15.6)
Irregular linear opacities	282 (74.3)
Traction bronchiectasis	49 (12.8)

Comparison of laboratory findings and activity score between SLE-ILD and SLE with non-ILD respiratory involvements

As shown in **Table 3**, the presence of ANA, anti-dsDNA, anti-Sm, ANCA, RF, ESR and CRP were not statistically relevant to SLE-ILD. Anti-

Independent predictors contributing to occurrence of SLE-ILD

Univariate logistic regression was performed to evaluate all clinical and laboratory parameters. Among all the factors, positive SSA, positive SSB, positive ACL, and positive anti-U1RNP

Table 6. Significant factors associated with SLE induced interstitial lung disease on univariate logistic regression

	P value	Crude OR (95% CI)
Positive SSA	<0.01	5.83 (1.84, 19.41)
Positive SSB	<0.01	4.79 (1.56, 12.34)
Positive ACL	<0.05	2.53 (1.23, 5.87)
Positive Scl-70	<0.05	4.02 (1.46, 7.07)
Positive U1RNP	<0.05	3.17 (1.33, 6.48)
Dry eyes/months	<0.01	5.17 (1.72, 16.13)
Pleuritis	<0.05	2.16 (1.04, 5.13)

Table 7. Significant variables for SLE induced interstitial lung disease on multivariate logistic regression

	β	P value	Adjusted OR* (95% CI)
Positive SSA	2.03	0.003	7.29 (1.96, 21.73)
Positive SSB	1.54	0.007	5.63 (1.63, 9.44)
Dry eyes/mouth	1.78	0.005	6.33 (1.84, 18.13)
Positive Scl-70	1.01	0.03	3.77 (1.26, 5.41)

*Adjusted odds ratio.

were significantly associated with occurrence of interstitial lung disease in SLE (**Table 6**).

Variables associated with outcome at $P < 0.20$ were then summarized into the multivariate logistic model for the calculation of adjusted odds ratio. Positive SSA, positive SSB, positive anti-Scl-70 and dry eyes/mouth turned out to be significant, which could be considered primarily the predictors for interstitial lung disease in SLE (**Table 7**).

Discussion

Lung involvements were commonly investigated in SLE. Pleural, parenchymal, vascular, and interstitial abnormalities were comprehensively reported [25]. Although the prevalence of ILD appears to be lower in SLE than in the other connective tissue diseases [6], SLE-related interstitial lung diseases (ILD) have been confirmed to increase the mortality. Quick response to the immunomodulatory medications is benefit to obtain relatively favorable outcomes. Prompt and early recognition of the ILD situation helps to adjust therapeutic options.

Previous studies suggested that 2-8% ILD occurred in SLE and most patients with multi-system disease [26]. According to the report of

Ghosh A, et al. from India, the prevalence of SLE-ILD was about 10% [27]. While Fenlon et al. [28] declared that ILD could be found in one third of the SLE patients. Based on our data, ILD affected 9.4% (379/4038) of the SLE cases. As asymptomatic or trivial SLE-ILD would be relatively more prevalent, the result may have been underestimated [29, 30].

We attempted to elucidate the clinical features and the predictive associated factors of SLE-ILD. SLE-ILD was more commonly investigated in males (14.6%) than in females (7.9%). Chronic SLE-ILD was much more than acute/subacute ones. Respiratory symptoms could be unnoticeably or minor at the early stage, and the late phase fibrotic lung disease occurred over a course of several months or even years. This insidious progression would hamper the appropriate therapeutic decision.

Most extrapulmonary symptoms of SLE-ILD were not significantly different from SLE patients without ILD, except that sicca symptoms, which commonly found in SLE-ILD. This could be a suggestive sign for more intensive detection of subclinical SLE-ILD.

As slight lesions had a very low incidence of positive findings on chest radiography, DLCO became the most sensitive variable on pulmonary function test, which usually observed before the respiratory symptoms, suggesting the necessities of HRCT for subclinical patients.

HRCT is a sensitive and reasonably accurate tool for the detection of ILD. The previous histological reports about ILD diagnosed by HRCT in SLE were mostly in non-specific interstitial pneumonia (NSIP) pattern [31-33], though usual interstitial pneumonia (UIP), lymphocytic interstitial pneumonia (LIP), and organizing pneumonia (OP) all have been described [8, 34]. Unfortunately, in this retrospective observational study, only a few patients performed lung biopsy to confirm the histological type. It is previously reported that histological analysis could be suggested by HRCT characteristics, such as honeycombing, basilar predominant reticulation and traction bronchiectasis with limited ground glass opacities for usual interstitial pneumonia (UIP), as well as predominant bilateral basilar ground glass opacities with small reticulation and absence of honeycombing for non-specific interstitial pneumonia

(NSIP) [35, 36]. We found that ground glass opacities were the most common features in our studied group, especially bilaterally distributed and without massive destruction of lung structure, which is most similar to the NSIP pattern. The 5-yr survival rate was relatively optimistic in patients with NSIP [37]. Honeycombing is a poor prognostic marker and positively correlated to respiratory decompensation. The extent of fibrosis is highly correlated with mortality. Only a small part (15.6%) of the ILD patients in the study had honeycombing, which was in accordance with the previous studies [28]. The honeycombing patients frequently presented with traction bronchiectasis and less ground glass abnormality, which could be a sign for UIP. Lung biopsy is invasive and may not be absolutely necessary for each patient. As HRCT is capable for not only quick diagnosis and prognosis evaluation, but also sensitive to identify the subclinical situations, it is an ideal tool for therapeutic decisions, especially for the patients with lung involvement preceding other systemic symptoms.

There were no specific screening tests for early identification of SLE-ILD or high risk patients. We conduct the univariate and multivariate logistic regression model, trying to find out the associated factors leading to these diseases, so as to help decision for making on targeted therapies. We believed that the serum markers anti-SSA, anti-SSB, anti-Scl-70, as well as the manifestation of dry mouth/dry eyes were much more frequently observed in SLE-ILD than in SLE patients without ILD, and they were strong predictors of the occurrence of SLE-ILD. Significance of the above factors was identified by the univariate and multivariate analysis. Disease activity index SLEDAI, other laboratory findings and clinical manifestations had little predictive value. Except a study demonstrating the association between anti-SSA and SLE-ILD [38], rare literature was found about the predictive markers of SLE-ILD. Interestingly, La Corte, et al. [?] reported myositis patients with SSA antibodies had more extensive ILD on HRCT.

Anti-Ro/SSA and anti-La/SSB autoantibodies are members of the anti-ENA family. Positive anti-SSA and anti-SSB are considered to be indicative to a unique group of patients with high prevalence of ocular and/or mouth dryness, though only a small part of SLE patients

with positive SSA/SSB satisfied the criteria of secondary Sjögren's syndrome [39]. ILD patients with positive anti-SSA may be described as a homogeneous group with more ground-glass opacity and more severely lung function impairment than those with ILD with negative anti-SSA antibody [39].

The positive rates of the anti-SSA in the anti-SSB antibody-positive group were higher than those in the anti-SSB antibody-negative group [40]. Anti-SSB antibody is relatively stable in the course of SLE and independent to the SLEDAI score [40].

Despite the association of Anti-SSB with the incidences of hair loss, cheek erythema and respiratory involvements has been reported, no specifically literature was reported about Anti-SSB as indicative for SLE-ILD, as well as the relationship between anti-SCL-70 and SLE-ILD. Although anti-Scl-70 antibody was reported strongly associated with ILD in Systemic sclerosis [41], it was not a specific marker for SLE and did not correlate with cutaneous involvement among our patients. Previous research reported 26% of positive anti-SCL-70 in SLE patients [42, 43], similar to that in SLE patients without ILD (22.4%) from our data. Interestingly, we discovered that anti-SCL-70 was highly expressed in SLE-ILD and proved to be a predictive factor on logistic regression analysis. As our study did not reflect the full relevance of anti-SSA, anti-SSB and anti-Scl-70 antibodies to SLE-ILD, further studies are required to explore the underlying mechanisms. Moreover, the reason why the above antibodies were related to ILD is not well known.

Parameters frequently presented in SLE-ILD group, such as ACL and anti-U1RNP, found to be significant in univariate but not in multivariate analysis, could still suggest a clinical relevance for contributing to the occurrence of ILD.

SLE diagnostic criteria do not include any pulmonary manifestations, except for pleuritis. However, lung involvement usually led to the increasing of mortality. Respiratory symptoms associated with SLE-ILD are often unnoticeably. Identification of these patients at potentially reversible patterns may help to better prognosis. We recommend HRCT and PFT scan in SLE patients in cases of positive anti-SSA/anti-SSB/anti-SCL-70 or dry eyes/mouth, even

the patients without respiratory manifestations. HRCT is a sensitive measurement to identify asymptomatic SLE-ILD and reflect pathologic patterns. It is necessary to Serial monitor the symptoms, pulmonary function and radiological changes. Early diagnosis is fundamental for making decision on effective strategy, thus prevent irreversible progression to more fibrotic stages.

In conclusion, we observed a population of SLE-ILD and summarized the clinical characteristics in these cases. The results of this study show that anti-SSA/anti-SSB/anti-SCI-70 and dry eyes/mouth were predictive associated factors for the occurrence of SLE-ILD. We recommend HRCT and PFT scan in these SLE patients. As most ILD lesions are sensitively observed in HRCT, it is not absolutely apply lung biopsy. Considering that the present study is a retrospective clinical observation and the samples are relative small, further biological research and prospective study with lager data is required to confirm the predictive value of the indexes.

Acknowledgements

Project supported by National Natural Science Foundation of China (No. 81102270, No. 81-101135), Guangdong Natural Science Foundation (No. 2014A030313053), and Guangdong Natural Science Foundation (No. S2012010-009075).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Hanshi Xu, Department of Rheumatology & Clinical Immunology, The First Affiliated Hospital of Sun Yat-sen University, No. 58, Zhongshan 2nd Road, Guangzhou 510080, China. Tel: +86-13922263595; E-mail: hanshiwxu@sina.com

References

- [1] Torre O and Harari S. Pleural and pulmonary involvement in systemic lupus erythematosus. *Presse Med* 2011; 40: e19-29.
- [2] Gutsche M, Rosen GD, Swigris JJ. Connective Tissue Disease-associated interstitial lung disease: A review. *Curr Respir Care Rep* 2012; 1: 224-232.

- [3] Maxwell S, Mercedes D, Prasad P, James P and Kevin L. Usual interstitial pneumonia-pattern fibrosis in surgical lung biopsies. Clinical, radiological and histopathological clues to aetiology. *J Clin Pathol* 2013; 66: 896-903.
- [4] Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A and Lavilla P. Morbidity and mortality in systemic lupus erythematosus during a 5-year period. A multicenter prospective study of 1,000 patients. *European Working Party on Systemic Lupus Erythematosus. Medicine (Baltimore)* 1999; 78: 167-175.
- [5] Stoll T, Seifert B and Isenberg DA. SLICC/ACR Damage Index is valid, and renal and pulmonary organ scores are predictors of severe outcome in patients with systemic lupus erythematosus. *Br J Rheumatol* 1996; 35: 248-254.
- [6] Castellino FV and Varga J. Interstitial lung disease in connective tissue diseases: evolving concepts of pathogenesis and management. *Arthritis Res Ther* 2010; 12: 213.
- [7] Colby TV. Pulmonary pathology in patients with systemic autoimmune diseases. *Clin Chest Med* 1998; 19: 587-612.
- [8] Min JK, Hong YS, Park SH, Park JH, Lee SH and Lee YS. Bronchiolitis obliterans organizing pneumonia as an initial manifestation in patients with systemic lupus erythematosus. *J Rheumatol* 1997; 24: 2254-2257.
- [9] Filipek MS, Thompson ME, Wang P, Gosselin MV and Primack L. S Lymphocytic interstitial pneumonitis in a patient with systemic lupus erythematosus: radiographic and high-resolution CT findings. *J Thorac Imaging* 2004; 19: 200-203.
- [10] British Thoracic Society. The diagnosis, assessment and treatment of diffuse parenchymal lung disease in adults. *Thorax* 1999; 54: S1-S28.
- [11] Lynch DA, Travis WD, Muller NL, Galvin JR, Hansell DM, Grenier PA and King TE Jr. Review: Idiopathic interstitial pneumonias: CT features. *Radiology* 2005; 236: 10-21.
- [12] Antoniou KM, Margaritopoulos G, Economidou F and Siafakas NM. Pivotal clinical dilemmas in collagen vascular diseases associated with interstitial lung involvement. *Eur Respir J* 2009; 33: 882-896.
- [13] Hochberg MC. For the diagnostic and therapeutic criteria committee of the American college of rheumatology. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 1725.
- [14] Bombardier C, Gladman DD, Urowitz MB, Caron D and Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The committee on prognosis studies in SLE. *Arthritis Rheum* 1992; 35: 630-640.

- [15] Van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, Matucci-Cerinic M, Naden RP, Medsger TA Jr, Carreira PE, Riemekasten G, Clements PJ, Denton CP, Distler O, Allanore Y, Furst DE, Gabrielli A, Mayes MD, van Laar JM, Seibold JR, Czirjak L, Steen VD, Inanc M, Kowal-Bielecka O, Müller-Ladner U, Valentini G, Veale DJ, Vonk MC, Walker UA, Chung L, Collier DH, Ellen Csuka M, Fessler BJ, Guiducci S, Herrick A, Hsu VM, Jimenez S, Kahaleh B, Merkel PA, Sierakowski S, Silver RM, Simms RW, Varga J and Pope JE. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/ European League against Rheumatism collaborative initiative. *Arthritis Rheum* 2013; 65: 2737-2747.
- [16] Demedts M and Costabel U. ATS/ERS international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. *Eur Respir J* 2002; 19: 794-796.
- [17] Akira M, Hamada H, Sakatani M, Kobayashi C, Nishioka M and Yamamoto S. CT findings during phase of accelerated deterioration in patients with idiopathic pulmonary fibrosis. *AJR Am J Roentgenol* 1997; 168: 79-83.
- [18] Suda T, Fujisawa T, Enomoto N, Nakamura Y, Inui N, Naito T, Hashimoto D, Sato J, Toyoshima M, Hashizume H and Chida K. Interstitial lung diseases associated with amyopathic dermatomyositis. *Eur Respir J* 2006; 28: 1005-1012.
- [19] American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). *Am J Respir Crit Care Med* 2000; 161: 646-664.
- [20] Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, Lynch DA, Ryu JH, Swigris JJ, Wells AU, Ancochea J, Bouros D, Carvalho C, Costabel U, Ebina M, Hansell DM, Johkoh T, Kim DS, King TE Jr, Kondoh Y, Myers J, Müller NL, Nicholson AG, Richeldi L, Selman M, Duden RF, Griss BS, Protzko SL, Schünemann HJ; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med* 2011; 183: 788-824.
- [21] Fujisawa T, Hozumi H, Kono M, Kono M, Enomoto N, Hashimoto D, Nakamura Y, Inui N, Yokomura K, Koshimizu N, Toyoshima M, Shirai T, Yasuda K, Hayakawa H and Suda T. Prognostic Factors for Myositis-Associated Interstitial Lung Disease. *PLoS One* 2014; 9: e98824.
- [22] Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, Daniels TE, Fox PC, Fox RI, Kassan SS, Pillemer SR, Talal N and Weisman MH. 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: 554-558.
- [23] Hansell DM, Bankier AA, MacMahon H, McLoud TC, Muller NL, Müller NL and Remy J. Fleischner Society: glossary of terms for thoracic imaging. *Radiology* 2008; 246: 69-722.
- [24] Miller A. Lung function testing: selection of reference values and interpretative strategies. *Am Rev Respir Dis* 1992; 146: 1368-1369.
- [25] King TE Jr, Cherniack RM, Schwarz MI, Murray JF and Nadel JA. The lungs and connective tissue diseases. *Textbook of Respiratory Medicine*. Philadelphia: WB Saunders; 1994. pp. 1850-1872.
- [26] Pego-Reigosa JM, Medeiros DA and Isenberg DA. Respiratory manifestations of systemic lupus erythematosus: old and new concepts. *Best Pract Res Clin Rheumatol* 2009; 23: 469-480.
- [27] Ghosh A, Das T, Ghosh A, Karmakar P and Pal J. Evaluation of respiratory manifestations in systemic lupus erythematosus with special reference to pulmonary interstitial involvement. *J Indian Med Assoc* 2012; 110: 109-111.
- [28] Fenlon HM, Doran M, Sant SM and Breatnach E. High resolution CT in systemic lupus erythematosus. *AJR Am J Roentgenol* 1996; 166: 301-307.
- [29] Bankier AA, Kiener HP, Wiesmayr MN, Fleischmann D, Kontrus M and Herold CJ. Discrete lung involvement in systemic lupus erythematosus: CT assessment. *Radiology* 1995; 196: 835-840.
- [30] Sant SM, Doran M, Fenelon HM, Breatnach ES. Pleuropulmonary abnormalities in patients with systemic lupus erythematosus: assessment with high resolution computed tomography, chest radiography and pulmonary function tests. *Clin Exp Rheumatol* 1997; 15: 507-513.
- [31] Devaraj A, Wells AU and Hansell DM. Computed tomographic imaging in connective tissue diseases. *Semin Respir Crit Care Med* 2007; 28: 389-397.
- [32] Eisenberg H, Dubois EL, Sherwin RP and Balchum OJ. Diffuse interstitial lung disease in systemic lupus erythematosus. *Ann Intern Med* 1973; 79: 37-45.
- [33] Weinrib L, Sharma OP and Quismorio FP Jr. A long-term study of interstitial lung disease in systemic lupus erythematosus. *Semin Arthritis Rheum* 1990; 20: 48-56.
- [34] Filipek MS, Thompson ME, Wang P, Gosselin MV and Primack L. S Lymphocytic interstitial pneumonitis in a patient with systemic lupus erythematosus: radiographic and high-resolu-

- tion CT findings. *J Thorac Imaging* 2004; 19: 200-203.
- [35] Kim EJ, Elicker BM, Maldonado F, Webb WR, Ryu JH, Van Uden JH, Lee JS, King TE Jr and Collard HR. Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease. *Eur Respir J* 2010; 35: 1322-1328.
- [36] Bongartz T, Nannini C, Medina-Velasquez YF, Achenbach SJ, Crowson CS, Ryu JH, Vassallo R, Gabriel SE and Matteson EL. Incidence and mortality of interstitial lung disease in rheumatoid arthritis-a population-based study. *Arthritis Rheum* 2010; 62: 1583-1591.
- [37] Honda O, Johkoh T, Ichikado K, Tomiyama N, Maeda M, Mihara N, Higashi M, Hamada S, Naito H, Yamamoto S and Nakamura H. Differential diagnosis of lymphocytic interstitial pneumonia and malignant lymphoma on high-resolution CT. *AJR Am J Roentgenol* 1999; 173: 71-74.
- [38] Boulware DW and Hedgpeth MT. Lupus pneumonitis and anti-SSA(Ro) antibodies. *J Rheumatol* 1989; 16: 479-481.
- [39] Boitiaux JF, Debray MP, Nicaise-Roland P, Adle-Biassette H, Danel C, Clérical C, Aubier M, Mariette X, Cadranel J and Crestani B. Idiopathic interstitial lung disease with anti-SSA antibody. *Rheumatology* 2011; 50: 2245-2450.
- [40] Rao L, Liu G, Li C, Li Y, Wang Z, Zhou Z, Tong S and Wu X. Specificity of anti-SSB as a diagnostic marker for the classification of systemic lupus erythematosus. *Exp Ther Med* 2013; 5: 1710-1714.
- [41] Reveille JD and Solomon DH. Evidence-based guidelines for the use of immunologic tests: anticentromere, Scl-70, and nucleolar antibodies. *Arthritis Rheum* 2003; 49: 399-412.
- [42] Geisler C and Hoier-Madsen M. An enzyme-linked immunosorbent assay for autoantibodies against the nuclear protein Scl-70. *J Immunol Methods* 1985; 80: 211-9.
- [43] Bronshtein IB, Shuster AM, Golobolov GV, Gromova II, Kvashuk OA, Belostotskaya KM, Alekberova ZS, Prokaeva TB and Gabibov AG. DNA-specific antiidiotypic antibodies in the sera of patients with autoimmune diseases. *FEBS Lett* 1992; 314: 259-263.