Review

Systemic Sclerosis - Associated Pulmonary Hypertension

Iraklis Tsangaris,
Frantzeska Frantzeskaki

2nd Department of Critical Care Medicine and Pulmonary Hypertension Clinic, ATTIKON University Hospital, National and Kapodistrian University of Athens, Chaidari, Greece

Key words:
- Pulmonary hypertension
- Scleroderm

Correspondence:
Iraklis Tsangaris
Associate Professor
2nd Department of Critical Care Medicine and Pulmonary Hypertension Clinic, ATTIKON University Hospital, National and Kapodistrian University of Athens
1 Rimini Str, Chaidari 12462, Greece
Tel.: 2105832179, 6944734600
Fax: 2105326414
E-mail: itsagkaris@med.uoa.gr

SUMMARY
Lung disease is a major complication of systemic sclerosis associated with high morbidity and mortality rates. Pulmonary hypertension and lung fibrosis are the prevalent manifestations of lung disease, usually with overlapping characteristics. A major challenge in the management of the disease, is to identify the phenotypes of patients who might benefit from specific therapeutic modalities. The aim of the present review is to describe the clinical and epidemiological characteristics, classification, risk assessment and management of systemic sclerosis associated pulmonary hypertension.
Pneumon 2018, 31(4):221-228.

INTRODUCTION

Systemic Sclerosis (SSc) is characterized by inflammation, fibrosis and diffuse vasculopathy, caused by an autoimmune mechanism, triggered by environmental stimulus in genetically susceptible persons. The fibrotic manifestations of SSc are provoked by fibroblast proliferation, stimulated by transforming growth factor (TGF)-β, tumor necrosis factor-α, platelet-derived growth factor and fibronectin, which are produced by macrophage activation[1]. Vascular endothelial growth factor is increased as well, leading to neoangiogenesis. The fibrotic process and the neoangiogenesis contribute to SSc lung disease, characterized by lung fibrosis, nonspecific interstitial pneumonia and pulmonary vasculopathy. Smooth muscles hypertrophy and proliferation of adventitia and intima with in situ thrombosis and plexiform lesions result in elevated pulmonary vascular resistance and subsequent pulmonary hypertension (PH)[2,3].

Pulmonary hypertension (PH) is a severe complication of SSc, and a main cause of mortality, despite the widespread use of targeted therapies[4]. The definition of PH is based on elevated mean pulmonary artery pressure ≥25 mmHg, assessed by right heart catheterization, while precapillary PH is characterized by pulmonary artery wedge pressure ≤15 mmHg[5].The prevalence of PH in SSc patients is more than 10%[6], while it may be caused in the setting of group 1 (pulmonary arterial hypertension-PAH), group 1'

(pulmonary veno-occlusive disease-PVOD/pulmonary capillary hemangiomatosis), group 2 (PH due to left heart disease), group 3 (PH caused by chronic lung disease) or group 4 (chronic thromboembolic PH)[7]. In this review, we will describe the current knowledge on clinical characteristics, diagnostic and screening issues, risk stratification, prognosis and treatment options in SSc - associated PH.

PREVALENCE AND RISK FACTORS

PAH is a significant cause of morbidity and mortality in SSc patients. Interestingly, according to a US study of causes of death in SSc patients, scleroderma renal crisis has been substituted by pulmonary fibrosis and PAH, as the commonest cause of death[8]. Additionally, the presence of PAH in SSc patients is associated with higher mortality compared to SScpatients without PAH[9]. Moreover, connective tissue disease – associated PAH is characterized by poorer survival rates compared to idiopathic PAH (IPAH)[10], whereas patients with SSc-associated PAH experience higher mortality compared to patients with IPAH[11]. SSc – associated PAH carries poorer survival rates compared to non-SSc CTD – PAH subgroups, including systemic lupus erythematosus and mixed connective tissue disease. This was confirmed by the REVEAL registry (Registry to Evaluate Early and Long-term PAH Disease Management), showing that the 3-year survival in patients with SSc-PAH was lower, as compared to non-SSc CTD-PAH patients[10].

The incidence of PAH in SSc ranges between 5 and 12% depending on the study[6]. As it has been indicated in the PHAROS cohort (Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma), PH developed in 10% of SSc patients after 2 years of attendance, 13% after 5 years and 25% after 5 years[12]. The incidence rate is estimated to 1-2% per year[13].

Risk factors for the development of PH in SSc are older age, late onset of the disease post-menopausal status and limited cutaneous type of the disease[14]. Moreover, the risk of PAH is higher in SSc patients, who show evidence of other aberrant vascular phenomena, like telangiectasias[15]. There are also several parameters measured in pulmonary function tests, which are associated to the development of PH: low DLCO (<50% of predicted), DLCO/alveolar volume less than 70% and FVC%/DLCO% ratio >1.6)[16]. Regarding the autoantibodies, the presence of anticentromere antibodies, nucleolar pattern of antinuclear antibodies (ANA), anti-U1-ribonucleoprotein (RNP), antiphospholipic antibodies against cardiolipin and beta2-glycoprotein 1 and the lack of anti-Scl-70, are risk factors for development of PAH in SSc patients[17].

DIAGNOSIS

Diagnosis of PAH is established by right heart catheterization (RHC). There are several screening approaches to identify SSc patients who should be early referred for RHC. According to ESC/ERS 2015 guidelines, patients should be referred for RHC if echocardiography reveals: triscupid regurgitant velocity (TVR) >3,4 m/sec, or TVR >2,8 ≤3.4 m/sec and current dyspnea, current syncope/near syncope, peripheral edema, or TVR ≤2.8 m/sec and additional suggestive echo variable[5]. Another screening algorithm is proposed by Australian Scleroderma Interest Group, including N-terminal pro b-type natriuretic peptide (NT-proBNP) and pulmonary function tests (PFTs)[18] (Fig. 1). Moreover, the DETECT algorithm integrates non-invasive

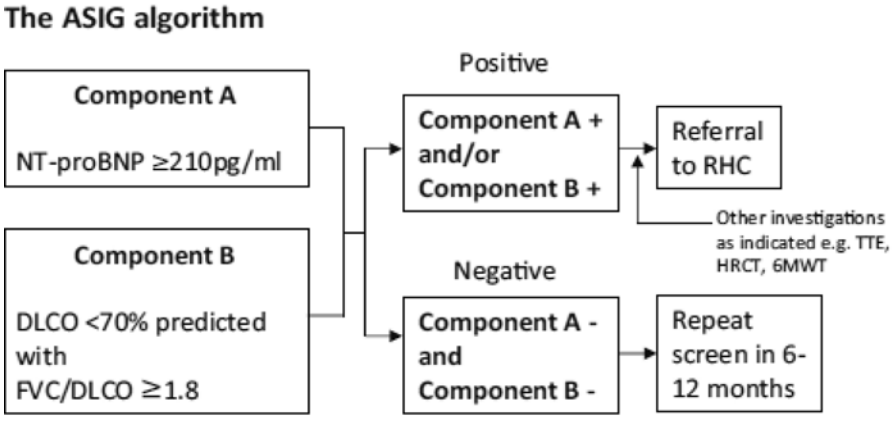

FIGURE 1. ASIG screening algorithm. ASIG: Australian scleroderma Interest Group, DLCO: Diffusing capacity for carbon monoxide, FVC: Forced vital capacity, RHC: Right heart catheterization.

clinical and laboratory parameters and echocardiography, in order to assess the risk of PH[19] (Fig 2). As a first step, six variables are recorded (FVC, telangiectasia, anticentromere antibody positivity, ECG right access deviation and serum levels of NT-proBNP and urate). Since the subsequent score surpasses a threshold, ECG parameters are calculated, and a new score is assessed. RHC is recommended if the risk of development of PH is considered high. DETECT algorithm has shown high sensitivity and negative predictive value[20]. However, it was derived from a cohort of patients with SSc duration of >3 years and predicted diffusing capacity for carbon monoxide (DLCO) <60%. In general, ECG, NT-proBNP levels, PFTs and clinical assessment, are useful for predicting the risk of development of PAH.

CLASSIFICATION

According to the ERS/ESC guidelines, PH is divided in 5 categories. The most common category of PH, observed in more than 50% of SSc patients with PH, is PAH (group I). There are histological similarities between SSc-associated PAH and idiopathic PAH, characterized by thickening of media and muscularization of arterioles, while plexiform lesions are less common[21]. Moreover, SSc-associated PAH might also present overt signs of venous and capillary involvement, in the context of pulmonary veno-occlusive disease (PVOD), which is classified as Group I' PAH. There are also SSc patients with post-capillary PH due to cardiac involvement (group II) or PH caused by interstitial lung disease (ILD) and hypoxia (group III)[13]. The extent of lung fibrosis is determined by computer tomography (CT) assessment and by FVC values. Lung fibrosis might be considered as a cause of PH, if it affects more than 20% of the lung volume, in high resolution CT (HRCT) imaging. Moreover, FVC <70% is consistent with extensive fibrosis[22]. Thrombosis might also be present in SSc patients implicating the development of chronic thromboembolic pulmonary hypertension (CTEPH), the Group IV of PH classification.

The classification of SSc patients in a certain PH group is challenging, as there are mixed phenotypes with overlapping clinical characteristics and different response to therapy. Moreover, in the same patient, clinical classification of PH may change during the course of the disease. In the prospective observational PHAROS cohort, it was shown that the pulmonary artery wedge pressure (PAWP) in SSc patients with PH could significantly change on follow up RHC[23]. These changes are meaningful as they affect the classification and the subsequent therapeutic choices. The increase of PAWP over time might be attributed to

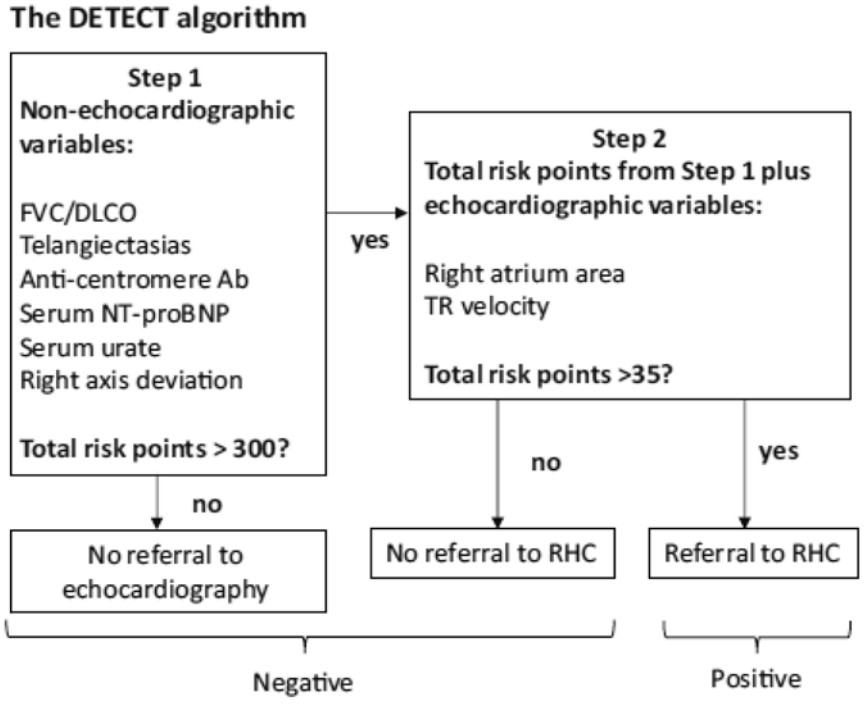

FIGURE 2. DETECT screening algorithm.

the development of heart failure with preserved ejection fraction (HFpEF)[24]. Moreover, the specific PH therapy and diuretics can alter right ventricular (RV) function and left ventricle (LV) filling pressures, by ventricular interdependence[25]. Helpful procedures to recognize group II PH are the fluid challenge and exercise test during RHC.

Therefore, PH in SSc patients can be precapillary or postcapillary, while the classification might change over time. However, SSc patients with precapillary PH form an heterogeneous group, in which the predominant mechanism of PH might be the parenchymal lung involvement or the vascular disease. Several patients present with clinical and pathological characteristics lying between these two extremes. In order to identify different phenotypes of precapillary PH in SSc, Launey et al performed a cluster analysis[26]. According to lung function tests, hemodynamic and radiological data, patients were classified to four clusters characterized by a different extent of PAH, ILD and DLCO. The worst prognosis was observed in patients with extensive ILD irrespectively of the hemodynamic values. The prognosis was also poor in patients with severe PAH with mild ILD and low DLCO, in whom hemodynamic parameters played a prognostic role. Therefore the classification of PH in SSc patients is important for the clinician, to identify the underline pathological mechanism of the disease, to define the future risk and to take therapeutic decisions.

DISEASE PROGRESSION

The DETECT study developed an algorithm aiming to identify SSc patients with high suspicion of PH, who should be referred for RHC, in order to be diagnosed earlier. As the prognosis of the milder stage of the disease was not clearly defined, 88 patients enrolled in the DETECT study, were longitudinally observed on a yearly basis, to identify parameters associated with a worse outcome. The study showed that 43.9% of patients with PAH developed a disease progression, while 16% of them died during the follow up period. The 1-year survival rate was 93%. Interestingly, most of these patients were on WHO FC I or II with mean PAP 29mmHg and PVR 270 dynes. Therefore, the development of even mild PAH might be a severe complication of SSc conferring an unfavorable prognosis. Factors associated with uneventful outcome were male gender, lower DLCO%, higher FVC%/DLCO% and higher Borg Dyspnea Index[27].

Another subgroup of SSc patients at risk for developing severe PAH, consists of patients with mPAP 21-24 mmHg, also called borderline PAH (BoPAH). In the PHAROS cohort, 88% of BoPAP patients developed exercise-induced PAH (mPAP >30mmHG) compared to 56% of patients with normal mPAP on RHC[28]. Moreover, 55% of the BoPAP patients developed PH after 2 years of follow up, compared to 32% of patients with initially normal hemodynamics. A more recent study of the incidence of PH in SSc patients showed that BoPAP was present in 32.4% of the population. During the follow up period, these patients showed a significantly higher probability to develop PAH as compared to patients with normal pressures at baseline. Independent risk factors for the development of PH were PVR, tricuspid regurgitation velocity, DLCO and size of inferior vena cava[29]. Moreover, patients with BoPAP showed a trend towards lower survival rate than those with normal mPAP at baseline. Therefore, BoPAP could be considered as an intermediate stage preceding the occurrence of PAH. Exercise RHC might help unmasking the group of SSc patients with BoPAP, who are more likely to develop PAH.

RISK STRATIFICATION

It has been shown, that PH patients with 3 or 4 low-risk risk stratification criteria included in the European PH guidelines, are characterized by better long-term outcome[30]. However, the prognostic value of these criteria is not well established in SSc patients with PA. The same analysis was repeated in a large group of SSc patients with PAH, who did not show signs of significant ILD in high resolution CT. The recorded low risk criteria were: NYHA FC I or II, 6MWD >440m, right atrial pressure (RAP) <8 mmHg and cardiac index (CI) ≥2.5 lt/min/m^2. Among these parameters, baseline values of 6MWD and CI were independently associated with the outcome. However, all the low risk criteria were associated with outcomes at first follow up. In patients with 3-4, 2, 1 and no low-risk criteria, the respective three year survival rate was 84%, 73%, 45% and 35% respectively[31].

Regarding the prognostic role of follow up hemodynamics in SSc PAH patients, Weatherald et al studied the association of hemodynamic parameters with transplant-free survival. At follow up, transplant – free survival was independently associated with 6-MWD, NYHA-FC, Cardiac Index (CI), Stroke Volume Index (SVI), Pulmonary arterial compliance and Pulmonary Vascular Resistance (PVR)[32]. However, at baseline, only 6MWD was an independent

predictor of survival and none of the hemodynamic parameters. Moreover, a cluster analysis of PHAROS database was performed, aiming to identify a high risk phenotype of the SSc-PAH patients[33]. The group of patients with the highest mortality showed a decline in 6MWD at follow up and a trend towards increased BNP values. Since the baseline measurements are insufficient to identify high risk patients, the authors suggest close follow-up and rapid titration of vasodilator therapy or referral to transplantation, in case of deterioration.

THERAPY

There are several algorithms guiding the therapeutic options in patients with SSc and ILD or PAH. Various parameters, as the extend of fibrosis in HRCT, the lung function tests and the disease duration and progression, contribute to the therapeutic decisions[34]. Immunosuppressive medication is the most commonly used treatment option for SSc-ILD, well studied in randomized controlled trials. Cyclophosphamide is an alkylating agent, which might lead to improvement in FVC and dyspnea[35]. Use of mycophenolate mofetil, an inhibitor of inosine monophosphate dehydrogenase, leads to a stabilization or improvement of FVC or DLCO, in SSc patients with ILD[36].

There are various experimental therapies for SSc-ILD targeting to molecular pathways involved in fibrosis procedure. Fresolimumab is one of these targeted therapies. It is a monoclonal antibody to transforming growth factor-beta (TGF-β), which plays an important role in fibrosis[34]. Other antifibrotic agents approved in idiopathic pulmonary fibrosis are pirfenidone and nintedanib[37]. Several clinical trials studying the therapeutic use of these antifibrotic agents in SSc patients are underway. Tocilizumab and Rituximab are other monoclonal antibodies that have come on interest in therapy of SSc-ILD[38].

PAH treatment in SSc patients aims to the improvement of functional class. In PH patients classified in Group I, all the categories of PH medications have been tried: Phosphodiesterase 5 (PDE-5) inhibitors, riociguat, endothelin receptor antagonists (ERA) and prostacyclins. IV epoprostenol improves exercise tolerance, WHO-FC and hemodynamics[39]. Selexipag, an oral prostacyclin receptor agonist, has been studied in a subgroup of patients with connective tissue disease, in the context of GRIPHON study[40]. The medication was well tolerated, leading to a delay of disease progression. Combination therapy with tadalafil and ambrisentan, has been studied in SSc-PAH patients, in a subgroup analysis of AMBITION study, showing improved outcomes[41]. In the PHAROS registry, patients receiving monotherapy with an ERA alone, showed a quicker time to clinical worsening, as compared to those receiving PDE-5 inhibitors or combination PDE-5/ERA[42]. Regarding anticoagulation, it has been shown that warfarin administration in SSc-PAH patients was associated with worse outcomes[43].

In SSc patients with ILD and PH there are not current treatment recommendations. A group of patients, in whom, PH is disproportionate to the degree of the underlying parenchymal disease, might benefit from specific PAH therapy[44]. An online survey was performed in US PH treatment centres, in order to investigate the administration of PAH – directed therapy in patients with non-group 1 PH[45]. 80% of centres participating in the survey reported the use of PAH directed therapy in group 3 of PH patients. The main parameters affecting the clinicians' decision to give PAH specific therapy were the presence of right heart failure, poor right ventricular (RV) function and the significantly impaired pulmonary hemodynamics (mean PAP >35 mmHg). However, any vasodilator therapy should be used with caution, as it might aggravate the ventilator-perfusion rate and worsen the subsequent hypoxia[3]. More clinical studies are necessary to identify the phenotype of SSc- associated ILD and PH, that might respond to PAH-targeted therapy. RV metrics should be included in these studies, in order to evaluate the effect of PAH – therapy on RV function.

Lung transplantation might be a therapeutic option for patients with SSc and PH/ILD. In several centres, SSc patients are not considered as candidates, as oesophageal involvement is associated with increased risk of aspiration, leading to potential graft failure. There also concerns about previous immunosuppressive and steroid therapies, which may lead to post-transplantation complications[3]. However, observational studies have shown that patients with SSc-PAH who were transplanted, had comparable survival to transplanted patients with idiopathic PAH or idiopathic pulmonary fibrosis[46,47]. Therefore, for SSc patients with end-stage lung disease, lung transplantation might be a treatment option.

CONCLUSIONS

PH is an important complication of SSc and a predominant cause of morbidity and mortality. Several screening approaches have been developed to identify high risk

patients who should early be referred for RHC. The classification of PH in SSc patients is challenging, since mixed phenotypes are usually present, with arterial, venous or capillary involvement. The prognosis of the disease is unfavourable, whereas baseline hemodynamic measurements are insufficient to identify the high risk population. Several treatment options are available, including immunosuppressives, PAH-specific therapy and transplantation. However, mortality rates remain high. Close clinical and hemodynamic monitoring of these patients and subsequent prompt administration of specific therapy or early referral for transplantation, might improve the prognosis of this devastating complication of SSc.

ΠΕΡΙΛΗΨΗ

Πνευμονική Υπέρταση και Σκληρόδερμα

Ηρακλής Τσαγκάρης, Φραντζέσκα Φαντζεσκάκη

Β' Τμήμα Εντατικής Θεραπείας και Κλινική Πνευμονικής Υπέρτασης,
Π.Γ.Ν. Αττικόν, Εθνικό και Καποδιστριακό Πανεπιστήμιο Αθηνών

Η πνευμονική νόσος αποτελεί σημαντική επιπλοκή του σκληροδέρματος συνδέεται με τα υψηλά ποσοστά νοσηρότητας και θνησιμότητας. Η πνευμονική υπέρταση και η ίνωση των πνευμόνων είναι οι κυρίαρχες εκδηλώσεις πνευμονικής νόσου, συνήθως με αλληλεπικαλυπτόμενα χαρακτηριστικά. Μια σημαντική πρόκληση στην αντιμετώπιση της νόσου, είναι να εντοπιστούν οι φαινότυποι των ασθενών που θα μπορούσαν να επωφεληθούν από συγκεκριμένες θεραπευτικές μεθόδους. Σκοπός της παρούσας ανασκόπησης είναι να περιγράψει τα κλινικά και επιδημιολογικά χαρακτηριστικά, την ταξινόμηση, την αξιολόγηση κινδύνου και τη διαχείριση της πνευμονικής υπέρτασης που σχετίζεται με το σκληρόδερμα.

Πνεύμων 2017, 30(4):221-228.

Λέξεις - Κλειδιά: *Πνευμονική υπέρταση, σκληρόδερμα*

REFERENCES

1. Johnson SR, Granton JT. Pulmonary hypertension in systemic sclerosis and systemic lupus erythematosus. European Respiratory Review: an Official Journal of the European Respiratory Society 2011;20:277-86.
2. Varga J, Whitfield ML. Transforming growth factor-beta in systemic sclerosis (scleroderma). Frontiers in bioscience (Scholar edition) 2009;1:226-35.
3. Denton CP, Wells AU, Coghlan JG. Major lung complications of systemic sclerosis. Nature Reviews Rheumatology 2018;14:511-27.
4. Sobanski V, Launay D, Hachulla E, Humbert M. Current Approaches to the Treatment of Systemic-Sclerosis-Associated Pulmonary Arterial Hypertension (SSc-PAH). Current Rheumatology Reports 2016;18:10.
5. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint 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: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). The European Respiratory Journal 2015;46:903-75.
6. Sundaram SM, Chung L. An Update on Systemic Sclerosis-Associated Pulmonary Arterial Hypertension: a Review of the Current Literature. Current Rheumatology Reports 2018;20:10.
7. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. Journal of the American College of Cardiology 2013;62(25 Suppl):D34-41.
8. Steen VD, Medsger TA. Changes in causes of death in systemic sclerosis, 1972-2002. Annals of the Rheumatic Diseases 2007;66:940-4.
9. Hao Y, Hudson M, Baron M, et al. Early mortality in a multinational systemic sclerosis inception cohort. Arthritis and Rheumatology 2017;69:1067-77.
10. Chung L, Farber HW, Benza R, et al. Unique predictors of mortality in patients with pulmonary arterial hypertension associated with systemic sclerosis in the REVEAL registry. Chest 2014;146:1494-504.
11. Ramjug S, Hussain N, Hurdman J, et al. Idiopathic and Systemic Sclerosis-Associated Pulmonary Arterial Hypertension: A Comparison of Demographic, Hemodynamic, and MRI Characteristics and Outcomes. Chest 2017;152:92-102.
12. Hsu VM, Chung L, Hummers LK, et al. Development of pulmonary hypertension in a high-risk population with systemic sclerosis

in the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) cohort study. Seminars in Arthritis and Rheumatism 2014;44:55-62.
13. Nihtyanova SI, Schreiber BE, Ong VH, et al. Prediction of pulmonary complications and long-term survival in systemic sclerosis. Arthritis and Rheumatology (Hoboken, NJ) 2014;66:1625-35.
14. Hachulla E, Launay D, Mouthon L, et al. Is pulmonary arterial hypertension really a late complication of systemic sclerosis? Chest 2009;136:1211-9.
15. Shah AA, Wigley FM, Hummers LK. Telangiectases in scleroderma: a potential clinical marker of pulmonary arterial hypertension. The Journal of Rheumatology 2010;37:98-104.
16. Allanore Y, Borderie D, Avouac J, et al. High N-terminal pro-brain natriuretic peptide levels and low diffusing capacity for carbon monoxide as independent predictors of the occurrence of precapillary pulmonary arterial hypertension in patients with systemic sclerosis. Arthritis and Rheumatism 2008;58:284-91.
17. Kampolis C, Plastiras S, Vlachoyiannopoulos P, Moyssakis I, Tzelepis G. The presence of anti-centromere antibodies may predict progression of estimated pulmonary arterial systolic pressure in systemic sclerosis. Scandinavian Journal of Rheumatology 2008;37:278-83.
18. Thakkar V, Stevens WM, Prior D, et al. N-terminal pro-brain natriuretic peptide in a novel screening algorithm for pulmonary arterial hypertension in systemic sclerosis: a case-control study. Arthritis Research and Therapy 2012;14:R143.
19. Coghlan JG, Denton CP, Grunig E, et al. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. Annals of the Rheumatic Diseases 2014; 73:1340-9.
20. Guillen-Del Castillo A, Callejas-Moraga EL, Garcia G, et al. High sensitivity and negative predictive value of the DETECT algorithm for an early diagnosis of pulmonary arterial hypertension in systemic sclerosis: application in a single center. Arthritis Research and Therapy 2017;19:135.
21. Hemnes AR, Humbert M. Pathobiology of pulmonary arterial hypertension: understanding the roads less travelled. European respiratory review: an Official Journal of the European Respiratory Society 2017;26(146):pii:170093.
22. Goh NS, Desai SR, Veeraraghavan S, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. American Journal of Respiratory and Critical Care Medicine 2008; 177:1248-54.
23. Lammi MR, Saketkoo LA, Gordon JK, Steen VD. Changes in hemodynamic classification over time are common in systemic sclerosis-associated pulmonary hypertension: insights from the PHAROS cohort. Pulmonary Circulation 2018;8(2):2045893218757404.
24. Ciurzynski M, Bienias P, Lichodziejewska B, et al. Assessment of left and right ventricular diastolic function in patients with systemic sclerosis. Kardiologia Polska 2008;66:269-76, discussion 77-8.
25. Lazar JM, Flores AR, Grandis DJ, Orie JE, Schulman DS. Effects of chronic right ventricular pressure overload on left ventricular diastolic function. The American Journal of Cardiology 1993;72:1179-82.
26. Launay D, Montani D, Hassoun PM, et al. Clinical phenotypes and survival of pre-capillary pulmonary hypertension in systemic sclerosis. PloS one 2018;13:e0197112.
27. Mihai C, Antic M, Dobrota R, et al. Factors associated with disease progression in early-diagnosed pulmonary arterial hypertension associated with systemic sclerosis: longitudinal data from the DETECT cohort. Annals of the Rheumatic Diseases 2018;77:128-32.
28. Bae S, Saggar R, Bolster MB, et al. Baseline characteristics and follow-up in patients with normal haemodynamics versus borderline mean pulmonary arterial pressure in systemic sclerosis: results from the PHAROS registry. Annals of the Rheumatic Diseases 2012;71:1335-42.
29. Coghlan JG, Wolf M, Distler O, et al. Incidence of pulmonary hypertension and determining factors in patients with systemic sclerosis. The European Respiratory Journal 2018;51(4):pii:17001197.
30. Boucly A, Weatherald J, Humbert M, Sitbon O. Risk assessment in pulmonary arterial hypertension. European Respiratory Journal 2018; 51(3):1800279.
31. Weatherald JC, Chaouat A, Cottin V, et al. Risk Assessment in Systemic Sclerosis-Associated Pulmonary Arterial Hypertension. A27 you got another thing coming: Diagnosis and prognostication in pulmonary hypertension. p. A1178-A.
32. Weatherald J, Boucly A, Launay D, et al. Haemodynamics and serial risk assessment in systemic-sclerosis associated pulmonary arterial hypertension. European Respiratory Journal 2018; 52(4): pii 1800678. doi: 10.1183/13993003.00678-2018.
33. Hyer M, Ramakrishnan V, Lammi MR, Steen V, Argula RG. Can the PHAROS Predict the Future? - Identifying High Risk Phenotypes Among Patients with Systemic Sclerosis Associated Pulmonary Arterial Hypertension (SSc-PAH). A27 you got another thing coming: Diagnosis and prognostication in pulmonary hypertension. p. A1177-A.
34. Schoenfeld SR, Castelino FV. Evaluation and management approaches for scleroderma lung disease. Therapeutic Advances in Respiratory Disease 2017;11:327-40.
35. 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 and Rheumatism 2006;54:3962-70.
36. Tashkin DP, Roth MD, Clements PJ, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. The Lancet Respiratory medicine. 2016;4:708-19.
37. Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. The New England Journal of Medicine 2014;370:2071-82.
38. Daoussis D, Liossis SN, Tsamandas AC, et al. Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study. Rheumatology (Oxford, England) 2010;49:271-80.
39. Badesch DB, Tapson VF, McGoon MD, et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the

scleroderma spectrum of disease. A randomized, controlled trial. Annals of Internal Medicine 2000;132:425-34.
40. Sitbon O, Channick R, Chin KM, et al. Selexipag for the Treatment of Pulmonary Arterial Hypertension. New England Journal of Medicine 2015;373:2522-33.
41. Coghlan JG, Galie N, Barbera JA, et al. Initial combination therapy with ambrisentan and tadalafil in connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH): subgroup analysis from the AMBITION trial. Annals of the Rheumatic Diseases 2017;76:1219-27.
42. Lammi MR, Mathai SC, Saketkoo LA, et al. Association between initial oral therapy and outcomes in systemic sclerosis-related pulmonary arterial hypertension. Arthritis and Rheumatology (Hoboken, NJ). 2016;68:740-8.
43. Preston IR, Roberts KE, Miller DP, et al. Effect of warfarin treatment on survival of patients with pulmonary arterial hypertension (PAH) in the registry to evaluate early and long-term PAH disease management (REVEAL). Circulation 2015;132:2403-11.
44. Seeger W, Adir Y, Barbera JA, et al. Pulmonary hypertension in chronic lung diseases. Journal of the American College of Cardiology 2013;62(25 Suppl):D109-16.
45. Trammell AW, Pugh ME, Newman JH, Hemnes AR, Robbins IM. Use of pulmonary arterial hypertension-approved therapy in the treatment of non-group 1 pulmonary hypertension at US referral centers. Pulmonary Circulation 2015;5:356-63.
46. Crespo MM, Bermudez CA, Dew MA, et al. Lung transplant in patients with scleroderma compared with pulmonary fibrosis. short- and long-term outcomes. Annals of the American Thoracic Society 2016;13:784-92.
47. Miele CH, Schwab K, Saggar R, et al. Lung Transplant outcomes in systemic sclerosis with significant esophageal dysfunction. A Comprehensive Single-Center Experience 2016;13:793-802.