Clinical and laboratory characteristics of systemic sclerosis patients with pulmonary arterial hypertension in China

J. Huang[1], M. Li[1], Z. Tian[2], E. Hsieh[3], Q. Wang[1], Y. Liu[1], D. Xu[1], Y. Hou[1], J. Zhao[1], X. Guo[2], J. Lai[2], C. Hu[1], N. Song[1], Q. Sun[4], F. Zhang[1], Y. Zhao[1], X. Zeng[1]

[1]Department of Rheumatology, Peking Union Medical College Hospital, Key Laboratory of Rheumatology and Clinical Immunology, Beijing, China;
[2]Department of Cardiology, Peking Union Medical College Hospital, Beijing, China;
[3]Sectionof Rheumatology, Department of Internal Medicine, Yale School of Medicine, New Haven, CT, USA;
[4]Department of Dermatology, Peking Union Medical College Hospital, Beijing, China.

*Jing Huang, MD**
*Mengtao Li, MD**
*Zhuang Tian, MD**
Evelyn Hsieh, MD
Qian Wang, MD
Yongtai Liu, MD
Dong Xu, MD
Yong Hou, MD
Jiuliang Zhao, MD
Xiaoxiao Guo, MD
Jinzhi Lai, MD
Chaojun Hu, MD
Ning Song, MD
Qiuning Sun, MD
Fengchun Zhang, MD
Yan Zhao, MD
Xiaofeng Zeng, MD

**These authors contributed equally to this study.*

Please address correspondence to:
Xiaofeng Zeng, MD,
Department of Rheumatology,
Peking Union Medical College Hospital,
Peking Union Medical College and Chinese Academy of Medical Sciences,
Beijing 100730, China.
E-mail: zengxfpumc@gmail.com

Reprint requests should be addressed to:
Mengtao Li: mengtao.li@cstar.org.cn

The work should be attributed to the Department of Rheumatology, Peking Union Medical College Hospital, Peking Union Medical College and Chinese Academy of Medical Sciences.

Received on April 27, 2014; accepted in revised form on September 4, 2014.

Clin Exp Rheumatol 2014; 32 (Suppl. 86): S115-S121.

Key words: systemic sclerosis, cohort study, pulmonary arterial hypertension, microvasculopathy

Competing interests: none declared.

ABSTRACT

Objective. *Pulmonary arterial hypertension (PAH) is associated with significant morbidity and mortality, especially in systemic sclerosis (SSc). Since there was no published study regarding PAH in the Chinese SSc population, we aimed to describe a cohort to provide some data for early diagnosis.*

Methods. *We evaluated 236 systemic sclerosis patients prospectively registered in the EUSTAR (European League Against Rheumatism Scleroderma Trial and Research Group) database from the Peking Union Medical College Hospital from 2009 to 2012. Among them, 33 individuals received right heart catheterisations (RHC) while the remaining patients were grouped by echocardiographic data. These patients were classified into two groups, PAH and non-PAH group. Their clinical and laboratory features were statistically analysed to identify possible risk factors for PAH in Chinese SSc population.*

Results. *The possible prevalence of PAH in SSc patients was approximately 11% in our study. Digital ulcers (52.0% vs. 31.2%), telangiectasias (64.0% vs. 37.6%) and gastroesophageal reflux disease (GERD) (60.0% vs. 36.2%) were more common in SSc patients with PAH. Some laboratory results were also proved to be significantly correlated with it. Logistic regression analysis showed that telangiectasias (OR=2.888, 95% CI=1.176-7.093), presence of GERD (OR=2.592, 95% CI=1.067–6.296), anti-RNP positivity (OR=24.384, 95% CI=1.978–36.651), IgA level elevation (OR=8.745, 95% CI 4.838–122.896) and FVC/TLCO ratio (OR=97.067, 95% CI 12.475–755.271) were associated with an increased odds for PAH in SSc patients.*

Conclusion. *This study described possible predictors of PAH in Chinese SSc population, which have been supported by similar studies in other ethnic groups.*

Introduction

Systemic sclerosis (SSc) is a multisystem autoimmune disease with unknown origin, characterised by excessive extracellular matrix protein accumulation, microvascular lesions and dysfunction of the immune system. The microvascular changes in SSc underlie many different clinical features of the disease, such as digital ulcers (DUs), telangiectasia, Raynaud's phenomenon (RP) and pulmonary arterial hypertension (PAH).

PAH is defined as precapillary pulmonary hypertension not related to lung diseases and is associated with significant morbidity and mortality. The one- and three-year survival rates after diagnosis of PAH are 78–90% and 47-56% respectively for SSc patients (1, 2). Among the rheumatic diseases, PAH is most commonly seen in SSc, and the prevalence of PAH in SSc patients is about 9% (3, 4). Despite advances in treatment, the long-term prognosis for SSc patients with PAH remains poor and recent evidence suggests that World Health Organisation functional class I and II patients have better survival rates than those in higher classes (5).

There are currently no published studies focused specifically on PAH in the Chinese SSc population. Therefore, we designed a study to evaluate a cohort of SSc patients with PAH in China and compared this group to a cohort of SSc patients without PAH with the goal of identifying clinical and laboratory characteristics that may facilitate early diagnosis of this fatal disorder in China.

Methods

Study population

This study was approved by the medical ethics committee of Peking Union Medical College Hospital (PUMCH) and the ethics committee of the European League Against Rheumatism Scleroderma Trial and Research Group

(EUSTAR). All subjects admitted in this study have signed the informed consents. The medical charts of 265 SSc patients from Peking Union Medical College Hospital (PUMCH) who were prospectively registered in the EUSTAR database from February 2009 to March 2012 were evaluated to identify potentially eligible subjects. Among these patients, four who did not satisfy the 1980 American Rheumatism Association classification criteria for SSc[6] were excluded. The remaining 261 patients fulfilled criteria for SSc, however 25 additional patients were excluded due to overlapping systemic lupus erythematosus, rheumatoid arthritis, polymyositis, and primary biliary cirrhosis. In total, 236 patients were defined as "pure SSc patients" and formed the study population. These "pure SSc patients" were screened for PAH by echocardiogram and 33 of them were ascertained by right heart catheterisation (RHC) which was conducted according to standardised procedures.

According to the guideline of the European Society of Cardiology and the European Respiratory Society, PAH cases were defined as patients whose mean pulmonary arterial pressures (mPAPs) during right heart catheterisation (RHC) was ≥25mmHg, while mean pulmonary capillary wedge pressures (PCWPs) were ≤15mmHg and without obvious interstial lung disease on CT scans, signifying PAH in the absence of left heart failure or interstitial lung disease associated pulmonary hypertension (25 patients). Non-PAH controls were defined as: a) patients whose RHC mPAPs were <25mmHg (7 patients); b) patients who did not have RHC exams, but had echocardiographic data showing pulmonary artery systolic pressure (PASP) ≤36 mmHg, tricuspid regurgitation velocity (TRV) ≤2.8m/s and other parameters supporting the absence of PAH (134 patients) (7). 47 cases without echocardiographic data and RHC data were excluded from the study, and so were 22 cases who could not be diagnosed by echocardiograms and did not take RHCs. One case, who had mPAP >25 mmHg but also PCWP >15 mmHg, was excluded from the study because of the confusion for pulmonary hypertension secondary to left heart failure (Pulmonary Hypertension Group 2). The flow chart demonstrating the patient selection process is shown in Figure 1.

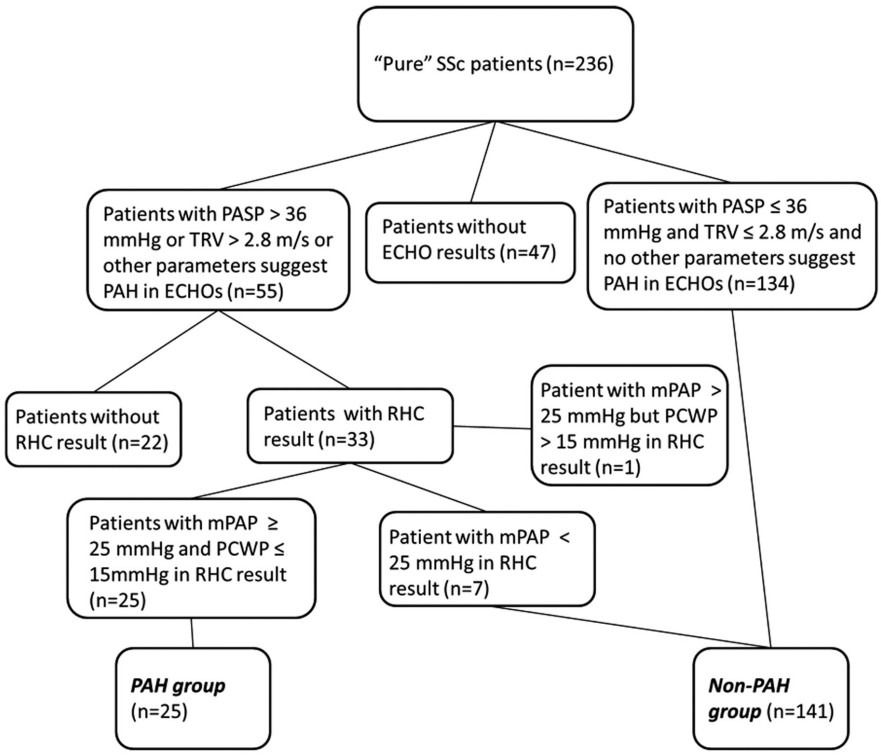

Fig. 1. Flow chart of the patient selection process.
(Parameters which suggest PAH in ECHOs refer to the increased velocity of pulmonary valve regurgitation and a short acceleration time of RV ejection into the PA) (7).

Clinical parameters

All clinical data were gathered by rheumatologists from the PUMCH Department of Rheumatology at the time of patient registration into the EUSTAR database. For the purposes of this study, information was collected regarding each patient's age, gender, disease characteristics and duration, and the modified Rodnan skin score (mRSS). SSc classification was further subdivided into diffuse cutaneous SSc (dcSSc, extension of skin sclerosis proximal to the cubital articulation and the articulation of knee), limited cutaneous SSc (lcSSc, skin sclerosis restricted to the hands and, to a lesser extent, to the face and neck) and sine scleroderma (ssSSc, disease characterised by the typical vascular features and visceral fibrosis of systemic disease without skin sclerosis) (8).

In terms of clinical symptoms, RP was defined as history of sudden onset of cold fingers (or toes) in association with sharply demarcated colour changes of skin pallor (white attack) and/or cyanotic skin (blue attack), followed by erythema upon warming and reperfusion. Arthritis and arthralgia were defined as swelling and tenderness of joints respectively. DUs were defined as denuded areas of the fingers with defined borders and loss of epithelialisation involving both the epidermis and dermis. ILD was defined as ground glass opacification, fibrosis or other interstitial changes on high-resolution computed tomography (HRCT) in the absence of pulmonary infections, cardiac diseases and drug-related changes. Gastroesophageal reflux disease (GERD) was defined as mild heartburn and/or regurgitation ≥2 days per week, or moderate/severe heartburn and/or regurgitation ≥1day per week, as stated by the Montreal Definition of GERD (9). Finally, telangiectasias were defined as macroscopically visible dilated capillaries or venules occurring in the skin.

Nailfold video capillaroscopy (NVC) was performed for 10 of the SSc patients with PAH and 91 of the patients

without PAH. Nailfold findings were classified as "normal" in the absence of microvascular alterations; "early pattern" in the presence of a few enlarged/giant capillaries, or a few capillary haemorrhages with no evident loss of capillaries; "active pattern" if the nailfold displayed frequent giant capillaries and/or frequent capillary haemorrhages with mild disorganisation of the capillary network; and "late pattern" if irregular enlargement of the capillaries and/or few or absent giant capillaries or haemorrhages with extensive avascular areas were observed (10).

Laboratory parameters

Laboratory data collected included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), hypersensitive CRP (hsCRP), immunoglobulin and complement levels, autoantibody results including antinuclear antibody (ANA), anti-dsDNA antibody, anti-Sm antibody, anti-U1RNP antibody, anti-SSA antibody, anti-SSB antibody, anti-Scl-70 antibody and anti-centromere antibody (ACA),and pulmonary function testing results. All tests were performed by the PUMCH laboratory and were recorded in the EUSTAR database. ANA and ACA were measured by indirect immunofluorescence (IIF) using HEp-2 cell substrates. Anti-dsDNA antibody was tested by IIF using flagellate protoctista substrates and enzyme linked immunosorbent assay (ELISA). Other antibodies were determined by immunodiffusion assay.

Based upon the normal range for each lab test at PUMCH, we defined elevation of ESR as >20 mm/h, elevation of CRP as >8 mg/L, elevation of hsCRP as >3 mg/L, elevation of IgG as >17 g/L, elevation of IgA as >3.8 g/L, elevation of IgM as >2.5 g/L, depression of total complement activity (CH50) as <26 U/ml, depression of complement component 3 (C3) as <0.60 g/L and the depression of complement component 4 (C4) as <0.12 g/L. Abnormal pulmonary function test results for the forced expiratory volume in one second (FEV_1) [% predicted], the forced vital capacity (FVC) [% predicted], the total lung diffusion capacity for carbon monoxide (TLCO) [% predicted] and the ratio of TLCO /the alveolar ventilation in one minute (VA) [% predicted] were defined as less than 80% of the predicted values in healthy people, while the depression of FEV_1/FVC was defined as < 70%. Finally, FVC[% predicted]/TLCO[% predicted] ratio was calculated for each group.

Statistical analysis

It was planned to enrol approximately 155 SSc patients including the planned number of 14 patients testing positive for PAH. This planned sample size assumed a prevalence rate of 9% (3, 4) for PAH in SSc patients with an estimation of 95% sensitivity of the detection algorithm and a precision of ±4.5%.

The Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS, Chicago, IL) was used for all data processing and analysis. Means and standard deviations were calculated to represent the continuous variables, and frequencies were calculated to represent the categorical variables. Comparisons between continuous variables (mean ± standard deviation) were determined using the independent-sample *t*-test for normally distributed variables and the Mann Whitney U-test for variables that were not normally distributed, and categorical variables were compared using the Pearson chi-squared test. Clinical manifestations and laboratory features that were statistically different in the univariate analysis were further evaluated using binary logistic regression analysis to identify potential predictors of PAH. Clinical and laboratory variables were considered separately and a two-tailed *p*-value of less than 0.05 was considered statistically significant.

Table I. Demographic characteristics of study participants, by PAH status.

	PAH (n=25)	Non-PAH (n=141)	*p*-value
Age(mean years)	44.76±10.84	44.73±12.51	0.308
Female (%)	23 (92.0%)	129 (91.5%)	0.933
Disease duration (mean years)	7.58±7.33	6.17±7.10	0.149
Classification			
dcSSc (%)	9 (36.0%)	56 (39.7%)	0.726
lcSSc (%)	16 (64.0%)	85 (60.3%)	
ssSSc (%)	0 (0.0%)	0 (0.0%)	
mRSS (mean)	4.78±4.76	8.16±7.47	0.068

dcSSc: diffuse cutaneous SSc; lcSSc: limited cutaneous SSc; ssSSc: sine scleroderma; mRSS: modified Rodnan skin score.

Results

Baseline characteristics

A total of 25 out of 236 "pure SSc" (10.6%) patients were found to meet criteria for PAH. Among the 25 patients, 23 were female (92.0%). The average age of PAH patients was 44.76 (SD=10.84) years. The average disease duration among this group was 7.58 (SD=7.33) years. Nine cases (36%) were classified as lcSSc, 16 cases (64%) were classified as dcSSc, and no cases of sine scleroderma cases were identified. The mRSS was 4.78 (SD=4.76). These characteristics were not significantly different when compared with the 141 non-PAH SSc patients (Table I).

Based on right heart catheterisation results, the average mPAP of SSc patients with PAH was 43.32 (SD=11.81) mmHg, the average PCWP was 8.77 (SD=3.42) mmHg and the average PVR was 8.29 (SD=3.52) WU. The distribution of World Health Organisation class among the PAH group was 20% Class I, 48% Class II and 32% Class III, while the average six-minute walking test distance for the group was 420.02 (SD=100.83) m.

Clinical manifestations

The clinical manifestations between the PAH group and the non-PAH group patients were compared (Table II). The presence of DUs (52.0% *vs*. 31.2%, *p*=0.044), GERD (60.0% *vs*. 36.2%, *p*=0.025) and telangiectasias (64.0% *vs*. 37.6%, *p*=0.014) were significantly more frequent in patients with PAH than those without. In both groups, a majority of patients had a history of RP (96% *vs*. 92.9%, *p*=0.567) and ILD (83.3% *vs*. 81.7%, *p*=0.846).

Fewer SSc patients with PAH reported arthritis or arthralgias compared with SSc patients without PAH, however this difference was not statistically significant (36.0% *vs*. 53.9%, *p*=0.099). NVC showed no significant difference in the distribution of nailfold changes between these two groups.

Laboratory features

Elevated levels of serum IgA was observed more frequently in SSc patients with PAH than in those without PAH (36.0% *vs*. 15.5%, *p*=0.016), while other markers of inflammation, including ESR, CRP, hsCRP, IgG, IgM, CH50, C3 and C4 displayed no significant difference between these two groups (Table III).

Positive anti-U1 RNP (60.0% *vs*. 18.4%, *p*=0.000), anti-SSA (36.0% *vs*. 17.9%, *p*=0.039) and anti-SSB antibodies (16.0% *vs*. 3.6%, *p*=0.012) appeared significantly more frequently in patients with PAH than in those without PAH, while positive anti-Scl-70 antibodies were seen significantly more frequently in patients without PAH (8.0% *vs*. 50.4%, *p*=0.000). No significant differences were observed between the two groups with regards to frequencies of positive anti-nuclear antibodies (ANA), anti-dsDNA antibodies, anti-Sm antibodies and anti-centromere antibodies (ACA) (Table III).

Pulmonary function testing

The FEV_1 [% predicted] (65.2% *vs*. 37.2%, *p*=0.012), the FVC [% predicted] (65.2% *vs*. 33.8%, *p*=0.004), the TLCO [% predicted] (100.0% *vs*. 73.8%, *p*=0.005) and the TLCO/VA ratio [% predicted] (100.0% *vs*. 60.2%, *p*=0.000) were significantly decreased in SSc patients with PAH compared with those without PAH, while the FVC [% predicted]/TLCO [% predicted] ratio, 1.93 (SD=0.67) *vs*. 1.29 (SD=0.29) (*p*=0.000), was significantly increased (Table III). The remaining pulmonary function testing parameters did not exhibit any significant differences between these two groups.

Logistic regression analysis

Binary logistic regression analysis showed the presence of telangiectasia (OR=2.888, 95% CI=1.176–7.093) and GERD (OR=2.592, 95% CI=1.067–6.296) were associated with an increased risk for PAH in SSc patients. With regard to laboratory and pulmonary function testing, patients with a positive anti-U1 RNP antibody (OR=24.384, 95% CI=1.978–36.651), elevations of IgA level (OR=8.745, 95% CI 4.838–122.896) and FVC [% predicted]/TLCO [% predicted] ratio (OR=97.067, 95% CI 12.475-755.271) had an increased odds for PAH. These results are presented in Table IV.

Table II. Clinical manifestations of study participants, by PAH status.
The values in bold type were those that showed significant differences between the two groups (*p*-values <0.05).

	PAH	non-PAH	*p*-value
RP	96.0% (24/25)	92.9% (131/141)	0.567
Arthritis/Arthralgia	36.0% (9/25)	53.9% (76/141)	0.099
DU	**52.0% (13/25)**	**31.2% (44/141)**	**0.044**
ILD	83.3% (20/24)	81.7% (107/131)	0.846
GERD	**60.0% (15/25)**	**36.2% (51/141)**	**0.025**
Telangiectasia	**64.0% (16/25)**	**37.6% (53/141)**	**0.014**
NCV			
Normal	0.0% (0/10)	5.5% (5/91)	0.711
Early pattern	0.0% (0/10)	4.4% (4/91)	
Active pattern	50.0% (5/10)	52.7% (48/91)	
Late pattern	50.0% (5/10)	37.4% (34/91)	

RP: Raynaud phenomenon; DU: digital ulcer; ILD: interstitial lung disease; GERD: gastroesophageal reflux disease; NVC: nailfold video capillaroscopy.

Table III. Laboratoryand pulmonary function testing results, by PAH status.
The values in bold type were those that showed significant differences between the two groups (*p*-values <0.05).

	PAH	non-PAH	*p*-value
Laboratory Tests			
ESR >20 mm/1h	45.5% (10/22)	32.1% (43/134)	0.220
CRP >8 mg/L	18.8% (3/16)	14.7% (11/75)	0.681
hsCRP>3 mg/L	38.9% (7/18)	38.7% (24/62)	0.989
IgG>17 g/l	52.0% (13/25)	33.8% (44/130)	0.085
IgA > 3.8g/l	**36.0% (9/25)**	**15.5% (20/129)**	**0.016**
IgM>2.5g/l	8.0% (2/25)	7.8% (10/128)	0.975
CH50 <26U/ml	0.0% (0/19)	0.0% (0/108)	-
C3 <0.60g/l	0.0% (0/21)	0.9% (1/112)	0.664
C4 <0.12g/l	9.5% (2/21)	4.5% (5/110)	0.353
ANA	92.0% (23/25)	88.7% (125/141)	0.620
dsDNA	8.0% (2/25)	7.9% (11/140)	0.981
anti-Sm	12.0% (3/25)	5.0% (7/141)	0.173
anti-RNP	**60.0% (15/25)**	**18.4% (26/141)**	**0.000**
anti-SSA	**36.0% (9/25)**	**17.9% (25/140)**	**0.039**
anti-SSB	**16.0% (4/25)**	**3.6% (5/140)**	**0.012**
anti-Scl-70	**8.0% (2/25)**	**50.4% (71/141)**	**0.000**
ACA	8.3% (2/24)	15.6% (22/141)	0.350
Pulmonary Function Tests			
TLC [% predicted] < 80%	34.8% (8/23)	28.3% (36/127)	0.533
FVC [% predicted] <80%	**65.2% (15/23)**	**33.8% (44/130)**	**0.004**
FEV_1 [% predicted] <80%	**65.2% (15/23)**	**37.2% (48/129)**	**0.012**
FEV_1/FVC< 70%	0.0% (0/23)	2.3% (3/128)	0.458
TLCO [% predicted] < 80%	**100.0% (23/23)**	**73.8% (90/122)**	**0.005**
TLCO/VA [% predicted] < 80%	**100.0% (22/22)**	**60.2% (53/88)**	**0.000**
FVC [% predicted] / TLCO [% predicted]	**1.93 ± 0.67**	**1.29 ± 0.29**	**0.000**

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; hsCRP: high sensitivityCRP; Igs: immunoglobulins; CH50: total complement activity; C3/4: complement component 3/4; ANA: anti-nuclear antibody; anti-dsDNA: anti-double strand DNA antibody; ACA: anti-centromere antibody; TLC: total lung capacity; FVC: the forced vital capacity; FEV_1: forced expiratory volume in one second; TLCO: total lung diffusion capacity for carbon monoxide; VA: alveolar ventilation in one minute.

Discussion

In the previous study, they analysed the risk factors for connective tissue disease associated PAH (11). Our study sought to investigate the clinical and laboratory characteristics that may play a role in predicting occurrence of PAH in Chinese patients with SSc. In our cohort, the prevalence of PAH in SSc patients was about 11%, which was consistent with the worldwide prevalence reported in other articles (12).

In our study, we found significant differences between SSc patients with and without PAH in terms of clinical and laboratory characteristics. In the SSc-PAH group, patients showed a higher prevalence of GERDs, telangiectasias and DUs than those in SSc-non-PAH group. Furthermore positive anti-U1RNP, anti-SSA and anti-SSB antibodies were seen more frequently in the PAH group compared with the non-PAH group, while anti-Scl-70 antibody was more frequently seen in the non-PAH group. However, there was no significant difference in levels of inflammatory markers between the two groups, except for an elevation of IgA levels. Among the pulmonary function test results, the FEV_1 [% predicted], FVC [% predicted], TLCO [% predicted] and TLCO/VA ratio [% predicted] levels were significantly decreased among patients in the PAH group, and the calculated FVC [% predicted]/TLCO [% predicted] ratio was significantly increased. Logistic regression analysis of clinical parameters found the presence of telangiectasia and GERD to be potential predictors for PAH, and among laboratory characteristics a positive anti-U1RNP antibody, elevated IgA level and FVC [% predicted]/TLCO [% predicted] ratio were associated with an increased odds for PAH among SSc patients.

In a prior Chinese study regarding the clinical implications of GERD among SSc patients, an association was similarly reported between GERD and PAH (13). However the study relied on echocardiographic diagnosis of PAH, where as in our study all cases of PAH were definitively diagnosed by RHC, allowing for a more rigorous PAH diagnosis. DUs (including both active and old lesions) and telangiectasias were also shown in our study to be risk factors for PAH in SSc patients. As with PAH, telangiectasias and DUs are both considered microvascular lesions in SSc, so the association between these symptoms and the presence of PAH is biologically plausible. Previous studies from the United States and Australia have suggested telangiectasias may be a possible clinical marker for PAH in SSc (14, 15) and our study provides further evidence to support this theory. An association between DUs and isolated pulmonary hypertension (defined as echocardiographic or RHC evidence for pulmonary hypertension in the absence of significant ILD) was also described previously by Cox *et al*. with subjects from the South Australian Scleroderma Register (16). In other autoimmune diseases such as SLE, RP has been shown to be a risk factor for future development of PAH.[17] However, in our patient population, no significant difference in prevalence of RP was found between the PAH and non-PAH groups, perhaps due to the high prevalence of RP in both groups. As well previous studies in SSc patients have suggested severity of RP is positively associated with likelihood of PAH, however data was not collected in our study regarding severity of RP therefore we were unable to evaluate this relationship.

The significant association between certain microvascular lesions (DUs, telangiectasias and GERD) and PAH in SSc patients would suggest that other similar lesions, such as nailfold microcirculatory lesions, would also be more prevalent among patients with PAH. Indeed, many physicians believe that NVC exams should be useful in the early diagnosis of PAH patients and there is some evidence to support the association between late patterns of NVC and pulmonary involvement by SSc, including PAH (18). However in our study, NVC findings did not significantly differ between patients with PAH and those without. This may be due to the small sample size of patients receiving NVC in both groups, and future studies should evaluate this potential association in greater detail (18).

With regards to laboratory features, there was no obvious correlation between elevation of inflammatory markers (including ESR, CRP, Ig levels, complements) and prevalence of PAH in SSc patients with the exception of IgA levels. It is possible that the significant elevation of IgA levels seen may be the result of gastrointestinal mucous membrane involvement in these patients. Positive anti-U1RNP, anti-SSA and anti-SSB antibodies were significantly more frequent in SSc patients with PAH than without in our study, while anti-Scl-70 antibody was significantly more frequent in SSc patients without PAH. The association between anti-U1RNP antibody and prevalence of PAH is consistent with results previously described in SLE and SSc patients (17, 19), however, studies have not previously reported a correlation between anti SSA, anti-SSB antibodies and the prevalence of PAH in connective tissue diseases (19, 20). It is possible that some patients in the SSc-PAH group may have had secondary Sjogren's syndrome which was not formally captured in the database, result-

Table IV. Multivariate analysis for SSc patients with PAH.

	OR95%	Confidence Interval Upper limit	Lower limit	*p*-value
Clinical Manifestations:				
Presence of telangiectasia	2.888	1.176	7.093	0.021
Presence of GERD	2.592	1.067	6.296	0.035
Laboratory Results:				
IgA elevation	8.745	1.978	38.651	0.004
Positive anti-RNP antibody	24.384	4.838	122.896	0.000
FVC [% predicted] / TLCO [% predicted] ratio	97.067	12.475	755.271	0.000

GERD: gastroesophageal reflux disease; FVC: forced vital capacity; TLCO: total lung diffusion capacity for carbon monoxide.

ing in bias. The anti-Scl-70 antibody has been more commonly associated with dcSSc and interstitial lung disease in the literature rather than PAH, which has been more commonly associated with lcSSc. Therefore the inverse relationship observed in our study between anti-Scl-70 antibody and PAH prevalence is not surprising (19). However, in our study, the ACA did not show a significant association with PAH prevalence in SSc patients.

Results from pulmonary function tests showed the TLCO [% predicted] and the TLCO/VA [% predicted] were significantly decreased in SSc patients with PAH, while the FVC [% predicted] / TLCO [% predicted] ratio was significantly elevated, which is consistent with findings from previous studies (5, 7, 21, 22). In our population, increased FVC [% predicted] / TLCO [% predicted] ratio was associated with an increased odds of 97.067 (95% CI=12.475–755.271, *p*-value=0.000), which is indicative of its relative importance in the prediction of PAH in Chinese SSc patients. Although SSc-PAH patients in this study were more likely to have low FVC [% predicted] and TLCO [% predicted] compared with SSc patients without PAH, the elevation of FVC [% predicted] / TLCO [% predicted] ratio in SSc-PAH patients suggested that the decrease in TLCO [% predicted] was predominant. One limitation of our study was the small total number of patients who received RHC exams. Therefore most of the non-PAH group cases were diagnosed by echocardiographic data which were not as accurate as RHCs. It was because RHCs were invasive exams so that most patients did not want to take them while echocardiographic data did not suggest PAHs. But most patients at risk for PAHs in echocardiographic data were further ascertained by RHCs. And also, our findings were generally consistent with previous larger studies (23), including the DETECT study in which RHC was carried out in 466 SSc patients to assess for PAH. In this study, the authors identify six simple screening tests (including FVC [% predicted]/TLCO [%predicted], current or past telangiectasias, positive ACA, N-terminal pro-brain natriuretic peptide, uric acid and right axis deviation on electrocardiography) as the first step to inform referral for echocardiogram (24). Similarly, our study found that FVC [% predicted]/ TLCO [%predicted] and telangiectasias were both markers for PAH in Chinese SSc patients. Future larger studies are needed to better elucidate whether other clinical and laboratory features described in DETECT and other studies, including positive ACA, positive anti-RNP, DUs, NVC, and severity of RP can also be used to predict PAH in Chinese SSc patients. Further research is also needed to explore the relationship between anti-SSA and SSB antibodies with PAH among Chinese SSc patients.

Conclusion

In conclusion, we found that five clinical and laboratory risk factors (presence of GERD, telangiectasias, positive anti-RNP antibody, the elevation of IgA levels and FVC [% predicted]/ TLCO [% predicted] ratio) may help predict which SSc patients require further invasive testing to rule out PAH, allowing for early diagnosis and management of this debilitating condition. Additional risk factors identified in the univariate analysis but excluded in the final regression model (negative anti-Scl-70 antibody, the presence of DU and decrease in TLCO [%, predicted]) warrant further study in future larger studies as well.

Funding

This study was supported by the EULAR Scleroderma Trial & Research group (EUSTAR), National Major Scientific and Technological Special Project (2012ZX09303006-002), Chinese National Key Technology R&D Program, Ministry of Science & Technology (2011BAI11B15), National Natural Science Foundation of China (81072485, 81071300), Research Special Fund for Public Welfare Industry of Health (201202004), Fund of the Capital Medical Development and Research (2009-2003), Clinical Research Project of the Chinese Medical Association (12040740374) and Young Investigator Project of PUMC.

References

1. CONDLIFFE R, KIELY DG, PEACOCK AJ *et al*.: Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era. *Am J Respir Crit Care Med* 2009; 179: 151-7.
2. LAUNAY D, SITBON O, HACHULLA E *et al*.: Survival in systemic sclerosis-associated pulmonary arterial hypertension in the modern management era. *Ann Rheum Dis* 2012.
3. AVOUAC J, AIRO P, MEUNE C *et al*.: Prevalence of pulmonary hypertension in systemic sclerosis in European Caucasians and metaanalysis of 5 studies. *J Rheumatol* 2010; 37: 2290-8.
4. SHAHANE A: Pulmonary hypertension in rheumatic diseases: epidemiology and pathogenesis. *Rheumatol Int* 2013.
5. HUMBERT M, GERRY COGHLAN J, KHANNA D: Early detection and management of pulmonary arterial hypertension. *Eur Respir Rev* 2012; 21: 306-12.
6. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. *Arthritis Rheum* 1980; 23: 581-90.
7. GALIE N, HOEPER MM, HUMBERT M *et al*.; GUIDELINES ESCCFP: Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2009; 30: 2493-537.
8. MOLINA JF, ANAYA JM, CABRERA GE, HOFFMAN E, ESPINOZA LR: Systemic sclerosis sine scleroderma: an unusual presentation in scleroderma renal crisis. *J Rheumatol*1995; 22: 557-60.
9. VAKIL N, VAN ZANTEN SV, KAHRILAS P, DENT J, JONES R: The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 2006, 101: 1900-20; quiz 43.
10. DE ANGELIS R, GRASSI W, CUTOLO M: A growing need for capillaroscopy in rheumatology. *Arthritis Rheum* 2009; 61: 405-10.
11. HAO YJ, JIANG X, ZHOU W *et al*.: Connective tissue disease-associated pulmonary arterial hypertension in Chinese patients. *Eur Respir J* 2014.
12. YAQUB A CL: Epidemiology and risk factors for pulmonary hypertension in systemic sclerosis. *Curr Rheumatol Rep* 2013; 15: 1.
13. LIU X, LI M, XU D *et al*.: Prevalence and clinical importance of gastroesophageal reflux in Chinese patients with systemic sclerosis. *Clin Exp Rheumatol* 2012; 30: S60-6.
14. SHAH AA, WIGLEY FM, HUMMERS LK: Telangiectases in scleroderma: a potential clinical marker of pulmonary arterial hypertension. *J Rheumatol* 2010; 37: 98-104.
15. ROBERT-THOMSON PJ MT, WALKER JG, SMITH MD, AHERN MJ: Clinical utility of telangiectasia of hands in scleroderma and other rheumatic disorders. *Asian Pac J Allergy*

Immunol 2002; 20: 6.
16. COX SR WJ, COLEMAN M, RISCHMUELLER M *et al*.: Isolated pulmonary hypertension in scleroderma. *Intern Med J* 2005; 35: 6.
17. DHALA A: Pulmonary arterial hypertension in systemic lupus erythematosus: current status and future direction. *Clin Dev Immunol* 2012; 2012: 854-941.
18. MARINO CLAVERIE L, KNOBEL E, TAKASHIMA L *et al*.: Organ involvement in Argentinian systemic sclerosis patients with "late" pattern as compared to patients with "early/active" pattern by nailfold capillaroscopy. *Clin Rheumatol* 2013; 32: 839-43.
19. GRAF SW HP, LESTER S, PATTERSON K *et al*.: South Australian Scleroderma Register: autoantibodies as predictive biomarkers of phenotype and outcome. *Int J Rheum Dis* 2012; 15: 8.
20. COJOCARU M CI, SILOSI I, VRABIE CD: Associated pulmonary arterial hypertension in connective tissue diseases. *Maedica* (Buchar) 2011; 6: 5.
21. AVOUAC J, HUSCHER D, FURST DE, OPITZ CF, DISTLER O, ALLANORE Y, FOR THE EG: Expert consensus for performing right heart catheterisation for suspected pulmonary arterial hypertension in systemic sclerosis: a Delphi consensus study with cluster analysis. *Ann Rheum Dis* 2013.
22. PROUDMAN SM, STEVENS WM, SAHHAR J, CELERMAJER D: Pulmonary arterial hypertension in systemic sclerosis: the need for early detection and treatment. *Intern Med J* 2007; 37: 485-94.
23. THAKKAR V, STEVENS WM, MOORE OA, NIKPOUR M: Performance of screening algorithms in systemic sclerosis-related pulmonary arterial hypertension: a systematic review. *Intern Med J* 2013.
24. COGHLAN JG, DENTON CP, GRUNIG E *et al*.; ON BEHALF OF THE DSG: Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. *Ann Rheum Dis* 2013.