Pulmonary hypertension and interstitial lung disease within PHAROS: impact of extent of fibrosis and pulmonary physiology on cardiac haemodynamic parameters

A. Fischer[1], J.J. Swigris[1], M.B. Bolster[2], L. Chung[3], M.E. Csuka[4], R.T. Domsic[5], T. Frech[6], M. Hinchcliff[7], V. Hsu[8], L.K. Hummers[9], M. Gomberg-Maitland[10], S.C. Mathai[9], R. Simms[11], V.D. Steen[12]

[1]National Jewish Health and University of Colorado School of Medicine, CO;
[2]Medical University of South Carolina, Charleston, SC;
[3]Stanford University, California;
[4]Medical University of Wisconsin, Milwaukee, WI;
[5]University of Pittsburgh, PA;
[6]University of Utah, Salt Lake City, UT;
[7]Northwestern University, Evanston, IL;
[8]UMDNJ Robert Wood Johnson Medical School, New Jersey, USA;
[9]John Hopkins University, Baltimore;
[10]University of Chicago, IL;
[11]Boston University, MA;
[12]Georgetown University, Washington, DC, USA.

Aryeh Fischer, MD
Jeffrey J. Swigris, DO
Marcy B. Bolster, MD
Lorinda Chung, MD
Mary Ellen Csuka, MD
Robyn T. Domsic, MD
Tracy Frech, MD
Monique Hinchcliff, MD
Vivien Hsu, MD
Laura K. Hummers, MD
Mardi Gomberg-Maitland, MD
Stephen C. Mathai, MD
Robert Simms, MD
Virginia D. Steen, MD

Please address correspondence to:
Aryeh Fischer, MD,
National Jewish Health,
1400 Jackson Street, G07,
80206 Denver, CO, USA.
E-mail: fischera@njhealth.org

Received on April 7, 2014; accepted in revised form on August 4, 2014.

Clin Exp Rheumatol 2014; 32 (Suppl. 86): S109-S114.

Key words: interstitial lung disease, pulmonary hypertension, pulmonary arterial hypertension, pulmonary fibrosis, PHAROS

Competing interests: see page S-113.

ABSTRACT

Objective. *We sought to examine the relationship between measures of ILD severity and PH in patients with SSc.*

Methods. *We identified 55 subjects from 12 PHAROS sites with RHC-proven PH and HRCT evidence of ILD. Subjects with PH due to left heart disease were excluded. Baseline HRCT scans were scored by a standardised system that graded severity of ILD. Summary statistics were generated for baseline characteristics. Spearman correlation and linear regression were used to examine relationships between ILD and PH severity variables.*

Results. *The majority of subjects were white women; nearly half had limited cutaneous SSc. Most subjects were New York Heart Association functional class II or III. Pulmonary function testing revealed moderate restriction (mean FVC 64.3±17.2% predicted) with severe reduction in diffusing capacity (mean DLco 34.2±13.3% predicted). RHC demonstrated mild to moderate PH (mean PAP 35±9 mmHg, mean PVR 5.1±3.7 WU). There was no correlation between severity of ILD (by either HRCT or PFT) and cardiac haemodynamic parameters of PH.*

Conclusion. *No association between severity of ILD and cardiac haemodynamic profiles were identified in this cohort. We believe this underscores the complex nature of PH and ILD in individuals with SSc. We do suspect that some individuals with SSc-ILD will also have concomitant pulmonary vascular disease but simple assessments to grade severity of ILD – by PFT or HRCT estimates of ILD extent – are likely not enough to reliably distinguish between PAH versus PH-ILD. Further research into how to distinguish and manage these subsets is warranted.*

Introduction

Pulmonary arterial hypertension (PAH) is identified in 10–15% of patients with systemic sclerosis (SSc, scleroderma) and is a leading cause of SSc-related morbidity and mortality (1). PAH can have a devastating impact on SSc patient survival; prior to the availability of PAH-specific therapies, the 5-year survival was 10% for SSc patients with PAH compared to 80% for SSc patients without PAH (2). Because SSc-associated PAH (SSc-PAH) has such a poor prognosis, there is emphasis on optimising screening of SSc patients for PAH (3). Effective screening for PAH should lead to more prompt diagnosis and earlier intervention with PAH-specific therapies to improve quality of life, right-heart function and possibly survival (3).

Recent clinical classification schemes of pulmonary hypertension (PH) separate patients into 5 specific categories of PH (Table I) (4, 5). Patients with SSc are unique in that they are at risk for the development of several types of PH including Group 1 PH (PAH), Group 2 PH (pulmonary hypertension due to left heart disease [PH-LHD]), and Group 3 PH (PH associated with lung disease and/or hypoxia, including PH related to interstitial lung disease [PH-ILD]) (6). (Patients with SSc are also at risk for developing pulmonary veno-occlusive disease (Group 1' PH) (7). Echocardiographic estimates of pulmonary artery pressure (PAP) may be unreliable, particularly in patients with SSc due to a lack of analysable tricuspid regurgitant jet (8, 9) and to presence of ILD (10). Thus, a diagnosis of PH requires a right-heart catheterisation (RHC) procedure to confirm PAP elevation (defined as a mean PAP [mPAP] ≥25 mmHg) and to distinguish PAH and PH-ILD from PH-

Table I. Categories of pulmonary hypertension.

Group 1 (Group 1')	Pulmonary arterial hypertension (Pulmonary veno-occlusive disease)
Group 2	Pulmonary hypertension related to left heart disease (*e.g.* diastolic dysfunction)
Group 3	PH associated with chronic lung disease and/or hypoxia (*e.g.* PH-ILD)
Group 4	Chronic thromboembolic PH
Group 5	PH associated with miscellaneous or multifactorial etiology (*e.g.* sarcoidosis)

PH: pulmonary hypertension; ILD: interstitial lung disease.

LHD (defined by a pulmonary capillary wedge pressure (PCWP) >15 mmHg) (5, 11). Furthermore, the RHC provides other specific cardiac haemodynamic parameters, such as pulmonary vascular resistance (PVR) and cardiac output (CO), that are known to help determine severity and prognosis of PH (11).

Distinguishing whether a SSc patient has PAH *versus* PH-ILD can be challenging for two primary reasons: i) both types of PH can have similar cardiac haemodynamics (elevated mPAP, low PCWP, and elevated PVR); and ii) extreme variability and complexity in the relationship between ILD severity and the development of PH, which begs the often-asked question of how one determines whether a SSc patient with both PH and ILD has *PAH* or *PH-ILD*? A SSc patient with mild ILD yet markedly elevated mPAP (with low PCWP and elevated PVR) would likely be considered to have PAH. In contrast, the SSc patient with severe ILD and long standing oxygen needs but only mild mPAP elevation (with low PCWP and elevated PVR) would likely be considered to have PH-ILD. However, many SSc patients fall between these two extremes and are more difficult to reliably classify as PAH or PH-ILD.

This scenario is neither uncommon nor trivial. ILD is an extremely common manifestation of SSc with an estimated prevalence as high as 75% (12, 13). Depending on the mode of detection, estimates of co-existent ILD and PH (SSc-PH-ILD) may be identified in 8-18% of SSc patients (14, 15). Patients with SSc-PH-ILD have a worse prognosis than patients with SSc-PAH (16-19). And finally, these two groups of SSc patients are managed differently: those with PAH are treated with PAH-specific therapies while those with PH-ILD are managed with immunomodulatory therapies targeting ILD (20-25).

In this study, we use data from a subgroup of subjects in the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) registry with RHC-confirmed SSc-PH and concomitant ILD to better understand distinctions between PAH *versus* PH-ILD. Specifically, we sought to examine the relationship between measures of ILD severity and cardiac haemodynamics in patients with RHC-confirmed SSc-PH. We hypothesised that we would identify an inverse relationship between severity of ILD and the degree of PH such that mild ILD would be associated with a higher mPAP on RHC and that more severe ILD would be associated with a lower mPAP on RHC.

Methods

Cohort derivation

The PHAROS registry was established in 2006 to prospectively follow SSc subjects at high risk for developing PH or those with a RHC-confirmed diagnosis of PH within the previous six months (6). PHAROS is a multicentre study, in compliance with the US Health Insurance Portability and Accountability Act (HIPAA), conducted at 18 US sites. Each participating centre's institutional review board approved the study protocol. Although funded by foundations and commercial support, the sponsors had no role in study design, data analyses, or preparation of this manuscript.

The PHAROS registry includes two subgroups of subjects (6):

i) SSc subjects at increased risk for developing PAH (as previously described) (6), who are classified as "pre-PAH"; and

ii) SSc subjects with incident PH enrolled within 6 months of RHC-confirmed diagnosis, according to the 2009 Dana Point criteria for PH [mean pulmonary artery pressure (mPAP) ≥25 mm Hg at rest] (11). As previously published (6), inclusion criteria for PHAROS are age >18 years and fulfillment of American College of Rheumatology criteria for SSc (26) or the LeRoy definitions (27) of limited cutaneous or diffuse cutaneous SSc. Patients with PH are excluded if they are receiving PAH-specific treatment at the time of the initial RHC or have a left ventricular ejection fraction <50% on echocardiography or signs or symptoms of systolic heart failure at the baseline clinical examination. An additional exclusion criterion includes PH attributed to other diseases included in the current PH classification system (*e.g.* HIV infection, cardiopulmonary disease attributed to drugs and toxins, sarcoidosis, etc.) (5, 6).

For this project, the study cohort was composed of 55 PHAROS subjects from 12 of the participating centres that had of evidence of RHC-proven PH along with the presence of ILD as confirmed by the presence of ground glass opacifications, reticulation, or honeycombing on thoracic high-resolution computed tomography (HRCT) imaging. Subjects with PH-LHD (defined as PCWP >15 mmHg) were excluded.

Estimating ILD extent by HRCT

Thoracic HRCT scans closest to the date of the RHC procedure were independently scored at each of the 12 PHAROS sites that participated in this study. The degree of ILD extent by HRCT imaging was estimated by the participating investigator, a radiologist, or pulmonologist in a manner similar to the methodology published by Goh and colleagues in which the presence of any of the following was considered ILD: ground glass opacities, reticulations, fibrosis, or honeycombing (28). The extent of ILD was recorded as none (score=0), mild (score=1), moderate (score=2), or severe (score=3) at

5 specific zones throughout the lungs. Zone 1 was at the level of the great vessels, zone 2 at the level of the aortic arch, zone 3 at the level of the carina bifurcation, zone 4 at the level of the venous confluence, and zone 5 at just above the diaphragm (28). A cumulative fibrosis score was generated by calculating the sum of the scores at the 5 zones for each scan and the maximum fibrosis score possible was 15.

Statistical analyses

Summary statistics were generated for baseline characteristics. Spearman correlation and linear regression were used to examine relationships between ILD and PH severity variables. We considered $p<0.05$ to represent statistical significance. All statistical analyses were run using SAS, Version 9.3 (SAS Institute, Inc.; Cary, NC).

Results

Clinical characteristics of the cohort (Table II)

The clinical characteristics of the cohort are given in Table II. All had SSc, evidence of varying degrees of ILD extent by HRCT, RHC-confirmed mPAP >25 mmHg, and a PCWP of <15 mmHg. The average time frame between the HRCT scan and the RHC procedure was 148 days (± 180 days). Their average age was 56 years; the majority were women (n=39); and most were White (n=40). Nearly half had limited cutaneous SSc. Most subjects were New York Heart Association functional class II or III. ILD and PH were both moderately severe.

Table III gives coefficients for correlation between ILD and PH severity variables. No correlations were identified between extent of fibrosis or degree of physiologic restriction (FVC) and mPAP, PVR, CO, or NYHA functional class. A higher mPAP was mildly correlated with a lower DLco and a higher FVC%/DLco% ratio. A higher PVR was moderately correlated with a short 6-minute walk distance. Figure 1 displays scatter plots and regression lines (with equations) for analyses of ILD severity variables (FVC and HRCT score) and mPAP. No relationships between FVC or extent of fibrosis and mPAP were identified.

Table II. Clinical demographics (n=55).

Age	56.4±10.6
Gender	39 F, 13 M (3 no data)
Ethnicity	40 W, 8 B, 2 H, 1 A, 1 NA (3 no data)
SSc type	25 D, 24 L, 6 unclassifiable
Autoantibody	3 negative, 5 ACA, 14 Scl-70, 10 isolated nucleolar, 4 u1RNP, 3 RNA polymerase III, 13 mixed, 3 no data
NYHA FC	4 FC I, 25 FC II, 21 FC III, 5 FC IV
FVC%	64.3±17.2
TLC%	67.2±16.5
DLco%	34.2±13
FVC% / DLco%	2.12±0.85
mPAP (mmHg)	35.3±9.4
Cardiac output (L/m)	5.3±1.5
PVR (WU)	5.1±3.7
Fibrosis score (maximum of 15)	7.7±3.4

Values expressed as mean ± standard deviation.
SSc: scleroderma; NYHA FC: New York Heart Association Functional Class; TLC%: total lung capacity; FVC%: forced vital capacity; DLco%: diffusing capacity for carbon monoxide; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; F: female; M: male; W: White; B: Black; H: Hispanic; A: Asian; NA: Native American; D: diffuse; L: limited; ACA: anti-centromere antibody.

Table III. Correlation between ILD and PH severity.

	MPAP	PVR	CO	NYHA
FVC%	0.03592 (0.80)	-0.15358 (0.29)	0.27052 (0.06)	0.04133 (0.77)
HRCT score	-0.1286 (0.35)	-0.12400 (0.38)	-0.00557 (0.97)	0.18209 (0.18)
DLCO%	-0.28628 (0.04)	-0.25299 (0.09)	0.27335 (0.06)	-0.26490 (0.06)
FVC%/DLCO%	0.29047 (0.04)	0.11392 (0.45)	-0.11311 (0.44)	0.23383 (0.10)
6MWD	-0.19740 (0.20)	-0.37212 (0.01)	0.14191 (0.36)	-0.26540 (0.08)
UCSD	0.11435 (0.43)	0.20365 (0.17)	-22042 (0.13)	0.21245 (0.14)

ILD: interstitial lung disease; PH: pulmonary hypertension; FVC%: forced vital capacity; HRCT: high-resolution computed tomography; DLco%: diffusing capacity for carbon monoxide; 6MWD: six-minute walk distance; UCSD: University of California San Diego Shortness of Breath Questionnaire; NYHA: New York Heart Association Functional Class; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; CO: cardiac output.

Discussion

With an aim towards better understanding distinctions in PAH *versus* PH-ILD in patients with SSc, we sought to determine the relationship between ILD severity and baseline cardiac haemodynamics in a well-characterised cohort of patients with RHC-proven SSc-PH. Varying degrees of ILD extent were identified by HRCT and overall, the cohort demonstrated moderate ILD (based on pulmonary physiology and extent of fibrosis seen on HRCT) and mild to moderate PH based on cardiac haemodynamics. We did not identify any significant relationships between extent of fibrosis on HRCT or degree of physiologic restriction on PFT and cardiac haemodynamics. In most patients with lung disease in SSc, the clinical picture is dominated by either progressive ILD or PAH. Although mild, subclinical ILD may be commonly identified in those with PAH, rarely does a patient have both severe ILD combined with severe PH. Given this, we had expected that subjects with mild ILD (as defined by FVC or HRCT score) would have haemodynamic profiles similar to patients with isolated PAH (*e.g.* worse cardiac haemodynamics), and those subjects with severe ILD would have cardiac haemodynamic profiles similar to patients with PH-ILD. However, our results demonstrate that ILD severity is unable to reliably inform on the cardiac haemodynamic profile of patients with SSc.

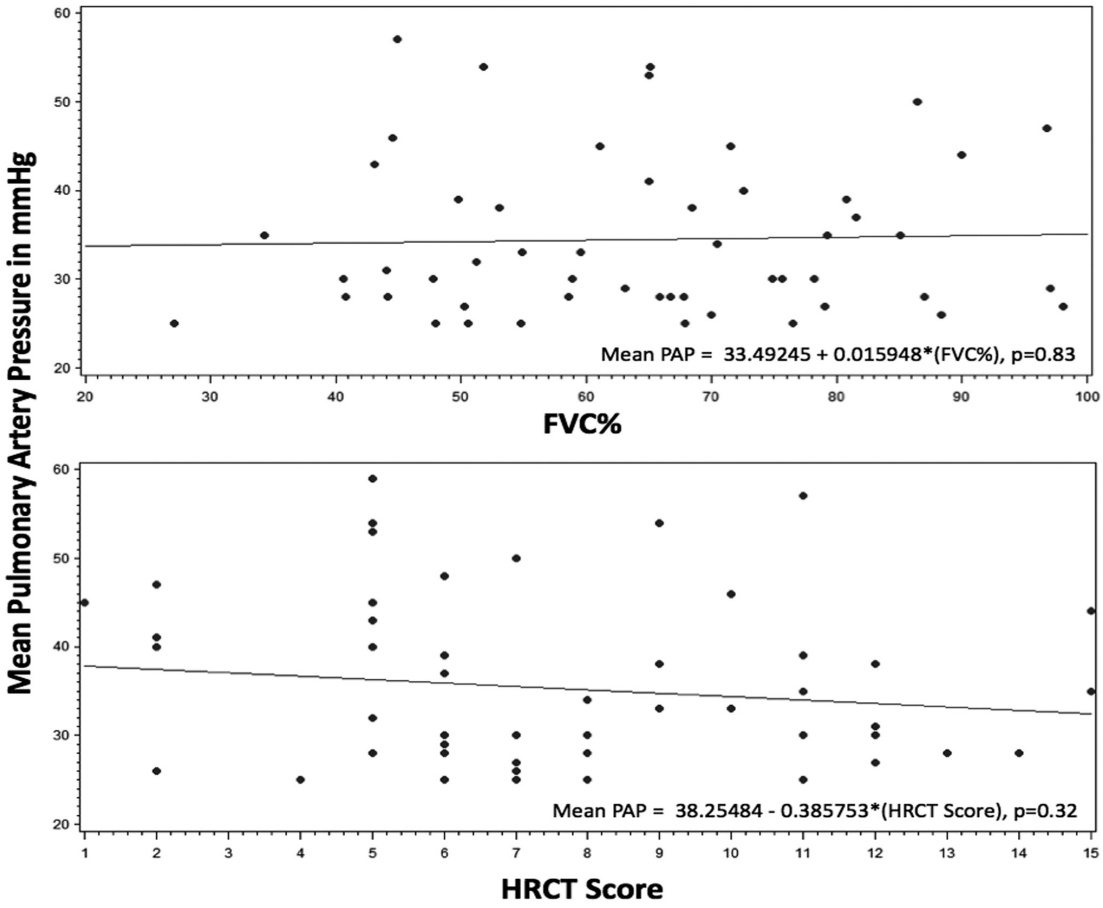

Fig. 1. Scatter plots and regression lines (with equations) for analyses of ILD severity variables (FVC% and HRCT extent of fibrosis).
ILD: interstitial lung disease;
FVC%: forced vital capacity;
HRCT: high-resolution computed tomography.

Prior studies in SSc-ILD cohorts and in other forms of ILD have also failed to consistently demonstrate a relationship between severity of ILD and PH. In a small cohort of diffuse SSc patients with ILD (n=52), 15 patients had SSc-ILD-PH as defined by echocardiography (29). When comparing PFT parameters, only DLco differed between those with and without PH (mean DLco 40±9.5% *vs*. 54.6±16% predicted, PH *vs*. no PH respectively). HRCT findings were also reported, demonstrating no significant difference in disease extent or severity between groups (29). Lettieri and colleagues reported on their experience with 79 patients with advanced idiopathic pulmonary fibrosis (IPF) referred for lung transplant evaluation (30). In this cohort, over 30% of the patients had RHC-proven PH. However, there were no significant differences noted in either FVC or TLC between those with and without PH; only a marginally significant difference in DLCO was noted (30). When compared to our cohort, the PH patients in the Lettieri study had more severe restriction based upon mean FVC and TLC, but similar reduction in DLco; conversely, PH was likely less severe (mPAP = 29.5±3.3 mmHg compared to 35.3±9.4 in our study) (30).

As these data support, determining whether a SSc patient has PAH or PH-associated with ILD is very challenging. However, it is an important distinction to make, because of the differences in the therapeutic approach to these two phenotypes. PAH-specific therapies are only indicated in those with PAH, and for those with PH-associated with ILD, treatment with PAH therapies have not been adequately studied (20). There have only been small series suggesting that treating these individuals with PAH therapies are either of no benefit or potentially harmful (19, 31).

A recent task force composed of an international panel of pulmonary experts aimed to address aspects of PH-associated with chronic lung disease (32). It sought to address complex issues surrounding PH arising in the context of IPF, emphysema, or combined pulmonary fibrosis with emphysema (CPFE). The task force provided criteria for this discrimination and suggested using the following definitions for Group 3 PH, as exemplified for emphysema, IPF, and CPFE: COPD/IPF/CPFE *without* PH (mPAP <25 mm Hg); COPD/IPF/CPFE *with* PH [mPAP ≥25 mm Hg]); COPD/IPF/CPFE *with severe* PH (mPAP ≥35 mm Hg or mPAP ≥25 mm Hg with low cardiac index) (32). The "severe PH group" includes only a minority of chronic lung disease patients who are suspected of having pulmonary vascular remodelling accompanying the parenchymal disease. Exertional dyspnea disproportionate to pulmonary function tests, low DLco, and rapid decline of arterial oxygenation upon exercise are typical clinical features of this subgroup (32). The task force emphasised that studies evaluating the effectiveness of PAH targeted therapies (currently not approved for Group 3 PH patients) should focus on this "severe PH" group, and for the time being,

these patients should be transferred to expert centres for individualised patient care (32). Whether such a classification scheme could apply to patients with SSc-PH-ILD is not known, but given the vasculopathic properties fundamental to SSc, we suspect that a significant proportion of SSc-ILD patients have the primary vasculopathy of PAH.

A notable limitation of this study relates to the method for scoring thoracic HRCT scans. Due to regulatory restrictions, HRCT images in the PHAROS registry are not stored in a single site. Thus, we were unable to have a uniform reading across all 12 participating sites. In an effort to minimise differences across sites, we held a webinar for the participating investigators. During the webinars, representative HRCT scans were shown and scored to try to ensure uniformity of estimation. Despite these efforts, we acknowledge that a uniform reading by an expert thoracic radiologist would have been preferred. And, we recognise that this may have impacted the reliability of the estimates of ILD extent and degree of fibrosis. However, the significant correlation between the extent of ILD (by HRCT score) and degree of physiologic restriction by PFT would suggest the scoring was reasonably valid. Furthermore, given the diagnostic challenges associated with pulmonary veno-occlusive disease (PVOD) and the fact that patients with PVOD may have imaging findings (*e.g.*, septal lines and ground glass opacifications) that could be suggestive of ILD (33) and these patients have a similar haemodynamic profile as with PAH, it is possible that some of these subjects classified as PH with ILD may have had PVOD. Other potentially important limitations to note include selection bias as these subjects are all from specialised SSc centres, delay in timing between HRCT and RHC (average of nearly 5 months), and small sample size of the cohort.

In conclusion, we studied a subset of PHAROS subjects with SSc and RHC-proven PH and concomitant ILD, and we found no association between severity of ILD and cardiac haemodynamic profiles. We believe this underscores the complex nature of PH and ILD in individuals with SSc. We do suspect that some individuals with SSc-ILD will also have concomitant PAH but simple assessments to grade severity of ILD – by PFT or HRCT estimates of ILD extent – are likely not enough to reliably distinguish between PAH *versus* PH-ILD. Further research into how to distinguish these subsets is warranted clinical trials of SSc patients with PH and ILD are needed to determine whether PAH-targeted therapies are of potential benefit in this cohort.

Competing interests

A. Fischer has received honoraria and research support from Actelion, Gilead, InterMune, Boehringer-Ingelheim.

M. Gomberg-Maitland has served as a consultant for Actelion, Bayer, Gilead, Medtronic, Merck, Bellerophon (formerly known as Ikaria), and United Therapeutics as a member of steering committees and DSMB/event committees. She has received honoraria for CME from Medscape and ABComm.

Actelion, Gilead, Medtronic, Novartis, Lung Biotechology, and Reata have provided funding to the University of Chicago during the last yeart to support Dr Gomberg-Maitland's conduct of clinical trials. Dr Gomberg-Maitland is a member of the PCORI Advisory Panel on Rare Diseases and a special government employee for the FDA Cardio-Renal division.

S.C. Mathai has served as a consultant for Actelion and Bayer Healthcare, has received grant funding from NIH/NHLBI, the Pulmonary Hypertension Association, and Gilead Sciences.

R. Simms has received grants from Actelion and InterMune, research support from Medimmune, and is a member of speakers' bureau for Gilead.

The other co-authors have declared no competing interests.

References

1. MUKERJEE D, ST GEORGE D, COLEIRO B *et al*.: Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. *Ann Rheum Dis* 2003; 62: 1088-93.
2. STEEN V, MEDSGER TA, JR.: Predictors of isolated pulmonary hypertension in patients with systemic sclerosis and limited cutaneous involvement. *Arthritis Rheum* 2003; 48: 516-22.
3. KHANNA D, GLADUE H, CHANNICK R *et al*.: Recommendations for screening and detection of connective tissue disease-associated pulmonary arterial hypertension. *Arthritis Rheum* 2013; 65: 3194-201.
4. SIMONNEAU G, ROBBINS IM, BEGHETTI M *et al*.: Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol* 2009; 54: S43-54.
5. HOEPER MM, BOGAARD HJ, CONDLIFFE R *et al*.: Definitions and diagnosis of pulmonary hypertension. *J Am Coll Cardiol* 2013; 62: D42-50.
6. HINCHCLIFF M, FISCHER A, SCHIOPU E, STEEN VD, INVESTIGATORS P: Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS): baseline characteristics and description of study population. *J Rheumatol* 2011; 38: 2172-9.
7. GALIE N, PALAZZINI M, MANES A: Pulmonary hypertension and pulmonary arterial hypertension: a clarification is needed. *Eur Respir J* 2010; 36: 986-90.
8. MATHAI SC, SIBLEY CT, FORFIA PR *et al*.: Tricuspid annular plane systolic excursion is a robust outcome measure in systemic sclerosis-associated pulmonary arterial hypertension. *J Rheumatol* 2011; 38: 2410-8.
9. MURATA I, KIHARA H, SHINOHARA S, ITO K: Echocardiographic evaluation of pulmonary arterial hypertension in patients with progressive systemic sclerosis and related syndromes. *Jpn Circ J* 1992; 56: 983-91.
10. ARCASOY SM, CHRISTIE JD, FERRARI VA *et al*.: Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. *Am J Respir Crit Care Med* 2003; 167: 735-40.
11. BADESCH DB, CHAMPION HC, SANCHEZ MA *et al*.: Diagnosis and assessment of pulmonary arterial hypertension. *J Am Coll Cardiol* 2009; 54: S55-66.
12. WHITE B: Interstitial lung disease in scleroderma. *Rheum Dis Clin North Am* 2003; 29: 371-90.
13. BUSSONE G, MOUTHON L: Interstitial lung disease in systemic sclerosis. *Autoimmunity reviews* 2011; 10: 248-55.
14. CHANG B, WIGLEY FM, WHITE B, WISE RA: Scleroderma patients with combined pulmonary hypertension and interstitial lung disease. *J Rheumatol* 2003; 30: 2398-405.
15. STEEN VD, LUCAS M, FERTIG N, MEDSGER TA, JR.: Pulmonary arterial hypertension and severe pulmonary fibrosis in systemic sclerosis patients with a nucleolar antibody. *J Rheumatol* 2007; 34: 2230-5.
16. 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.
17. LAUNAY D, HUMBERT M, BEREZNE A *et al*.: Clinical characteristics and survival in systemic sclerosis-related pulmonary hypertension associated with interstitial lung disease. *Chest* 2011; 140: 1016-24.
18. MATHAI SC, HUMMERS LK, CHAMPION HC *et al*.: Survival in pulmonary hypertension associated with the scleroderma spectrum of diseases: impact of interstitial lung disease. *Arthritis Rheum* 2009; 60: 569-77.

19. LE PAVEC J, GIRGIS RE, LECHTZIN N *et al*.: Systemic sclerosis-related pulmonary hypertension associated with interstitial lung disease: impact of pulmonary arterial hypertension therapies. *Arthritis Rheum* 2011; 63: 2456-64.
20. TANI C, BELLANDO RANDONE S, GUIDUCCI S, DELLA ROSSA A: Systemic sclerosis: a critical digest of the recent literature. *Clin Exp Rheumatol* 2013; 31: 172-9.
21. ANDO K, NAKASHITA T, KANEKO N, TAKAHASHI K, MOTOJIMA S: Long-term efficacy and safety of maintenance therapy with azathioprine or cyclosporine for interstitial lung disease with diffuse cutaneous scleroderma. *Clin Exp Rheumatol* 2013; 31: 191-2.
22. IUDICI M, CODULLO V, GIUGGIOLI D *et al*.: Pulmonary hypertension in systemic sclerosis: prevalence, incidence and predictive factors in a large multicentric Italian cohort. *Clin Exp Rheumatol* 2013; 31: 31-6.
23. FISCHER A, BROWN KK, DU BOIS RM *et al*.: Mycophenolate mofetil improves lung function in connective tissue disease-associated interstitial lung disease. *J Rheumatol* 2013; 40: 640-6.
24. HOYLES RK, ELLIS RW, WELLSBURY J *et al*.: A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. *Arthritis Rheum* 2006; 54: 3962-70.
25. TASHKIN DP, ELASHOFF R, CLEMENTS PJ *et al*.: Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med* 2006; 354: 2655-66.
26. 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.
27. LEROY EC, BLACK C, FLEISCHMAJER R *et al*.: Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988; 15: 202-5.
28. GOH NS, DESAI SR, VEERARAGHAVAN S *et al*.: Interstitial lung disease in systemic sclerosis: a simple staging system. *Am J Respir Crit Care Med* 2008; 177: 1248-54.
29. TRAD S, AMOURA Z, BEIGELMAN C *et al*.: Pulmonary arterial hypertension is a major mortality factor in diffuse systemic sclerosis, independent of interstitial lung disease. *Arthritis Rheum* 2006; 54: 184-91.
30. LETTIERI CJ, NATHAN SD, BARNETT SD, AHMAD S, SHORR AF: Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. *Chest* 2006; 129: 746-52.
31. CORTE TJ, KEIR GJ, DIMOPOULOS K *et al*.: Bosentan in pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia. *Am J Respir Crit Care Med* 2014; 190: 208-17.
32. SEEGER W, ADIR Y, BARBERA JA *et al*.: Pulmonary hypertension in chronic lung diseases. *J Am Coll Cardiol* 2013; 62: D109-16.
33. GUNTHER S, JAIS X, MAITRE S *et al*.: Computed tomography findings of pulmonary venoocclusive disease in scleroderma patients presenting with precapillary pulmonary hypertension. *Arthritis Rheum* 2012; 64: 2995-3005.